Management of Complications in Refractive Surgery

Second Edition

Jorge L. Alio
Dimitri T. Azar
Editors

Springer

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Part I

Overview

Refractive Surgery Outcomes and Frequency of Complications

1

Wallace Chamon, Norma Allemann, Jorge L. Alio, and Ahmed A. Abdelghany

Core Messages

- In refractive surgery, there is no risk-free surgical procedure. The evaluation of the risk/benefit ratio should be part of a continuous process of patient care.
- Refractive surgery risks and benefits should be evaluated individually in order to choose the surgical approach properly.
- Disease distribution of each possible complication should be considered.
- Decision-making in refractive procedure is an individualized process that should be based on scientific knowledge, patient's characteristics, and surgeon experience.
- The informed consent should reflect all risks/benefits clearly to the patient candidate for any refractive surgery procedure.

1.1 Introduction

Refractive surgical procedures are generally divided into additive procedures, with implantation of phakic intraocular lens (IOL), and subtractive procedures, with ablation of the corneal tissue [1].

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In 2004, the European Society of Cataract and Refractive Surgeons (ESCRS) took the initiative to establish a registry for refractive surgery outcomes: the Refractive Surgery Outcomes Information System (RSOIS). The purpose of this web-based system was to record outcomes of refractive surgery and improve quality of care for these procedures. Reasons behind the initiative were the growing health in truest within the field and increasing patient complaints after refractive surgery reported in the press, in some countries [2, 3]. Patient complaints were thought to be associated with inappropriate indications and surgery outside the limits of the procedure, leading to suboptimal outcomes in refractive surgery.

In refractive surgery, the goal is to achieve optimal visual acuity, optimal refraction (usually emmetropia), and no complications [4]. Complications during and after surgery are of distinct concern as the eyes undergoing refractive surgery are usually healthy eyes.

In this chapter, we are going to discuss refractive surgery outcomes and complications in each group of refractive surgical procedures.

1.2 Laser Refractive Surgery

Laser refractive surgery is one of the most commonly performed eye surgeries worldwide and has been established to be successful in correcting refractive errors [5].

Several benchmarks have been established for laser keratorefractive surgery. The Food and Drug Administration (FDA) based on data presented by several evidence-based reviews defined the correction limitation of excimer laser (Table 1.1) [6].

The American Academy of Ophthalmologist (AAO) reports stated that the substantial level II and III evidence proved that excimer laser refractive surgery, whether laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK), is a safe and effective tool of correcting the full

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Table 1.1 FDA indications for LASIK and PRK [6]

	LASIK	PRK
Myopia	Less than −14.0 D with or without astigmatism between −50 and −5.00 D	Up to −12.0 D with or without astigmatism up to −4.00 D
Hyperopia	Up to +5.00 D with or without astigmatism up to +3.00 D	Up to +5.00 D with or without astigmatism up to +4.00 D
Mixed astigmatism	Astigmatism up to 6.00 D, the cylinder is greater than the sphere and of opposite sign	

spectrum of refractive errors but with some limitations in high hyperopic refractive errors [6, 7].

The latest generation of excimer laser platforms had introduced a large number of features such as faster laser, smaller spot size, a high speed tracker, pupil monitoring, and online pachymetry, all of which provided superior treatment with significant improvement of induced postoperative high-order aberrations (HOA) and control of thermal damage [8].

With the advent of keratomileusis procedures, primarily LASIK, a new anatomic region in the cornea came into existence: the potential space between anterior and posterior corneal lamellae commonly referred to as the LASIK interface. Within this region, a number of biochemical processes occur after creation of the corneal flap, including limited wound healing and intercellular reorganization [9]. The anatomy of the LASIK interface allows for a variety of potential unique complications to arise from different etiologies with often overlapping clinical presentations.

1.2.1 Common Complications Associated with Laser Refractive Surgery

1.2.1.1 Refractive Imprecision and Loss of Spectacle-Corrected Visual Acuity

The most frequent complication observed in any refractive procedure is the lack in achieving accurate refractive outcome. As a general rule, accuracy decreases with the amount of refractive error. Photoablative procedures tend to be the most accurate ones for low ametropias. PRK and LASIK deal with different variables that may affect predictability, such as corneal wound healing and stromal bed elasticity, respectively [10].

We may expect that in any photoablative procedure, approximately 60–70% of eyes will achieve 20/20 uncorrected visual acuity and will be within +/−0.50 D after surgery. If we analyze only low myopias (under 6.00 D), approximately 70–80% will achieve 20/20 uncorrected visual acuity [10–18].

1.2.1.2 Infectious Keratitis

Determining the risk of infection on photoablative procedures is a difficult task due to misdiagnoses and lack of laboratorial information. We may expect an incidence between 0.1:10.000 and 1:10.000, favoring LASIK over PRK [19–21]. Infection has been reported after LASIK with femtosecond laser [22].

Risk factors for the development of infectious keratitis include blepharitis, dry eye, intraoperative epithelial defects, intraoperative contamination, delayed postoperative reepithelialization of the cornea, use of topical corticosteroids, and patients in the health profession [23–25].

Infectious keratitis after LASIK has been divided into infections occurring within the first 2 weeks (early onset) and after 2 weeks to 3 months (late onset) [26]. The organisms responsible for early onset infections include staphylococcal and streptococcal species, whereas organisms more commonly seen in late onset infections include atypical mycobacteria and fungi [27].

In the initial phase of treatment, LASIK flaps should be lifted, cultures taken, the flap bed irrigated with fortified antibiotics, and broad-spectrum topical antibiotics started. For infections with a delayed onset, the use of amikacin may be beneficial in treating atypical mycobacteria [26]. In nonresponsive LASIK infections, flap amputation may be necessary to facilitate antibiotic penetration.

Most infections resolve with mild to moderate loss of best visual acuity [28], but rarely therapeutic penetrating keratoplasty is necessary.

1.3 LASIK

1.3.1 Interface Complications

- *Diffuse lamellar keratitis*

Diffuse lamellar keratitis (DLK) is a white blood cell infiltrate that coalesces between the flap and stromal bed that appears within a few days (1–5) after LASIK [29–31]. Confocal microscopy has confirmed the presence of inflammatory cells in the corneal stroma and interface in DLK [32]. This nonspecific interface inflammation is certainly associated with intraoperative epithelial defects [33] and has been linked to multiple rare potential inciting factors [34].

DLK has been associated with factors such as bacterial endotoxin [35], chemicals or debris [36], surgical gloves [37], and surgical marking pens [38, 39]. Patient factors shown to affect the risk for DLK include Meibomian gland secretions and peripheral immune infiltrates [40, 41] and atopy. Ultimately, DLK is likely the result of how a patient's endogenous factors respond to exogenous exposures [42].

DLK after LASIK has been reported to occur at higher frequency with femtosecond laser flap creation than with microkeratome flap creation. The incidence of DLK is estimated to range from 0.2 to 19.4% after femtosecond laser flap creation [43–47] and from 0.1 to 7.7% after microkeratome flap creation [31, 46, 48–52]. Higher energy level for flap creation with femtosecond laser and larger flap diameter were associated with an increased risk for DLK [53].

DLK is typically classified clinically into four stages as described by Linebarger and colleagues [42]. Stage 1 has inflammatory cells in the far periphery only, which are first present in the corneal stroma and then coalesce in the LASIK interface. Stage 2 has a diffuse infiltrate frequently involving the paracentral and peripheral flap margins but sparing the central axis. Stage 3 has a denser infiltrate within the flap interface, which involves the visual axis and is frequently associated with decreased visual acuity. Stage 4 has a focal, coalesced dense haze with scarring, signifying flap necrosis and usually results in permanent corneal scarring.

- *Pressure-induced stromal keratopathy* (*PISK*)

In the setting of LASIK, PISK is a relatively rapid steroid response resulting in high intraocular pressure with fluid accumulation in the interface. The amount of fluid present may be relatively small, resulting in diffuse haziness in the interface and overlying stroma without an obvious fluid layer [54], or it may be pronounced, resulting in a visible fluid cleft separating the anterior flap from the posterior residual bed [55].

The degree of interface fluid accumulation masks true IOP in various ways when measured using standard approaches. In all cases, actual IOP is greater than IOP measured centrally, and peripheral measurements generate a more accurate IOP.

- *Central toxic keratopathy* (*CTK*)

CTK is a rare, acute, noninflammatory central corneal opacification that can occur within days after uneventful LASIK or PRK [56–62]. Etiology is unknown but may be related to enzymatic degradation of keratocytes [57, 60].

CTK is almost always painless, as opposed to DLK, which in almost all cases has at least a moderate foreign body sensation, and CTK is acute in onset, as opposed to the progression over time to stage 4 DLK. CTK is self-limited and treatment is not warranted [57], while some have advocated aggressive topical steroid use [61] or flap lift and irrigation [63].

- *Epithelial ingrowth*

Epithelial ingrowth at the far periphery is a normal healing response to LASIK flap creation [9], but clinically relevant epithelial ingrowth occurs when a fistula develops under the flap allowing epithelial cell growth into the interface [64]. Most cases can be observed without requiring intervention [64].

For primary LASIK, increased epithelial ingrowth incidence is associated with hyperopic LASIK treatment [65], LASIK after RK [66], epithelial defects during surgery [67], and older age [68]. For LASIK retreatment, increased epithelial ingrowth incidence is associated with the use of contact lenses after retreatment [68] and flap-lift retreatment performed three or more years after primary LASIK [69].

With femtosecond laser flap creation, the overall incidence of visually significant epithelial ingrowth has decreased [70]. The lower incidence of epithelial ingrowth after femtosecond LASIK surgery compared with mechanical microkeratome-assisted LASIK may be attributed to the anatomy of the femtosecond laser-created side cut, in contrast to that created with a mechanical microkeratome, and the creation of less peripheral trauma at the time of flap creation [71].

Treatment depends on the clinical situation. The majority of cases of mild, clinically insignificant ingrowth are managed with observation. Initial surgical treatment for epithelial ingrowth is performed with flap lift, removal of epithelial cells from the posterior surface of the flap and the stromal bed with a blade or similar instrument, and replacement of the flap without sutures or tissue glue [64, 72]. With recurrent episodes of epithelial ingrowth, additional measures are typically taken, including flap sutures [73] or YAG laser treatment [74].

1.3.2 Flap Complications

Irregular flaps related to the microkeratome cut maybe presented as incomplete flaps, free caps, buttonholed flaps, thin flaps, thick flaps, and partially cut flaps [75].

- *Bowman strip and button hole in LASIK flaps*
  The incidence of intraoperative complications related to flap creation during LASIK is between 0.19 [76] and 21.2% [77]. Several explanations have been proposed to account for Bowman strip or "buttonhole" complications, such as steep corneas, partially opened eyes, and microkeratome deficits, such as blade defect and insufficient synchronization between the movement of the blade and microkeratome translational movement. High astigmatism or conjunctival entrapment may also lead to Bowman strip or buttonhole flap [78, 79].
  Some refractive surgeons recommend waiting 3 months, relifting the flap, and bathing the bed with mitomycin C (MMC) followed by surface ablation [75, 80].

- *Early flap displacement after LASIK*

The application of femtosecond laser technology to LASIK flap creation has increased greatly since its

introduction. These lasers have improved the safety and predictability of the lamellar incision step. The majority of the femtosecond laser-assisted flap complications can be well managed without significant effects on refractive outcomes [81].

The incidence of flap displacement during 12-month follow-up period after LASIK has been reported to be extremely low (0.012%). Femtosecond laser has lower incidence of flap displacement than microkeratome [82].

1.3.2.1 Keratectasia

One of the most troublesome complications after LASIK is progressive iatrogenic keratectasia, which can occur up to several months after surgery [83]. Although the actual incidence of ectasia is unknown, it has been estimated to be 0.04–0.6% [84–86]. Several risk factors have been suggested in an attempt to avoid ectasia [87, 88]. However, controversy exists as to the predictability of these factors, and some cases continue to occur without a clear etiological explanation [84, 89]. Ideally, patients at risk of ectasia would be identified prior to laser surgery and be classified as unsuitable candidates for LASIK; however, at present, there is no absolute test, system, or marker that can identify patients at risk of developing ectasia.

Randleman et al. designed the Ectasia Risk Score System, which is a method of preoperative screening based upon the use of risk scales and identification of a number of preoperative parameters that may be associated with increased risk of ectasia [90]. The most common risk factors, in order of significance, include abnormal preoperative corneal topography, low residual stromal bed thickness, young age, thin preoperative corneal thickness, and higher attempted refractive correction. These factors are then amalgamated into a risk scale. However, this risk factor scale may miss a significant proportion of patients at risk of ectasia because other factors also play a role in the risk of ectasia [91–93].

Post-LASIK ectasia can potentially be avoided by careful patient screening preoperatively to identify risk factors which might lead to this complication.

Management of iatrogenic keratectasia consists of penetrating keratoplasty and, more recently, lamellar keratoplasty [94] and collagen cross-linking (CXL) [95]. In fact, with the success observed for CXL in the treatment of progressive keratoconus, some studies have reported on the use of CXL for postoperative keratectasia in very thin corneas [96].

1.3.2.2 High-Order Aberrations After LASIK

LASIK like other corneal refractive surgeries (such as radial keratotomy, photorefractive keratectomy), is designed to modify the central corneal curvature, making it flatter to correct myopia and steeper to correct hyperopia [97]. This surgical modification might influence the optical quality of the cornea, creating aberrations that will lead to distorted images [98].

LASIK eliminates conventional refractive errors (lower-order aberration like myopia, hyperopia, and astigmatism) leaving higher-order aberrations uncorrected or inducing some higher-order aberrations (HOAs) particularly spherical aberrations [99–102] which are thought to be responsible for the patients' complaints of poor quality of vision, even with visual acuity of 20/25 or 20/20, postoperatively.

Wavefront-guided ablations for intraLase treatment have been shown to be effective and predictable in reducing the astigmatism and higher-order aberrations [103–107].

1.3.2.3 Post-LASIK Tear Dysfunction and Dysesthesia

Symptoms of tear dysfunction after LASIK occur in nearly all patients and resolve in the vast majority. Although dry eye complaints are a leading cause of patient discomfort and dissatisfaction after LASIK, the symptoms are not uniform, and the disease is not a single entity. Post-LASIK tear dysfunction syndrome or dry eye is a term used to describe a spectrum of disease encompassing transient or persistent postoperative neurotrophic disease, tear instability, true aqueous tear deficiency, and neuropathic pain states. Neural changes in the cornea and neuropathic causes of ocular surface discomfort may play a separate or synergistic role in the development of symptoms in some patients. Most cases of early postoperative dry eye symptoms resolve with appropriate management, which includes optimizing ocular surface health before and after surgery. Severe symptoms or symptoms persisting after 9 months rarely respond satisfactorily to traditional treatment modalities and require aggressive management [108].

1.3.2.4 Ocular Surface Syndrome

This complex multifactorial entity distresses patients and physicians and is characterized by the following symptoms: dry eye, micropunctate keratitis, decreased and unstable tear film, and decreased best spectacle-corrected visual acuity (BSCVA) and visual quality. Ocular surface syndrome has a neurotrophic etiology, is long lasting, and is difficult to treat [109].

1.3.2.5 Retinal Complications

There are several reports in the literature about retinal complications after LASIK for the correction of myopia. These include macular holes [110–113], retinal tears and detachments [114], retinal hemorrhages [115], and choroidal neovascular membranes [116].

1.4 PRK

1.4.1 Haze

Corneal haze reduces corneal transparency at variable degrees [117, 118]. Subepithelial haze occurs in all patients

1 month after PRK, reaching the greatest intensity at 3–6 months, and then gradually decreasing [119].

Besides the ablation depth, the severity of corneal haze is correlated with excessive ocular UV-B radiation, duration of the epithelial defect, postoperative steroid treatment, and male sex, and with certain population with brown iris [120–122].

Recently, the densitometry program of Pentacam Scheimpflug imaging system (Oculus Optikgeräte GmbH) has been proven to be a useful method for measuring corneal haze [123].

1.4.2 Mitomycin C

The use of intraoperative mitomycin C has raised the expectation for treating higher ametropias with PRK [118, 124–128].

Mitomycin C is an alkylating agent with cytotoxic and antiproliferative effects that reduces the myofibroblast repopulation after laser surface ablation and, therefore, reducing the risk of postoperative corneal haze. It is used prophylactically to avoid haze after primary surface ablation and therapeutically to treat preexisting haze. There is no definite evidence that establishes an exact diopter limit or ablation depth at which to apply prophylactic mitomycin C. It is usually applied at a concentration of 0.2 mg/ml (0.02%) for 12–120 s over the ablated stroma, although some studies suggest that lower concentrations (0.01, 0.002%) could also be effective in preventing haze when treating low to moderate myopia. This dose of mitomycin C has not been associated with any clinically relevant epithelial corneal toxicity. Its effect on the endothelium is more controversial [129].

1.4.3 Keratectasia

Although there are reports of keratectasia that occurred in normal eyes after PRK [130], most of the few cases reported so far are of forme fruste keratoconus that progressed after PRK [131–133] or phototherapeutic keratectomy (PTK) [134, 135].

1.5 Phakic Intraocular Lenses

The option of phakic IOLs (PIOLs) has gained popularity, having usually the widest range of correction (myopia up to 23D, hyperopia up to 21D, and astigmatism up to 7.00D) and being affordable and easily implantable [136–138]. It has potential advantages, including fast visual recovery, preservation of accommodation, and reversibility [139–141]. Compared to LASIK, PIOLs offer a higher range of refractive error correction and better quality of vision for high ametropes [142].

There are two available phakic IOLs now: the iris-fixated Artisan and the posterior chamber implantable Collamer lens (ICL). The Artiflex myopia phakic IOL was developed based on the Artisan platform, with a flexible, convex-concave, 6 mm silicone optic, PMMA haptics [143, 144]. It can achieve precise centration over the pupil and high rotational stability, but requires some surgical skills for enclavation [142]. It also requires some safety limitations like flat iris, endothelial cell count (ECC) of $\geq$2100 cell/mm^2, scotopic pupil diameter < 6.0 mm, and AC depths of $\geq$2.8 mm [145, 146]. The Visian ICL is made from Collamer (biocompatible material). Another type of phakic IOLs was angle supported, but is not in use now.

The toric Artisan corrects astigmatism from 1D to 7D, and toric ICL is capable of correcting astigmatism up to 6D. It is a good option especially for high errors with low baseline corneal thickness, shallow AC, and wide scotopic pupils [147, 148].

1.5.1 Common Complications Associated with Phakic IOLs

1.5.1.1 Pupil Ovalization

Eyes with anterior chamber angle-supported phakic IOLs have a tendency to present sectorial iris atrophy and consequent pupil ovalization [149].

1.5.1.2 Endothelial Cell Loss

The long-term impact of anterior chamber PIOL implantation on corneal endothelial cell loss has been a matter of significant research and debate. As a result of numerous randomized clinical trials, the safety of Artisan and Artiflex IOLs is now well established, with reported endothelial cell losses of 4.8% at 6 months, 8.3% at 5 years, and 12.6% at 7 years and long-term maintenance of the hexagonality and the cell coefficient of variation [150–152]. The minimum E-IOL distance from the center of the IOL to minimize the risk of endothelial cell loss was 1.7 mm [153].

Although posterior chamber IOLs have a lower risk of endothelial cell loss, a decrease in 5–10% after 2 years of the surgery may be expected [154].

1.5.1.3 Infection

Risk of infection in intraocular surgeries should follow the incidence of infection in cataract surgery that is approximately 1:1,000 [155–157].

1.5.1.4 Glaucoma

Pupillary block glaucoma has been reported in anterior chamber iris-supported [158], in angle-supported [159, 160],

and in posterior chamber phakic IOLs [161–163]. Preoperative iridectomy is mandatory, but pupillary block has been reported even in the presence of effective iridectomy [163].

1.5.1.5 Cataract

There are two basic cataract types: anterior subcapsular opacification (in cases of ICL) and nuclear cataract (in cases of Artisan). The mean time to nuclear cataract appearance after Artisan IOL implantation was 54.83 ± 22.12, and ICL implantation was 20 ± 1 month [164].

Cataract is the main cause of PIOL explantation, especially in posterior chamber PIOLs [165].

1.5.1.6 Uveitis

Postoperative sterile uveitis has been reported in previous studies [166]. The pathogenesis of uveitis after PIOL implantation is still obscure but may be related to an inflammatory reaction caused by perioperative and postoperative mechanical irritation of the iris. It is possible to detect chronic subclinical inflammation with a laser flare-cell matter after PIOL implantation [166].

Age-related changes in the anatomy of the anterior segment may create a long-term hazard for the implanted eye [167].

1.5.1.7 IOL Dislocation

Traumatic and spontaneous IOL dislocations have been described in anterior chamber iris-supported phakic IOLs [168, 169].

1.5.1.8 Retinal Complications

Implantation of ICL or Artisan phakic IOL demonstrated comparable rates of retinal complications. Anterior chamber PIOL does not increase the risk of retinal detachment or CNVM in patients with myopia [170].

Take-Home Pearls

- Refractive surgery provides a variety of elective procedures to be performed in otherwise healthy eyes. Selecting the best surgical treatment is dependent on knowing all the associated complications.

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Influence of Refractive Surgery Complications on Quality of Life

2

Konrad Pesudovs

Core Messages

- A number of questionnaires exist for the measurement of quality of life (QoL) for refractive surgery patients, but validity varies among questionnaires.
- Rasch analysis is important in the development of questionnaires to optimize question inclusion and unidimensionality and to provide valid linear scoring.
- A quality-of-life instrument should include a breadth of content areas, e.g., well-being, convenience, and concerns, not just functioning or satisfaction.
- Quality-of-life instruments readily demonstrate the benefits of refractive surgery.
- A sound QoL instrument is also sensitive to the negative impacts of surgical complications, providing an insight into the real impact of the intervention on the person.

2.1 Introduction

It has been customary to evaluate the success of refractive surgery using objective clinical measures such as postoperative uncorrected visual acuity (UCVA) and residual refractive error [1]. However, these measures do not necessarily correlate well with patients' postoperative subjective impressions [2]. Ultimately, the patient's perspective is an important outcome of refractive surgery, and a number of instruments have been developed to assess quality of life (QoL), including the Quality of Life Impact of Refractive Correction (QIRC) questionnaire, [3] the Refractive Status Vision Profile (RSVP) [4], and the National Eye Institute Refractive Quality of Life (NEI-RQL) [5]. While these instruments, and others, have been used to show the improvement in QoL that occurs with laser refractive surgery, [2, 5–9] a sound QoL instrument should also be sensitive to the effect of complications from refractive surgery.

The purpose of this chapter is to outline the key issues in QoL measurement and discuss the instruments available for use, and to specifically summarize what is known about the impact of the complications of refractive surgery on quality of life.

2.2 Measurement Concepts

Perhaps the most important issue in questionnaire selection is the validity of the scoring system. Without this, the information gathered is meaningless. The RSVP and NEI-RQL instruments use traditional summary scoring methods where an overall score is derived through summative scoring of responses [10]. Summary scoring is based on the hypothesis that all questions have equal importance and response categories are accordingly scaled to have equal value with uniform increments from category to category. For example, in a summary-scaled visual disability questionnaire, the Activities of Daily Vision Scale (ADVS), [11] "a little difficulty" scores 4, while "extreme difficulty" is twice as bad and scores 2, and "unable to perform the activity due to vision" is similarly two times worse with a score of 1. The same scale is applied across all questions. This rationale of "one size fits all" is flawed, and Rasch analysis has been used to confirm that differently weighted response categories are necessary to provide a valid and contextual scale that truly represents QoL [12]. For instance, the ADVS questionnaire ascribes the same value to "a little difficulty" regarding visual ability "driving at night" as "a little difficulty" with "driving during the day" though the former is by far the more difficult and complex task and it defies logic to equate the two.

Rasch analysis is a new approach to questionnaire development that utilizes modern statistical methods to

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measure health outcomes in a meaningful way. It incorporates an appropriate weighting factor for each QoL measure to provide true linear scoring and improved validity in terms of question inclusion and demonstration of unidimensionality [13–15].

2.3 Instruments

2.3.1 The Quality-of-Life Impact of Refractive Correction (QIRC) Questionnaire

Pesudovs et al. developed and validated the Quality of Life Impact of Refractive Correction (QIRC) questionnaire [3] to measure the comprehensive impact of refractive correction on QoL. Visual function, symptoms, convenience, cost, health concerns, and well-being are included in the content of this instrument which was rigorously developed using literature review, expert opinion, and focus groups. Content was determined using a pilot questionnaire with Rasch analysis for item reduction; [16] this resulted in the final 20-item questionnaire (Table 2.1, available in full at konrad.pesudovs.com/konrad/questionnaire.html). QIRC is ratified as a valid and reliable measure of refractive correction-related QoL by both Rasch analysis and standard psychometric techniques [3, 13]. QIRC scores are reported on a 0–100 scale which is free of floor and ceiling effects with a higher score representing better QoL and the average score being close to 50 units. QIRC has been used for measuring outcomes of refractive surgery [7, 17–19] and for comparing the QoL of patients wearing spectacles, contact lenses, or post-refractive surgery [20].

The QIRC questionnaire effectively differentiates between spectacle wearers, contact lens wearers, and post-refractive surgery patients—with the refractive surgery group having a better QIRC score (50.23 ± 6.31) than contact lens wearers (46.70 ± 5.49, $p < 0.01$) and spectacle wearers (44.13 ± 5.86, $p < 0.001$) [21]. There were significant differences between scores on 16 of the 20 questions; of the remaining four questions, two health concerns and two well-being questions did not detect differences between groups. QIRC scores have also been shown to improve after LASIK refractive surgery from a mean ± SD of 40.07 ± 4.30 to 53.09 ± 5.25 [7]. Similar improvements have also been demonstrated with phakic lens implantation, femtosecond LASIK, and small-incision lenticule extraction [17–19].

Individual item analysis showed 15 of the 20 items demonstrated statistically significant improvement. Patients reported improved QoL on all five convenience items, both economic items, all four health concern items, and on 4 of the 7 items in the well-being domain (Fig. 2.1).

Table 2.1 The 20 items included in the QIRC questionnaire

	Item description
1	How much difficulty do you have driving in glare conditions?
2	During the past month, how often have you experienced your eyes feeling tired or strained?
3	How much trouble is not being able to use off-the-shelf (nonprescription) sunglasses?
4	How much trouble is having to think about your spectacles or contact lenses or your eyes after refractive surgery before doing things, e.g., traveling, sport, going swimming?
5	How much trouble is not being able to see when you wake up, e.g., to go to the bathroom, look after a baby, see alarm clock?
6	How much trouble is not being able to see when you are on the beach or swimming in the sea or pool, because you do these activities without spectacles or contact lenses?
7	How much trouble are your spectacles or contact lenses when you wear them when using the gym/doing keep-fit classes/circuit training, etc.?
8	How concerned are you about the initial and ongoing cost to buy your current spectacles/contact lenses/refractive surgery?
9	How concerned are you about the cost of unscheduled maintenance of your spectacles/contact lenses/refractive surgery, e.g., breakage, loss, new eye problems?
10	How concerned are you about having to increasingly rely on your spectacles or contact lenses since you started to wear them?
11	How concerned are you about your vision not being as good as it could be?
12	How concerned are you about medical complications from your choice of optical correction (spectacles, contact lenses, and/or refractive surgery)?
13	How concerned are you about eye protection from ultraviolet (UV) radiation?
14	During the past month, how much of the time have you felt that you have looked your best?
15	During the past month, how much of the time have you felt that you think others see you the way you would like them to (e.g., intelligent, sophisticated, successful, cool, etc.)?
16	During the past month, how much of the time have you felt complimented/flattered?
17	During the past month, how much of the time have you felt confident?
18	During the past month, how much of the time have you felt happy?
19	During the past month, how much of the time have you felt able to do the things you want to do?
20	During the past month, how much of the time have you felt eager to try new things?

2.3.2 The Refractive Status Vision Profile (RSVP)

The RSVP was developed almost exclusively on a refractive surgery population (92% of subjects), so it is really only valid for refractive surgery [4]. Its 42 items fall into the domains of concern (6), expectations (2), physical/social functioning (11), driving (3), symptoms (5), glare (3), optical problems (5), and problems with corrective lenses (7)

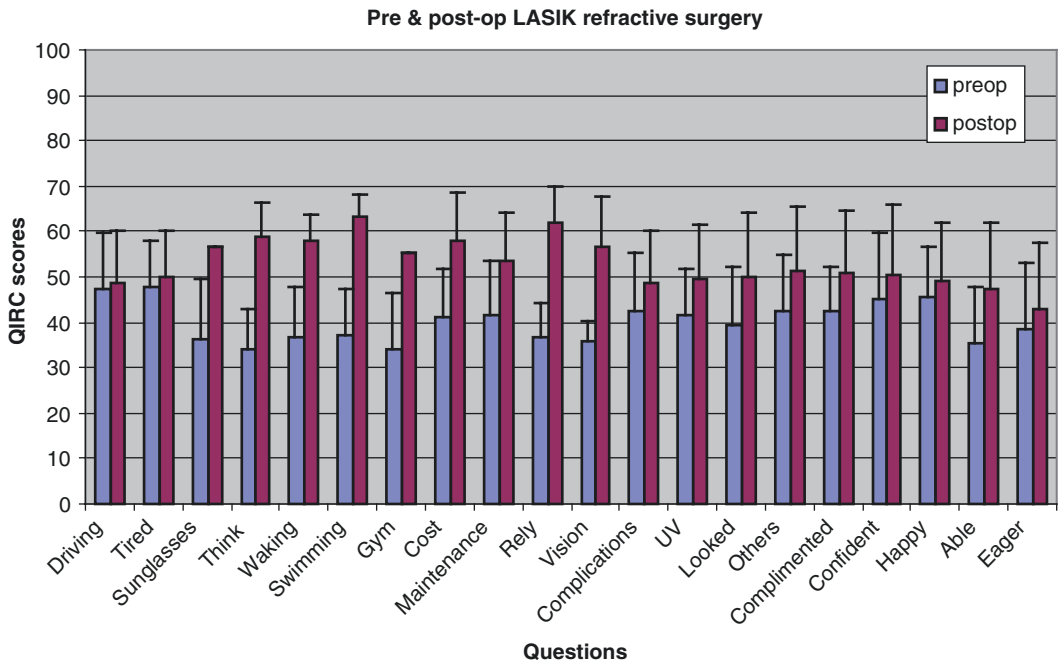

Fig. 2.1 Pre- and post-LASIK mean (error bars ± 1SD) responses on each QIRC question

[9]. The RSVP produces an overall score and subscale scores. The RSVP has been shown to be sensitive to QoL changes related to visual functioning and refractive error and is responsive to refractive surgery [9]. Improvements after laser refractive surgery occurred in the subscales: expectations, physical, and social functioning and problems with corrective lenses. The RSVP has also demonstrated improvements with topographically guided LASIK and phakic lens implantation [22, 47].

The RSVP was developed using traditional techniques, but its psychometric properties were reevaluated by Garamendi et al. and Gothwal et al. using Rasch analysis [23, 24]. The original 42-item questionnaire showed poor targeting of items to patient QoL, items with a ceiling effect, underutilized response categories, and a high level of redundancy [23]. None of the subscales were shown to have adequate measurement properties [24]. The subscales could not be repaired, but Rasch analysis-guided response scale restructuring and item reduction to a 20-item instrument, improved internal consistency and precision for discriminating people. Fourteen items relating to functioning and driving were reduced to 5 items, and 8 related to symptoms and glare were reduced to 3. This is consistent with the content of the QIRC questionnaire, in which Rasch analysis identified that patients with corrected refractive error experienced few problems with visual function, and issues of convenience, cost, health concerns, and well-being were more influential on QoL [3]. Perhaps the reason why the original RSVP was so heavily weighted with functioning and symptoms questions was because the items were principally determined by clinicians [4], who tend to deal with patients' presenting complaints of symptoms or functional difficulties, instead of using more objective methodology to discover the less acute but still important QoL issues.

2.3.3 The National Eye Institute Refractive Quality of Life (NEI-RQL)

The NEI-RQL is a conventionally developed 42-item questionnaire that included subscales related to clarity of vision, expectations, near and far vision, diurnal fluctuations, activity limitations, glare, symptoms, dependence on correction, worry, suboptimal correction, appearance, and satisfaction. The development and validation of the NEI-RQL was spread across 3 papers, and despite rigorous work with focus groups, there is no report on how the final 42 items were selected [5, 25, 26]. However, the NEI-RQL can discriminate between modes of refractive correction and is sensitive to QoL changes related to visual functioning and refractive error [27, 28]. Studies have used the NEI-RQL to demonstrate improved QoL after LASIK [5, 29–31], posterior chamber phakic lens implantation [32, 33], and refractive lens exchange with multifocal intraocular lens implantation [34–36].

The psychometric properties of the NEI-RQL have been examined using Rasch analysis [37, 38]. The NEI-RQL does not produce an overall score, but a score for each of 12 subscales. None of these 12 subscales demonstrated sufficient person separation so as to discriminate people [38]. Therefore,

the NEI-RQL cannot make valid measurement. The NEI-RQL, like the RSVP, also showed problems with the response scales, item misfit, and targeting of items to persons [37, 38]. A specific problem for the NEI-RQL appeared to exist in the way questions were asked with 16 different questions and response formats for 42 questions causing noise, particularly among visual symptoms questions, where frequency and severity were interchanged, yet should have been kept as separate constructs. Attempts to reorganize the NEI-RQL to repair it proved unsuccessful [31, 37].

2.3.4 The Quality of Vision Questionnaire (QoV)

The Quality of Vision Questionnaire (QoV) was not designed to measure quality of life with refractive surgery comprehensively like QIRC, RSVP, and NEI-RQL, instead it measures a single quality-of-life domain: visual symptoms. Since visual symptoms represent an important patient-reported outcome of refractive surgery, the QoV deserves to be covered here. The QoV requires ratings of ten visual symptoms (glare, haloes, starbursts, hazy vision, blurred vision, distortion, double of multiple images, fluctuation in your vision, focusing difficulties, difficulty judging distance, or depth perception) in three constructs (frequency, severity, and bothersomeness) [20]. Therefore, 30 ratings are made. The QoV was developed using focus groups, a pilot questionnaire, Rasch analysis-guided item reduction, and exploration of its psychometric properties. The QoV is rated as having excellent psychometric properties [13]. The three scales, frequency, severity, and bothersomeness, have been shown to measure different constructs and, therefore, are not interchangeable [39]. This is consistent with the commonly observed high rates of glare and halos after refractive surgery (frequency) but very low rates of dissatisfaction (bothersomeness) [40]. The QoV questionnaire provides three scores of visual symptoms on a 100-unit scale.

The QoV has been used to show that both myopic and hyperopic LASEK lead to less visual symptoms postoperatively than preoperatively [41]. The QoV has been used to assess the outcome of bi-aspheric multifocal central presby-LASIK treatment [42]. The QoV questionnaire has also been used in refractive lens exchange with monofocal and multifocal intraocular lenses [43–45]. The focus of the QoV instrument being visual symptoms makes it ideal for detecting visual complications of refractive surgery.

2.3.5 Others

The Myopia Specific Quality of Life and the Canadian Refractive Surgery Research Group Questionnaires have been conventionally validated and shown to be responsive to refractive surgery [46, 47]. Other studies that report QoL issues before and after refractive surgery have used informal, nonvalidated questionnaires, [2, 6, 8, 48, 49] providing only limited evidence.

2.4 Complications and Quality of Life

2.4.1 QIRC

Two studies using the QIRC questionnaire have highlighted QoL problems after LASIK. In a cross-sectional comparison of spectacle, contact lens, and refractive surgery patients, the post-refractive surgery group was also asked to report any visual disturbances that arose after their surgery, and a small number optionally reported post-operative complications. Nine LASIK patients (8.6%) volunteered written comments regarding their postoperative status (including poor vision in low light, dry eyes, regression, and haloes at night); five of these nine were very negative about their refractive surgery. Seven patients (6.7%) had a very low QIRC score (37.86 ± 2.13), which included the five who volunteered negative comments and two who did not comment. Three of these patients were still wearing spectacles all day every day and two suffered from significant dry eye [21]. In another study looking at the outcome of LASIK, large improvements in QoL were found in the majority of subjects [7]. Three subjects (4.5%) had decreased QIRC scores and these were associated with complications. All reported decreased quality of vision including driving at night, and one reported light sensitivity. Low scores were manifested in visual function, symptoms, concerns, and well-being items. None of the patients with improved QIRC scores experienced any serious complications after LASIK.

2.4.2 RSVP

Schein et al. investigated laser refractive surgery outcomes using the RSVP and found a worsening of overall score in 4.5% of patients [9]. With regard to individual subscales, poorer postoperative scores occurred for 29.5% of subjects on the driving subscale, 19.9% for optical problems, 16.3% for glare, 12.7% for symptoms, 7.4% for concern, 5.9% for functioning, and 2.3% having trouble with corrective lenses. A worsening of at least one subscale score was found in 26% of patients, and 15% reported dissatisfaction with vision postoperatively. Increased age at surgery was the strongest predictor of poorer RSVP scores or dissatisfaction with vision. Lane and Waycaster found that the RSVP did not detect any problems in their phakic IOL cohort [22]. Waring et al. found a 3% rate of increased night vision symptoms after topographically guided LASIK [48].

2.4.3 NEI-RQL

McDonnell et al. found QoL, as measured with the NEI-RQL, improved overall after LASIK, but symptoms of glare were significantly worse, and clarity of vision showed no significant change [5]. Schmidt et al. used the NEI-RQL to identify subjective problems of glare, halos, nighttime problems, distorted vision, blurry vision, and discomfort symptoms after LASIK [31]. Pérez-Cambrodí et al. identified visual symptoms after phakic lens implantation which was correlated with photopic contrast sensitivity [33]. Similarly, Iijima et al. found visual symptoms after phakic lens implantation which was correlated with forward light scatter [32]. A number of authors have identified a deterioration of visual symptoms after refractive lens exchanges with implantation of various multifocal intraocular lenses [27, 34, 35].

2.4.4 QoV

McAlinden et al. found that visual symptoms after LASEK were worse at 5 days and 2 weeks after surgery, but normalized by 1 month post-op [41]. This corresponds to the time required for re-epithelialization. This study showed that the QoV was highly sensitive to visual symptoms induced by refractive surgery. Similarly, the QoV has been shown to be highly sensitive to visual symptoms arising from LASIK presbyopic treatments using a hybrid bi-aspheric micro-monovision ablation profile [42]. De Wit et al. showed that the QoV could detect visual symptoms after refractive lens exchange with a multifocal intraocular lens, albeit at extremely low incidence [43]. Maurino et al. also showed the QoV could detect visual symptoms occurring with multifocal IOLs [26].

2.4.5 Outcomes Reported with Other Instruments

In early PRK outcomes research, 77.5% of 173 patients reported improvement in their general QoL, but 16.8% were debilitated by subjective visual symptoms [6]. The only significant preoperative predictor was refractive error – higher preoperative refraction leads to lower satisfaction rates. In another large PRK study, 31.7% of 690 patients reported worsening night vision after surgery, and 30% reported dissatisfaction with night vision [46]. The frequency of each of the reported symptoms was 34.3% for starbursts, 52.4% for halos, and 61.5% for glare from oncoming headlights. For the patients who experienced glare, 55.6% reported that it was more debilitating post PRK. These findings are in contrast to those reported after LASIK.

McGhee et al. reported only 3 of 50 LASIK patients experienced night vision symptoms, and only one reported dissatisfaction or that their QoL was not improved [2]. They also reported that patients who aimed for a residual myopic refraction expressed disappointment with UCVA and that presbyopes experienced suboptimal near vision. However, limitations of this study are that the only content area tested was functioning and no patients had any serious complications. Hill found that only 3 in 200 subjects would not have LASIK again despite 24% reporting worsening night vision and 27% reporting light sensitivity [8]. The 3 individuals cited worsening night vision, presbyopia, and psychological distress as reasons for opting against the intervention. Bailey et al., in a patient satisfaction survey, found 16 of 604 patients were dissatisfied after LASIK, and a high percentage of these reported symptoms were of glare, halos, or starbursts (81.3%) [49]. Those who had surgical enhancement were found to be more likely to experience these symptoms. Additionally, those with increased age, greater corneal toricity, or smaller pupil size were less likely to be satisfied with the intervention.

Lee et al. developed the Myopia Specific Quality of Life Questionnaire which contains 4 domains: visual function, symptoms, social role function, and psychological well-being [47]. They identified eight adverse symptoms that were most frequently reported after LASIK: eye dryness, blurred vision, lowered indoor or night vision, halos, regression, glare, temporary reduction in near vision, and infection. Multivariate analysis showed that patients having more adverse symptoms experienced significantly less improvement in QoL, so they concluded that freedom from adverse effects is one of the most important requirements for achieving excellent outcomes.

2.4.6 Implications

The caveat with the usually high QoL afforded by refractive surgery is the associated risk of complications. Common complications of laser refractive surgery such as loss of contrast vision, loss of best-corrected vision, regression, and dry eye problems are effectively identified by QoL instruments, with patients requiring spectacle or contact lens correction or experiencing severe dry eye faring the worst. Night vision symptoms are common, but these do not necessarily negatively impact QoL. While quality-of-life research has identified some risk factors for poorer outcome, e.g., older age and multiple treatments, this information does not translate into an altered patient selection strategy. While these results suggest that night vision symptoms are less prevalent with LASIK than PRK, there is no evidence that newer laser treatment paradigms provide any QoL benefit compared to older systems. Ongoing evaluation of refractive surgery outcomes using QoL measurement is required to demonstrate the benefits of technological increments.

Take-Home Pearls

- Questionnaires can effectively demonstrate improved QoL from laser refractive surgery.
- Serious complications of refractive surgery lead to markedly reduced quality of life, but minor complications, like night vision disturbances, may not negatively impact QoL.
- Routine evaluation of refractive surgery outcomes should include QoL measurement.
- The ideal QoL instrument for refractive surgery would contain broad content, be developed and validated with Rasch analysis, and have valid linear scoring, e.g., QIRC.

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Part II

LASIK Intraoperative Complications

Thin, Irregular, Buttonhole Flaps

3

O. Bennett Walton and Stephen G. Slade

Core Messages

- A thin, irregular, or buttonhole flap is a significant complication of lamellar surgery that typically calls for aborting the case.
- Thin, irregular, or buttonhole flaps can occur with both femtosecond lasers and microkeratomes.
- The cause of a thin, irregular, or buttonhole flap is often unclear and can be multifactorial.
- Causes of a thin, irregular, or buttonhole flap may include low pressure, loss of suction, poor applanation, poor corneal lubrication, preexisting corneal pathology, poor metal blade quality, or keratome malfunction.
- Most thin, irregular, or buttonhole flap cases can be reperformed at a later date with either LASIK or PRK and do have a good prognosis.
- The key to successful management is to avoid ablation and avoid femtosecond flap lift.

3.1 Introduction

Many of the serious complications of LASIK are related to flap creation. Fortunately, as femtosecond lasers have replaced microkeratomes in many areas, these complications are becoming less frequent. In this chapter, we will look at the causes, prevention, diagnosis, and treatment of thin, irregular, or buttonhole flaps of poor quality. The incidence of buttonhole flaps using a mechanical microkeratome ranges between 0.06 and 2.6% of general LASIK procedures [1–3]. The main incidence of femtosecond laser buttonhole flaps, gas breakthrough, seems less frequent than mechanical keratome causes. The occurrence of a buttonhole flap is the most likely to result in a poor refractive outcome if not managed properly (Fig. 3.1).

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3.2 Causes

Complications due to poor keratectomy can cause major visual problems. Keratectomies can be incomplete, decentered, or uneven. Steep corneas are associated with buttonhole flaps, and flat corneas are associated with free caps. An incomplete keratectomy is usually caused by a suction break. It is critical to have good suction for the duration of the laser activity or keratome pass. If the dissection stops before the pass is complete, there might not be room to place the ablation. The keratectomy can be extended by hand but will not be of the same quality. An irregular or damaged blade can cause a grossly irregular keratectomy.

During creation of the femtosecond corneal flap, dissection is only complete after the flap is manually loosened and lifted. Because the flap isn't complete until lifted, complications may occur during lift if there are areas of opaque bubble layer or irregular adhesion. These can rarely lead to a defect similar to a "buttonhole" or "donut-shaped" flap that can occur with a mechanical keratectomy. The buttonhole flap can also be created when the focus of the laser beam begins the cut at the desired depth in the stroma but features gas breakthrough anterior to the epithelium and then returns back to the stroma. Buttonhole flaps can be associated with one or more of the following factors in femtosecond procedures:

1. Attempted creation of very thin corneal flap (<100 μm)
2. Poor applanation with contact glass
3. Patient movement during the procedure

In summary, poor quality flaps can be associated with one or more of the following factors in flap creation:

1. Loss of suction during the cut
2. Patient cornea steeper than 46.00 D prior to surgery [4]
3. Low or reduction in patient intraocular pressure [5]

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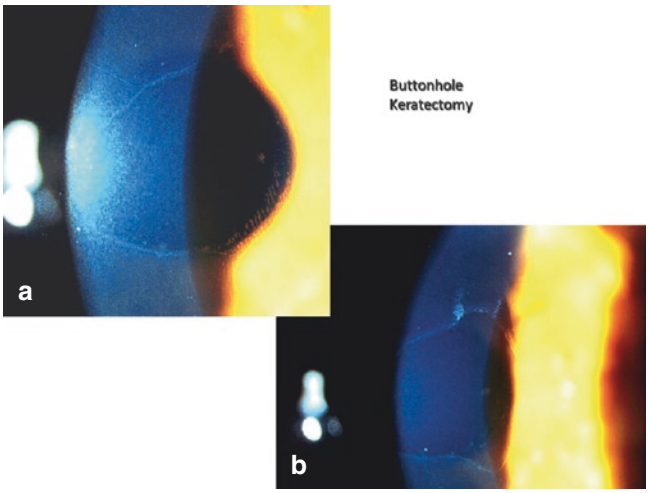

Fig. 3.1 In these two pictures of the same cornea, a microkeratome cut only the outer portion of the flap, leaving the central zone unaffected. Lifting and ablating is not advised in the case of incomplete flaps, whether due to microkeratome buttonhole or centrally incomplete femtosecond treatment (Courtesy of Stephen G. Slade, MD)

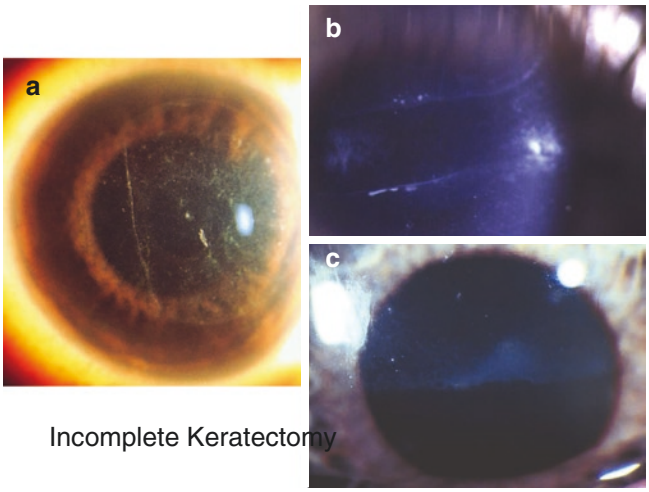

Fig. 3.2 Three incomplete flaps are shown: (**a**) partial flap with the hinge in the pupil space, (**b**) a strip of uncut cornea directly over the visual axis caused by debris on the microkeratome blade, and (**c**) a hemi flap with the entire bottom half of the cornea uncut due to a damaged blade. Excessive fluid, meibom or other optical media interruption can result in a similar finding with a femtosecond laser. Lifting and ablating is not advised after an incomplete keratectomy (Courtesy of Stephen G. Slade, MD)

4. Poor lubrication of the corneal surface or keratome malfunction
5. Excess tissue being compressed beyond applanation by a keratome foot plate, causing buckling of the cornea [6]

3.3 Diagnosis

A poor quality flap should be suspected whenever the visualized laser pattern or keratome cut does not proceed as expected. A buttonhole or thin flap often can be seen without manipulating the flap at all. Sometimes allowing the corneal surface to dry slightly or wiping off the tear film will reveal the edges of a buttonhole, for example. If the diagnosis is uncertain, carefully inspect the flap. Always use caution in lifting such a flap. Buttonhole flaps can be incomplete with a continuous layer of epithelium overlying the hole in Bowman's.

One advantage of diagnosing a poor quality flap with the femtosecond laser is that a poor quality flap can often be seen during its creation as discussed below (Fig. 3.2).

3.4 Prevention

The inspection, setup, and preoperative testing or calibration of these instruments is critical. Careful attention to minute details is essential to minimize and avoid potential complications, as well as to obtain an excellent flap. Exposure is also vital to the keratectomy. This is largely dependent on orbital anatomy. The deep-set eye with an overhanging brow is best avoided in the early cases. Proper anesthesia and sedation will aid in achieving good exposure. The main goal is to provide a stable suction and applanation, with clear path and gear track for microkeratomes. Fluid management is important in both femtosecond and microkeratome use, in the former to ensure good corneal or limbal suction and in the latter to avoid a false meniscus in the measurement of the cap diameter and IOP. The cornea should be a little dry for the applanation yet wet for a microkeratome pass. Always take a moment to inspect the eye before the placement of the suction ring. There should be no chemosis and the pupil should be centered between the speculum. A speculum that provides maximum exposure with reasonable patient comfort is desirable. If chemosis is present, the fluid should be milked down beneath the lid speculum. The pupil should be constricted only with the light from the microscope. As with any surgery, the success of each step is dependent on the success of the preceding step. Positioning, exposure, and stable suction are crucial to either type of successful flap creation. At this point, laser may be fired, or a carefully inspected microkeratome with a sharp, accurate blade with a slow, controlled pass may be used. Of note, there appears to be evidence that second eyes in consecutive microkeratome treatment may be at higher risk, [2] and this may be explained by differential blade sharpness between in the two passes.

The femtosecond laser offers a unique advantage to the prevention of complications from poor quality flaps. Quite often a poor quality flap can be actually detected during the creation of the flap with a femtosecond laser. This is because the flap is visible at all times during the procedure. With experience, a thin flap or buttonhole flap with gas breakthrough can be seen in its creation and the procedure stopped. More commonly, risks of variable adhesion in the bed may be noted by the presence of opaque bubble layer during the femtosecond treatment. Additionally, while not a flap quality issue, femtosecond flaps 90 microns or thinner had a higher incidence of postoperative haze than 100 micron flaps [7].

Of course avoidance and awareness of patients at risk are the best way to prevent flap complications. Patients with the following conditions may be more prone to experiencing flap quality complications:

- History of collagen vascular disease
- Patient cornea steeper than 46.00 D prior to surgery
- Conjunctival scarring after prior ocular surgery
- Previous incisional keratotomy
- Prior ocular, specifically cornea injury
- History of keratoconus
- Previous scleral buckling surgery
- Patient with unusually thick epithelial layer (>90 μm)

3.5 Treatment

Clinical concerns when dealing with poor quality flaps include the potential for epithelial cells to infiltrate the interface, causing epithelial ingrowth in the central axis. This may result in corneal scarring in the visual field, affecting visual acuity. Worse, invasive epithelial ingrowth can lead to stromal melt.

If a keratectomy has an irregular surface, there is an important and simple safety feature of lamellar surgery that should not be forgotten. No matter how irregular the surface of the bed might be, there is a perfect match in the underside of the flap. Therefore, if the flap is simply replaced, the patient will usually return to the preoperative refraction and best corrected vision by the next morning. The femtosecond laser is even more forgiving in this regard, in that the flap is held in place by the micro tissue bridges of uncut stroma. These tags hold the flap in place so that once the diagnosis is made, since the flap is securely attached, there is plenty of time to wait until a retreatment is advisable. An additional advantage is that the epithelium and Bowman's are cut last with a femtosecond laser and so the procedure may be aborted prior to the vertical cut, leaving epithelium and Bowman's intact. In cases of partial flaps without buttonhole or gas escape, if a recut is ever attempted with a laser, keeping the same patient interface is crucial for achieving the same depth. Raster patterns are more forgiving, as dissection can be started from the distal, single-cut end of the flap to avoid accidentally ending up in the dead-end partial cut. Problems are created when an irregular bed is altered with an attempted ablation that no longer matches the flap. This is also important to remember with incomplete resections. When in doubt, put the flap back and do not ablate. One of the more pleasant features of lamellar surgery is that the eye can be essentially back to the preoperative shape and clarity the next day and then reoperated on in the next few weeks or months depending on the situation. If an incomplete resection is present, and there is room for the ablation, one can proceed.

With resections that stop short of the needed diameter, surgeons have extended the flap by hand, but this is dangerous and will not give as smooth as a surface as the microkeratome. Remember that incomplete resections can also be caused by a blade that has been damaged, dulling the cutting edge so that a vertically incomplete resection is produced. With severe suction breaks and very small eccentric resections, never attempt to ablate; just try to replace the cap as best as possible (Fig. 3.3).

Ablation of an eye with a buttonhole flap at the time of primary surgery has been associated with a loss of best corrected acuity and must be avoided [2]. If it is apparent during the femtosecond cut itself that a buttonhole is forming, then the procedure should be terminated at once (Fig. 3.4). The advantage of the femtosecond laser in this situation is that the epithelium will remain uncut and the potential flap undisturbed. In this case, the flap should not be lifted or explored. In order to minimize epithelial ingrowth, some surgeons prefer to remove the epithelium from the central button or island of Bowman's layer [8]. Again, *ablation should not be performed under the flap*. There have been reports of immediate phototherapeutic keratectomy for epithelial removal with photorefractive keratectomy treatment with mitomycin C [9]. In such cases, haze is considered a risk, and it is strongly recommended that the ablation depths be carefully checked before such cases to ensure that there is either no significant flap left or enough to lie stably on the stroma. Leaving an ultrathin and irregular flap after surface ablation of a buttonhole is not advised, and either PRK or a repeated LASIK can always be attempted later with a more stable cornea than at the time of the initial buttonhole flap creation. Usually, a bandage lens is placed over the buttonhole flap. A deeper flap may be recut (20–60 μm deeper) approximately 3–6 months later, once best corrected visual acuity returns and the refraction is stable. Some surgeons advocate scraping the epithelium and performing PRK laser ablation. However, this procedure is subject to the risk of haze for higher ablations [10].

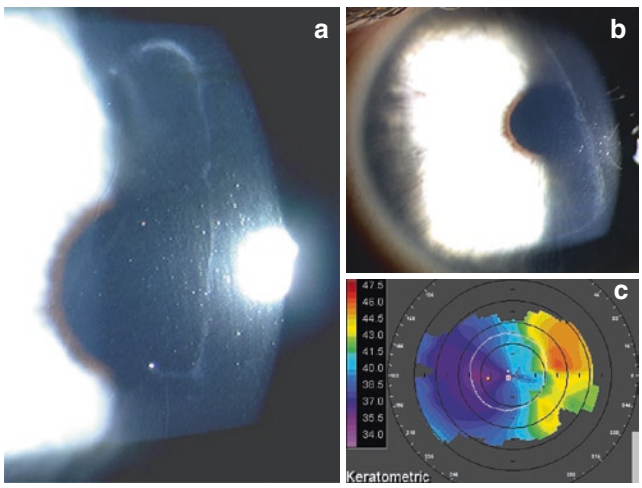

Fig. 3.3 Incomplete flaps (**a, b**) that were misguidedly lifted and ablated. Keratometry (**c**) shows that nearly half the cornea received none of the intended myopic ablation, whereas the the flat area was doubly flattened because the stromal side of the flap had shielded the untreated area and received that treatment (Courtesy of Stephen G. Slade, MD)

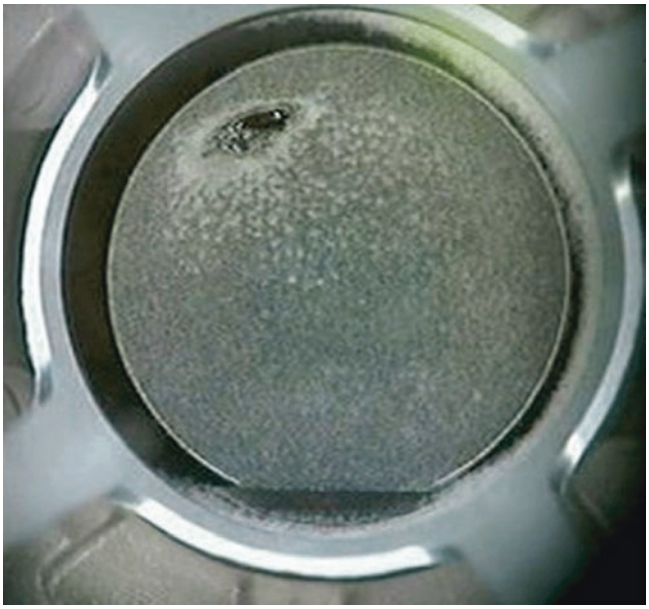

Fig. 3.4 Vertical gas breakthrough in femtosecond flap creation. This is effectively a buttonhole, and it would not be recommended to lift this flap (Courtesy Perry S. Binder MS, MD)

Take-Home Pearls

- The refractive surgeon is advised to.
- Identify patients at risk for flap complications.
- Carefully set up and review your microkeratome, laser, and surgical protocol.
- Be aware of these complications and suspect them in any uncertain situation.
- Do not ablate a poor quality bed.

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Intraoperative Flap Complications in LASIK: Prevention and Management of Free Flaps

4

Mauro Tiveron Jr. and Jorge L. Alió

Core Messages

- Free cap is a flap which lacks the hinge that attaches it to the cornea.
- This complication is closely linked with the use of microkeratomes for flap creation.
- Prevention of free flaps in microkeratome-assisted LASIK surgery is critical.
- Careful inspection of the corneal marks assists flap repositioning.
- Management of free flap without corneal marks is possible.

4.1 Definition of Free Flap

A flap which lacks the hinge that attaches it to the cornea is defined as a free flap or cap. Free flaps result by shallow engagement of the keratome on the corneal surface due to a loss of suction during the microkeratome pass, allowing the blade to skim the top of the cornea [1].

More than a complication, a free flap should be considered an inconvenience that slows up the procedure and forces the surgeon to manage the flap more delicately and meticulously. In addition, this inconvenience can become a serious complication when the corneal marks have not been performed before the flap cutting or in case of a flap loss.

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4.2 Frequency and Etiology of Free Flap

The incidence of free flap ranges from 0.7% to 5.9% [2]. Lin and Maloney reported a free flap incidence of 1% in a retrospective study using the Automated Corneal Shaper microkeratome, and the incidence of this complication was lower using the Hansatome microkeratome as reported by Walker and Wilson [3]. The incidence of free flap with a mechanical microkeratome was reported to be up to 10% [4], although this varies in the literature depending on the microkeratome type and surgeon experience.

This flap complication mainly results from low intraoperative intraocular pressure and large flat corneas with an average keratometric power of <41 diopters. The low intraoperative pressure in this situation is known as "pseudosuction," affecting flap creation by the occlusion of the suction port other than at the globe and generally producing a very thin flap. Pseudosuction is when the vacuum registers high because the conjunctiva or drapes are occluding the suction holes. In this case, the intraocular pressure will not be sufficiently elevated to pass the microkeratome [5].

In cases of flatter preoperative keratometry, a small corneal area exposes through the ring, and then the blade engages late in its passage across the cornea and exits early, increasing the incidence of a free cap.

4.3 Prevention of Free Flap in LASIK Surgery

The prevention of free flaps using microkeratome is not always possible. However, to avoid free flaps with this device, the surgeon should complete the following checks before cutting the flap: (1) perform adequate corneal marks preoperatively, (2) ensure the suction ring has a firm grasp of the eye, (3) confirm that the intraocular pressure has risen, and (4) confirm that the patient's vision has decreased [6].

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Adequate corneal marks must be performed preoperatively by making asymmetrical marks that clearly cross the sclerocorneal limbus to avoid improper orientation (Fig. 4.1). When the flap is repositioned inversely (epithelium vs. stroma), distinguishable non-coinciding marks are observed between the flap and the peripheral cornea (Fig. 4.2).

Making corneal marks with different sized circles or by using asymmetrical linear marks, one more central and the other more peripheral, ensures that the edge of the flap will be crossed by one of them. These marks can aid in the alignment with proper orientation if a free flap occurs.

As it is not radial, the landmark forms a distinguishable non-coincident mirror image when the flap is repositioned inversely (epithelium vs. stroma).

A flat keratometry reading on the preoperative cornea should be factored into preoperative planning due to higher incidence of free flaps and thin flaps. Thus, in flat corneas, the corneal marks are still more important to prevent further complications in case of a free cap.

The femtosecond laser technology for LASIK surgery may prevent free flap. Moreover, the flap performed by femtosecond laser is safer and more predictable, even in preventing other complications related to the flap-cutting process [7].

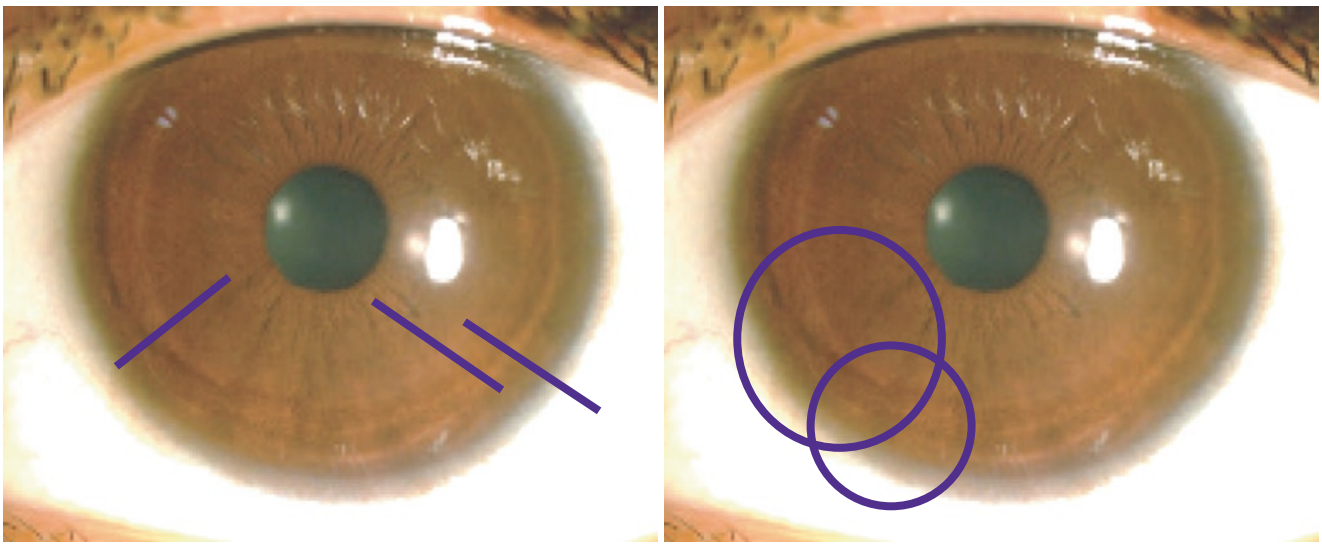

Fig. 4.1 Making corneal marks with different sized *circles* or by using asymmetrical linear marks, one more central and the other more peripheral, guarantees us that, in any case, the edge of the flap will be crossed by one of them. These marks can aid in the alignment with proper orientation if a free flap occurs

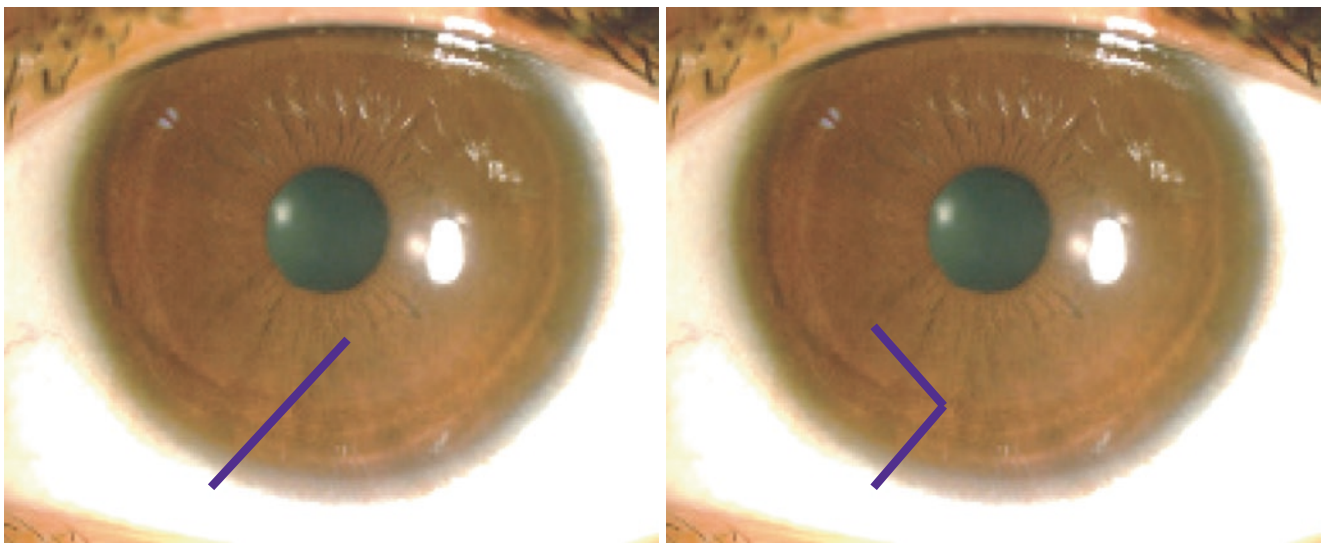

Fig. 4.2 As it is not radial, the landmark forms a distinguishable non-coincident mirror image when the flap is repositioned inversely (epithelium vs. stroma)

4.4 Intraoperative Assessment and Handling the Problem

In the majority of free flaps, the cap is recovered from the blade platform of the microkeratome. In account of this, the corneal marks preoperatively are essential to better manage the problem and allow it to be repositioned in the proper direction.

During excimer laser ablation, the cap should be kept covered in the microkeratome or carefully protected with a moist Merocel sponge. The next adequate management approach involves inspection of the surgical marks and correctly replacing the free cap on the stromal bed to obtain the best realignment. It is imperative to replace the cap stromal surface down. After a period of 3–5 min of air drying, the placement of therapeutic contact lenses is recommended for 48 h to protect the flap from the eyelids and to promote adherence to the stromal bed. Other methods for securing free flaps include running or interrupted sutures with 10-0 monofilament nylon, but usually they are not necessary to keep the cap in place [6, 8, 9].

4.5 Management of Free Flap Without Corneal Marks

If a free cap is created without marks, the cap should be carefully replaced over the stromal bed. After adequate air drying or sutures on the flap, a therapeutic contact lens must be placed to avoid a flap loss. In this situation, it is recommended to cancel the laser ablation and after at least 3 months of healing, the surgeon can consider a retreatment to reach a better final visual outcome [10, 11].

Some of the potential complications associated with such cases include irregular astigmatism, recurrent flap dislodgement, epithelial ingrowth, interface deposits, and flap loss.

4.5.1 Free Flap Rotational Study

According to Baviera J [12], theoretically, a free flap has parallel faces that are the result of a perfect cut leaving a flap with a uniform thickness. If this were 100% true, there would be no optical effects. The rotation of the flap would be similar to the rotation on the eye of a therapeutic contact lens with neutral dioptric power. However, it is virtually impossible to obtain a flap with these characteristics. The flap is usually thinner at the beginning and gradually becomes thicker at the center as the microkeratome advances.

Therefore, if we suppose that the flap once again becomes thinner at the end of the cut, when the blade leaves the eye, we will obtain a flap that behaves optically like a plus-power cylindrical lens, with its axis at 90° and power at 0° (microkeratome pass along the 0–180° axis). Logically, the resulting corneal bed would be the negative image of the flap and would behave like a minus-power cylinder of the same power and axis (Fig. 4.3). If the flap was reset in its original position, both cylinders would balance and the optical result would be neutral [13].

An irregular microkeratome cut, leads to a thicker flap in the center and a thinner one at the periphery (plus cylinder). The stromal bed contains the negative image of the flap (minus cylinder).

Now, if, due to loss of the marks, the cylinders do not fit back into their original position, then we have crossed cylinders in which the plus-power cylinder (flap) has rotated on the minus-power cylinder (corneal bed). This results in mixed astigmatism with a neutral spherical equivalent, where the axis and power depend on the angle of rotation and the power of the cylinders by microkeratome cutting.

If we assume that the laser ablation has not induced and has eliminated any preexisting astigmatism, the astigmatism that appears after an undesired rotation of the flap would be a consequence of this bicylindrical effect between the flap and the corneal bed.

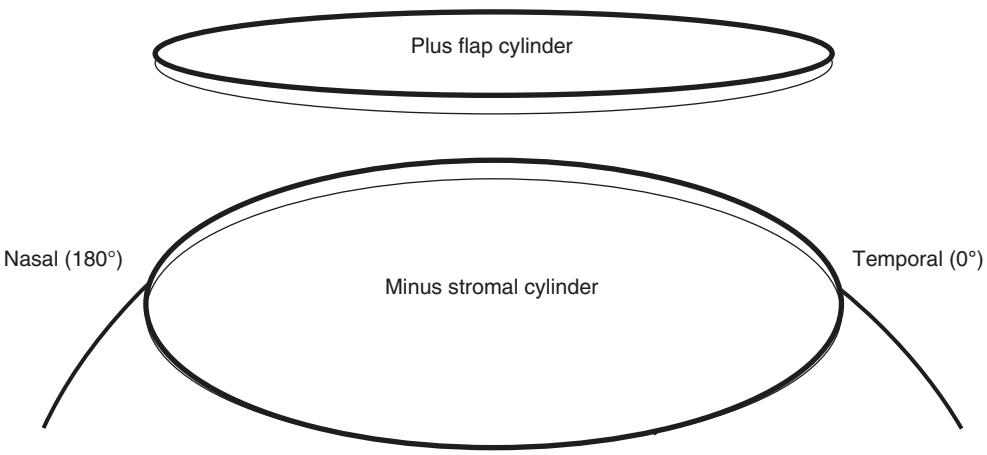

Fig. 4.3 Consequence of an irregular microkeratome cut. This leads to a thicker flap in the center and a thinner one at the periphery (plus cylinder). The stromal bed contains the negative image of the flap (minus cylinder)

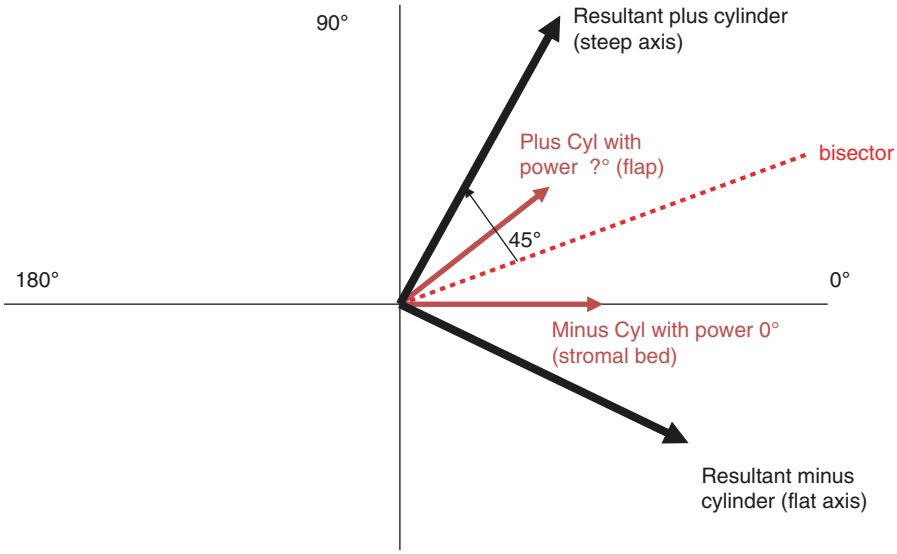

Fig. 4.4 Cross cylinders share the bisector with the flat and steep axes of the mixed astigmatism resulting from the turn of the first two. The resultant plus cylinder (steep axis) is at 45° counterclockwise from the bisector of the two cross cylinders

According to Rubin [14], the bisector of the cylinders that have rotated on one another coincides with the bisector formed between the steep and flat axes of the refractive mixed astigmatism resulting from the rotation. Therefore, the steep axis of the resulting refractive astigmatism would be at 45° counterclockwise of the bisector formed by the two cylinders that have rotated on one another (Fig. 4.4).

Cross cylinders share the bisector with the flat and steep axes of the mixed astigmatism resulting from the turn of the first two. The resultant plus cylinder (steep axis) is at 45° counterclockwise from the bisector of the two cross cylinders.

We could derive the following formula: postoperative axis (in plus cyl) = initial axis (MQ pass) + 45 + angle of flap rotation/2. Thus, flap angle rotation = 2 × postoperative axis − 90.

Then

- If the resulting value of the angle of flap rotation is positive, we would consider the turn clockwise, and if it is negative, counterclockwise.
- If a microkeratome with an up-down cut was used, the initial axis (MQ pass) would not be 0°, but 90°; therefore, the formula would be flap angle rotation = 2 × postoperative axis − 270.

Clinical Cases

Case 1 (loss of corneal marks): For a 34-year-old woman with OS −2.50 sph, VA = 20/20−, LASIK was programmed for emmetropia, and a free flap was obtained on which the marks were erased.

Result at 4 weeks: *−2.50 sph + 4.25 cyl × 15°.*

The following formula was applied: flap angle rotation = 2 × postoperative axis − 90° = 2 × 15 − 90 = −60.

As the sign was negative, the rotation was considered counterclockwise. The patient was taken into the operating room, and after the relevant ink marks were made on the flap, it was lifted and turned 60° counterclockwise with the help of a 360° graduated ring.

Result after 6 weeks: *VA = 20/20−.*

Case 2 (loss of corneal marks): For a 29-year-old man, OD −1.25 sph + 4 cyl × 75°, VA = 20/20. LASIK was programmed for emmetropia, and a free flap was obtained on which the marks were erased.

Result at 5 weeks: *−2.25 sph + 6 cyl × 4, VA = 20/30+.*

The following formula was applied: flap angle rotation = 2 × postoperative axis − 90 = 2 × 4 − 90 = −82. As the sign was negative, rotation was considered counterclockwise. The patient was taken to the operating room, and after the relevant ink marks were made on the flap, it was lifted and turned 82° counterclockwise in the same way as the previous case (Figs. 4.5 and 4.6).

Result: *−0.75 sph + 1 cyl × 96, with improvement in VA to 20/20−.*

Corneal topography shows the inverse astigmatism resulting from incorrect repositioning of the free flap

Topographic appearance after solving the induced astigmatism by lifting and rotating the flap 82° counterclockwise

Case 6 (loss of corneal marks): For a 40-year-old woman, OS with −1.75 sph + 0.25 cyl × 137°, VA = 20/20, LASIK was programmed for emmetropia and resulted in a free flap with loss of marks.

Result at 6 weeks: *−1.25 sph + 2.5 cyl × 57°, VA = 20/25.*

If the following formula had been applied, flap angle rotation = 2 × postoperative axis − 90 = 2 × 57 − 90 = 24, then the flap would have had to be turned 24° clockwise. Nevertheless, the surgeon chose to carry out LASIK enhancement.

Result: *+0.5 cyl × 165°, VA = 20/20−.*

A review of the literature reported three similar cases [13]. All three finished with induced mixed astigmatism accompanied by a reduction in the corrected distance visual acuity. The cases were solved using rotation of the

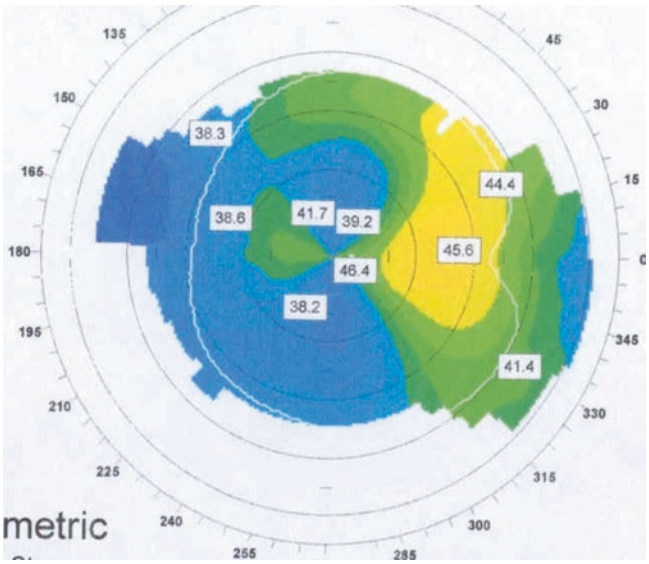

Fig. 4.5 Corneal topography shows the inverse astigmatism resulting from incorrect repositioning of the free flap

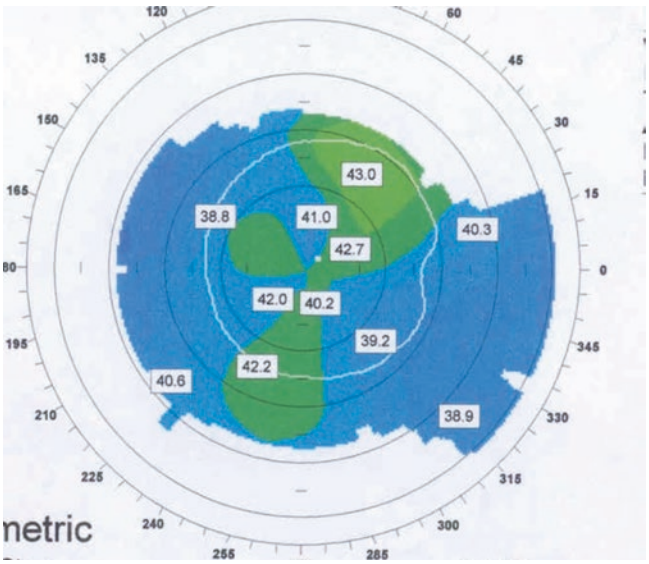

Fig. 4.6 Topographic appearance after solving the induced astigmatism by lifting and rotating the flap 82° counterclockwise

free flap and applying the formula described, although the third case needed a second rotation, which the authors attribute to the fact that the microkeratome did not pass exactly on the usual 0–180° axis.

Take-Home Pearls

- Making asymmetrical marks sufficiently long can aid in alignment with proper orientation if a free flap occurs.
- Non-radial marks that are distinguishable should be made, even when so the flap is repositioned inversely (epithelium vs. stroma).
- If the marks are lost completely, try to reposition the free flap using the epithelial details from the edge of the flap.
- Inadequate repositioning (rotation) leads to mixed astigmatism, generally accompanied by reduced BCVA.
- Astigmatism induced by rotation of the flap can be solved, using the optical genesis of the astigmatism induced by rotation of equal cylinders with opposite signs.
- Always pass the microkeratome on the same axis (0–180° or 90–270°), and then if there is rotation when repositioning the flap, this can be corrected as described.
- The femtosecond laser technology for LASIK surgery is considered the best prevention for free flap.

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Management of the Distorted Flap

5

David R. Hardten, Adeline G. Hardten,
and Sophia A. Hardten

Core Messages

- Distortion, striae, or folds are one of the most commonly encountered LASIK flap complications.
- This chapter covers the etiology and prevention and management of the distorted flap.

5.1 Introduction

Most of the severe complications associated with LASIK are due to the initial creation of the flap, although some are due to later manipulation of the corneal lamellar flap by the patient. Distortion, striae, or folds in the corneal flap are one of the most commonly encountered flap complications with LASIK (Figs. 5.1 and 5.2). The presence of this distortion can result in patient dissatisfaction due to quality of vision complaints, or even loss of best-corrected visual acuity (BCVA).

5.2 Frequency

Distortion of the corneal flap has been reported to occur in 1–4% of cases in reported studies [1–5]. Because striae can often be very mild or peripheral and may be subclinical and not noted by the patient or physician, these studies probably underreport the frequency of any visible striae. More severe striae can be associated with discomfort and much distorted vision and so are more easily detected. They may be more common in eyes with thicker or thinner flaps than average. They have even been reported after femtosecond laser flap creation and may be more common after keratoplasty, as the endothelial cell function is poor in the periphery [6, 7]. They become more difficult to manage in the presence of a free corneal cap or when an epithelial defect is present.

5.3 Etiology and Prevention

Factors that increase the potential for flap striae can be present intraoperatively. If the flap becomes desiccated during the portion of the case when the flap is retracted back, then when the flap is replaced, it is contracted compared to its original state and can be difficult to properly reposition. Trying to maintain neutral hydration of the flap is important, as this may lessen the tendency toward flap distortion. If the flap is dehydrated prior to repositioning, taking extra care to rehydrate the flap with balanced saline solution, and carefully stretching the flap so that the edge of the flap is in line with the gutter created by the microkeratome entry site, should reduce the striae (Figs. 5.3, 5.4, 5.5, and 5.6). It may take time for the flap to stick well in the proper position, and the flap should be stretched until it no longer retracts out of position. This will occur when the interface tension between the flap and underlying stromal bed is greater than the retraction tension caused by the striae from dehydration. Similarly if the flap is wrinkled due to intraoperative manipulation or initial misalignment intraoperatively during the initial case, this may result in flap irregularities. Immediate repositioning once this is identified intraoperatively makes permanent striae less likely to be an issue and allows the flap to be repositioned with alignment of the gutter to flap interface.

Flap distortion may also occur after the procedure, such as during removal of the lid speculum or drapes, or if the patient rubs the eye or touches the eye with an eye dropper tip after surgery [5, 8, 9]. If the patient is looking straight ahead and tries not to squeeze the eyelids during speculum or

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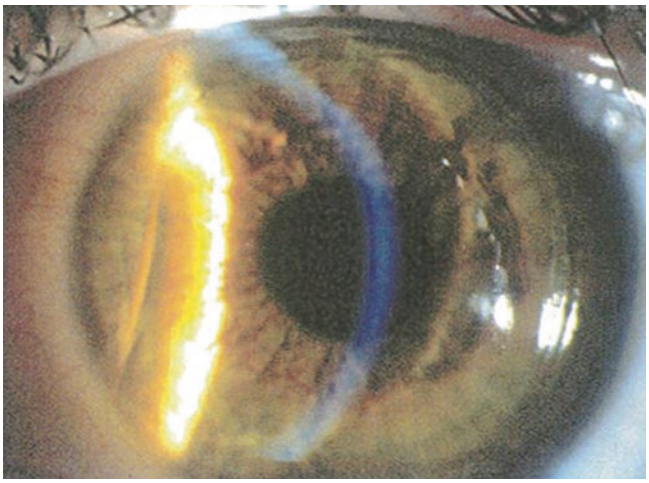

Fig. 5.1 Large striae in the flap with distortion of the flap. This patient inadvertently rubbed his eye on the first day after LASIK

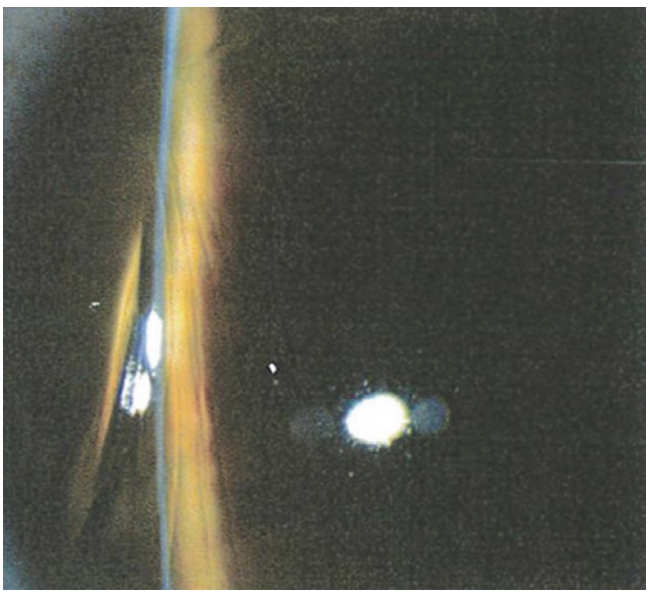

Fig. 5.2 Striae seen near the hinge in a LASIK patient

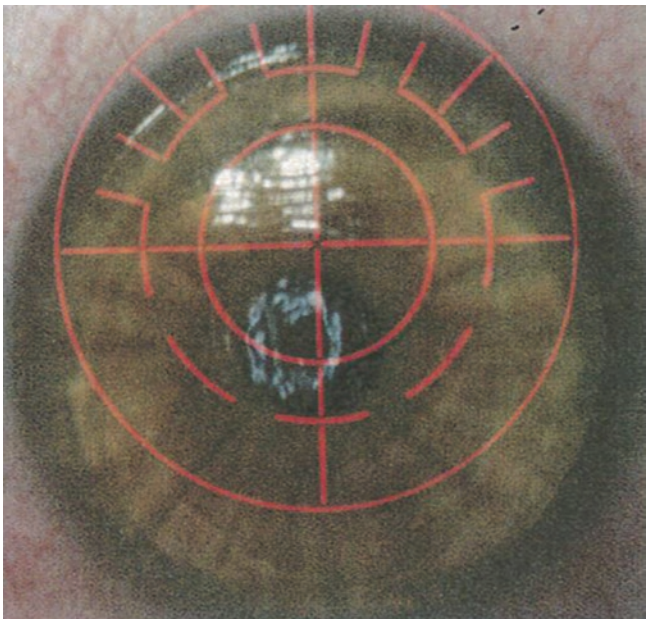

Fig. 5.3 Intraoperative striae indicating that the gutter is too large inferiorly, with distortion of the flap and bunching of the flap centrally

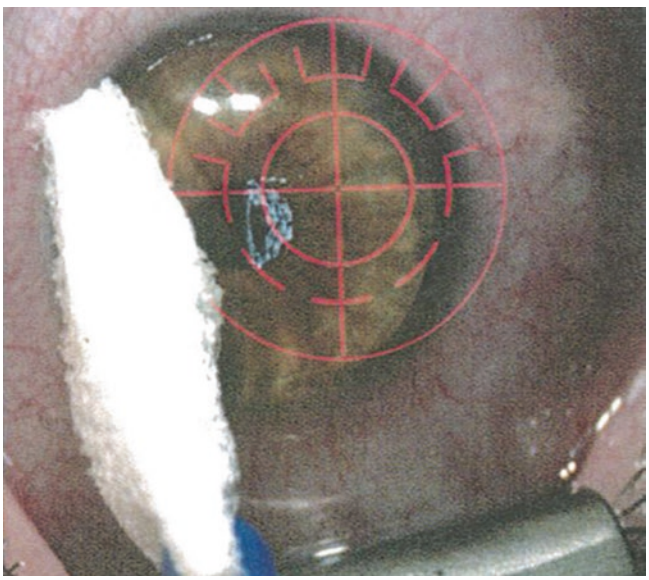

Fig. 5.4 Striae are improved after stretching yet are still present as seen in the ring light reflection

drape removal, then this may reduce the incidence of flap dislocation during this stage of the surgery.

If the patient takes a long nap or goes a long time without lubrication postoperatively, then the lid may stick to the flap and cause distortion of the flap when the patient opens his/her eye. We usually have the patient try to nap no longer than 2 h postoperatively without lubrication to reduce the incidence of this cause of a distorted flap. Patients that are very photophobic or squeeze or tear excessively may also dislocate their flaps postoperatively.

Postoperative examination of the flap, after removal of the speculum at the operating microscope or at the slit lamp prior to discharge and on the first postoperative day, is useful in the detection of flap striae. To detect fine striae, retroillumination through the dilated pupil may be necessary to identify these more subtle flap irregularities, which are typically not clinically significant. Fluorescein stain may be useful to detect the negative staining pattern seen in striae due to elevation alternating with depression of the flap [10]. Striae are most often perpendicular to the orientation of the hinge. For example, horizontal striae are more frequent with nasal hinges and vertical striae are more typical in flaps made with a vertical hinge.

Prior to creating the corneal flap, ink marks may be placed on the cornea to provide visual marks that aid in flap repositioning. Care must be taken to make the marks long enough to allow for a range of flap diameters that may end up being cre-

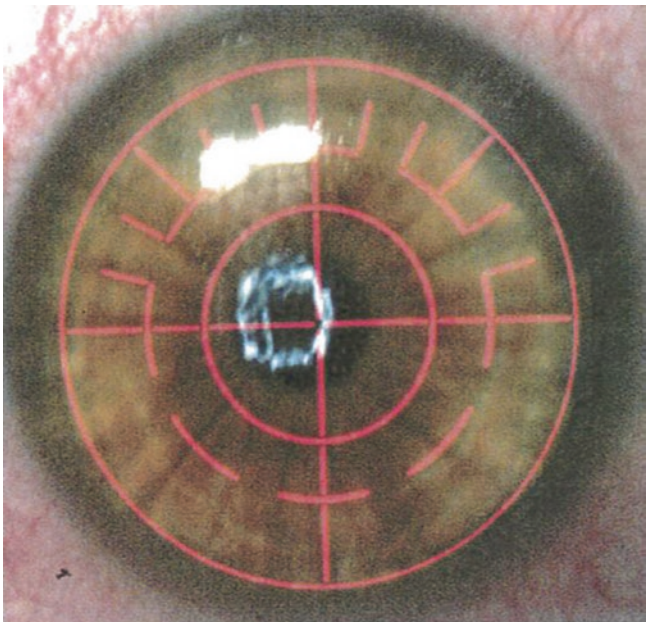

Fig. 5.5 A Merocel sponge is used to stretch the flap to close the gutter

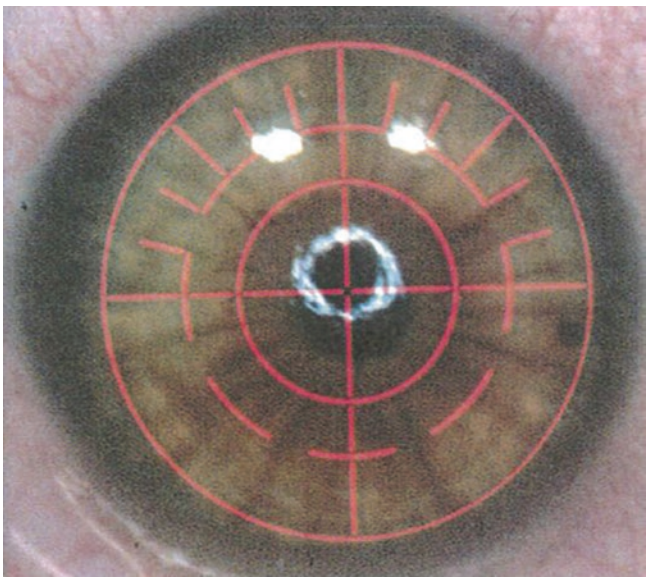

Fig. 5.6 Striae resolved after stretching

ated. If the epithelium, however, shifts at the periphery of the flap, then these marks may no longer be useful. The marks may also prove toxic to the epithelium; so many surgeons have abandoned marking the flap surface. Asymmetric hydration of the flap, with excessive hydration in one region, and excessive dehydration in another region can result in asymmetric size of the flap with striae. In the area of excessive hydration, the flap may be swollen and therefore thicker, which causes the flap to be shorter. If it were to dry in this position, then the gutter would be larger than normal, causing striae. Poor interface adherence due to excessive hydration may also cause retraction of the flap with distortion and misalignment [5]. Instruments such as the Johnston flap applanator (Rhein Medical, Tampa, Florida) or the Lindstrom LASIK flap roller (BD Visitec, Franklin Lakes, NJ) can be used to roll or massage or depress the flap center at the end of the procedure to remove excess fluid from the flap interface, which some feel may reduce the incidence of striae. At the end of the case, the cornea outside of the flap can be depressed with a forceps to assure that the flap moves with the underlying bed and is identified by the presence of striae radiating from the peripheral cornea into the flap. We prefer to use dry Merocel sponges to stretch the flap from center to periphery to assure that the flap doesn't move when stretched gently and that the gutter is visible and well opposed for the entire length of the gutter. Thick lubricating drops are placed over the cornea, and the lid speculum is left in place for a few minutes before removing. The thick drops such as Celluvisc (Allergan, Irvine, Calif.) protect the flap from lid movement when the lid speculum is removed. After removal of the surgical drapes and lid speculum, we have the patient blink to make sure that no movement or displacement of the flap is observed during blinking.

5.4 Management

If striae exist after LASIK, then the first step is to identify whether the visual acuity or the quality of vision is affected. If striae are peripheral or minimal enough that they do not affect vision, then they do not require intervention. Visual symptoms can include induced astigmatism (the cornea is thicker in peripheral striae, and this can cause flattening in the meridian of the striae). Visual symptoms can also include ghosting or shadowing due to irregular astigmatism when central. Striae that are going to impact the vision over the long term are best dealt with soon, as the longer they are present, the more difficult they become to remove [5, 8, 9]. Mild striae that only minimally affect the vision may become less symptomatic with time, as the epithelium thickens and reduces their visual significance by smoothing the anterior corneal surface. Contact lens fitting can be considered to improve vision in those patients where surgical intervention is not desired [11]. Fine flap distortion may be from mismatch of the flap and stromal bed, especially in high myopes, and may not influence the vision significantly, nor respond to flap repositioning [12]. Significant striae identified intraoperatively or immediately postoperatively are best dealt with at that time. This reduces the incidence of long-term striae or epithelial ingrowth which can be caused by the epithelium growing into the gutter where the edge of the flap should have been. Most striae are identified on the first postoperative day, as patient rubbing, inadvertent touch of the eye with the eye dropper bottles, or drying during sleep with the lid distorting the flap are the most common reasons for striae. Some have advocated addressing the striae at the slit lamp by either stretching

with a cotton-tip applicator or lifting the flap fully at the slit lamp [13, 14]. Care should be taken in these settings to prevent pulling the flap over epithelium that may have grown onto the stromal bed. If striae are found to be visually significant in the early period, we prefer lifting of the flap, removing the epithelium from the gutter and stromal bed where the flap should have been, and stretching the flap back into position with Merocel sponges at the operating microscope. Because the flap now has wrinkles that have been present for some time, and the compressed areas are relatively dehydrated compared with the expanded areas, the striae are more difficult to remove, and the flap is more difficult to position to where there are no gaps in the gutter. The endpoint of repositioning should be a tight gutter with no gap for 360°. It may appear that there are still some striae at the end of the repositioning, as the flap may be more dehydrated in the compressed areas when it was distorted before lifting the flap. Some report good success with hydration of the flap with a hypotonic solution. They advocate lifting the flap, refloating it, and then compressing the flap [5]. We have not found this technique as useful, as the flap is not as adherent when very swollen, and the striae appear to return after 2–3 days if the flap position is not resolved through stretching the flap to maintain a small tight gutter.

For striae present a long time, we still initially manage these striae in the same manner as described above, with lifting of the flap, removing epithelium from the gutter, and then careful stretching of the flap to reestablish a tight gutter. Some recommend epithelial debridement to break epithelial attachments that may be holding the flap in a distorted position [15]. We have successfully reduced striae up to 24 months after surgery with lifting and stretching without epithelial debridement. In some case, they can be recalcitrant to several methods, and some have recommended suturing of the flap to hold the flap in a taught position to reduce recalcitrant striae [16, 17]. Suture tension symmetry is important if this is performed. Warming the flap may be useful in manipulating flaps that have striae [18]. Transepithelial phototherapeutic keratectomy (PTK) can be used to smooth Bowman's layer to remove the striae [19]. The endpoint for the PTK should not be total removal of the striae, as the epithelium can still smooth a significant degree of striae, and hyperopia can result from removal of central corneal tissue. We prefer to use mitomycin C in this situation to reduce the incidence of flap haze.

Flap distortion with reduction in visual quality or best-corrected visual acuity is infrequent but is an important cause of intraoperative and early postoperative complications with lamellar surgery such as LASIK. Early recognition and treatment are beneficial to aid in resolution of this complication. There are varieties of methods to improve flap striae, and there is no consensus as to which one works the best, so familiarity with all techniques is useful.

Take-Home Pearls

- Significant striae can be managed early by lifting and stretching of the flap.
- Mild striae or flap distortion may improve with time through epithelial remodeling, but may require lifting the flap to realign the flap, or phototherapeutic keratectomy.

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Part III

LASIK Postoperative Complications

Scarring

6

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Jorge L. Alió-del Barrio, and Jorge L. Alió

Core Messages

- Scarring may occur following LASIK and PRK, as it is a natural process of wound healing.
- This chapter covers the potential causes of scarrs, their location (Flap margin, Flap interface), their link to complications or postoperative trauma and to the patient's history.

6.1 Introduction

The cornea contributes to most of the refractive power of the eye. Its transparency, regular shape, and smooth surface are crucial to preserve this function. After any epithelial and stromal wound, an immediate process starts to repair the wound and restore normal corneal structure and function. This wound healing response is a complex cascade of events that affect the predictability and stability of laser corneal refractive procedures.

Scarring is a natural part of the process of wound healing. Every wound, with the exception of very minor *lesions*, results in some degree of scarring. During this process, the body forms new collagen fibers to mend the damage, resulting in a scar. Under a microscope, scars are composed of fibrous tissue and collagen deposits. The choice between normal regeneration and fibrosis production seems to lie in the control of fibroblast activation [1].

The presence of myofibroblasts in the wound repair process favors the formation of scarring [2, 3]. These specialized fibroblastic contractile cells (with reduced transparency) are generated in the cornea by keratocyte-derived precursor cells. Once they are present in the wound repair process, they start producing disorganized extracellular matrix components (ECM), leading to decreased expression of corneal crystalline in these cells [4]. Myofibroblast persistence has been demonstrated to be the primary cellular contributor to the development of corneal haze [4–6].

Scar tissue is composed of the same protein (*collagen*) as the tissue that it replaces but with different fiber composition; in scarring, collagen cross-links and forms a pronounced alignment in a single direction instead of the normal specific basket weave formation found in the normal tissue [7]. Scar tissue is not identical to the tissue it replaces and is usually of inferior structural and functional quality.

Multiple studies [8–10] showed that wound healing response in the cornea is mediated by growth factors, cytokines, and chemokines. Platelet-derived growth factor-B (PDGF-BB), transforming growth factor-α (TGF-α), transforming growth factor-β (TGF-β), and basic fibroblast growth factor (bFGF) are mainly involved in chemotaxis and proliferation of fibroblasts and collagen synthesis, resulting in scar formation. Recently [11, 12], the role of mesenchymal stem cells to restore corneal transparency following corneal injury has evolved.

It seems that competition between keratocytes and fibroblasts is critical in haze development. Also the level of keratocytes apoptosis is very important to determine opacity formation. Apoptosis following laser stromal ablation is proportional to the level of attempted correction. It leads to an early decrease in anterior keratocyte density and hence diminished perlecan and nidogen-2 required for normal

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regeneration of the epithelial basement membrane (EBM). TGF-β enhances the development of mature myofibroblasts [12] and suppresses interleukin-1 (IL-1)-mediated apoptosis of mature myofibroblasts leading to haze formation [13].

The integrity of the epithelial basement membrane plays the major role in regulating corneal epithelial–stromal interactions and corneal wound repair process consequently [14]. Defective regeneration of the epithelial basement membrane after infection, trauma, or surgical injury leads to the development of stromal haze. This haze persists till repair of the defective epithelial membrane or formation of a scar.

LASIK and photorefractive keratectomy (PRK) are the most common refractive surgeries performed for refractive error correction. Corneal wound healing determines a lot of the clinical outcomes of these procedures. While PRK includes extensive removal of the epithelium and central corneal epithelial membrane, followed by subsequent photoablation of the anterior stroma, LASIK's injury is limited to the edge of the hinged flap created for photoablation. So for the same amount of attempted correction, the stimulus for fibrotic response in the corneal wound healing response is usually stronger after PRK [15, 16]. Defective regeneration of the epithelial basement membrane seems to have a critical role in determining whether a cornea heals with scarring at the LASIK flap edge or with late haze after PRK [14].

6.2 LASIK: A Scarless Procedure?

LASIK gained its popularity worldwide due to the minimal changes in corneal architecture that it produces. After LASIK, only minimal wound healing with traces of scar tissue is generally detected in corneas [17]. That is in comparison to the wound healing in corneas that have had photorefractive keratectomy (PRK) [18]. These results may support the clinical findings of less corneal haze observed in the human cornea after LASIK in comparison to PRK. It is believed that the difference in stromal wound healing intensity after LASIK versus PRK is mainly due to the preserved integrity of the corneal epithelium and its basement membrane [18]. Disruption of the epithelial basement membrane amplifies the stromal wound healing response, leading to intense haze development and extracellular matrix deposition [19]. But is LASIK a scarless procedure?

In LASIK, the most significant healing response and resultant scarring, secondary to epithelial–stromal interactions responsible for myofibroblast generation, is mainly present at the flap edge; that is where the epithelial basement membrane is damaged and myofibroblast-related haze is commonly noted. The epithelial basement membrane break allows direct contact of epithelium-derived cytokines such as TGF-beta and stromal cells. This process leads to peripheral myofibroblast formation, clinically recognized as a circumferential haze at the edge of the flap. However, central interface haze has been reported after LASIK. Multiple conditions like severe diffuse lamellar keratitis (DLK), epithelial ingrowth, or thin flaps increase this risk [20]. The idea in "thin-flap femtosecond laser LASIK" technique is to create thinner flaps and hence to minimize the biomechanical injury to the anterior corneal stroma, reducing the risk of postoperative ectasia. However, there is greater chance for haze formation with this approach, related to epithelial basement membrane injury caused by the proximity of the femtosecond laser photodisruption process to it [21].

So unusual scarring associated with visual loss may occur following LASIK, due to intraoperative or postoperative complications or abnormal wound healing. These changes might present even post uncomplicated, asymptomatic LASIK procedures. These minor changes may be part of the normal LASIK healing process or might be linked to the patient's medical history, intraoperative complications, or postoperative care and events.

6.3 Flap Margin

After uneventful LASIK surgery, it is usually difficult to recognize the margins of the corneal flap with the slit lamp. While laser photoablation involves the central cornea in both LASIK and PRK, the corneal fibrotic response to these insults is maximal in the central subepithelial area after PRK and in the subepithelial area of the flap margin after LASIK [22]. This response is minimal post LASIK, and this manifests clinically as LASIK interface is still readily accessible for re-treatment even more than 1 year after the initial treatment. Corneal flap dehiscence has even been reported many years after LASIK [23, 24].

Data published describing keratocyte activation status at the interface are conflicting though. While several studies did not show any activation below the flap using tandem scanning confocal microscopy, others showed keratocyte activation in the posterior stroma. Regardless of how intense this activity is, definitely it is not aggressive enough to cause extensive wound healing and scarring following LASIK [18, 25, 26].

Slit lamp biomicroscopy of the flap margin in rabbits reveals a white reflective circumferential band of fibrosis as early as 3 weeks after LASIK. Confocal microscopy [27] during the first week after LASIK reveals a well-defined circular band which, in the following weeks, becomes increasingly reflective as it acquires a more pronounced fibrillar texture. By 2 months, gradual condensation has occurred, and the band appears more organized. At 4 and 6 months, the reflectivity of the flap edge falls considerably, leaving a poorly reflective region which, with time, gradually narrows.

Postmortem studies of human eyes subject previously to LASIK revealed certain changes in or adjacent to the wound (Fig. 6.1a, b) [28]. These changes included collagen lamellar disarray; activated keratocytes; quiescent keratocytes with small vacuoles; epithelial ingrowths; eosino-

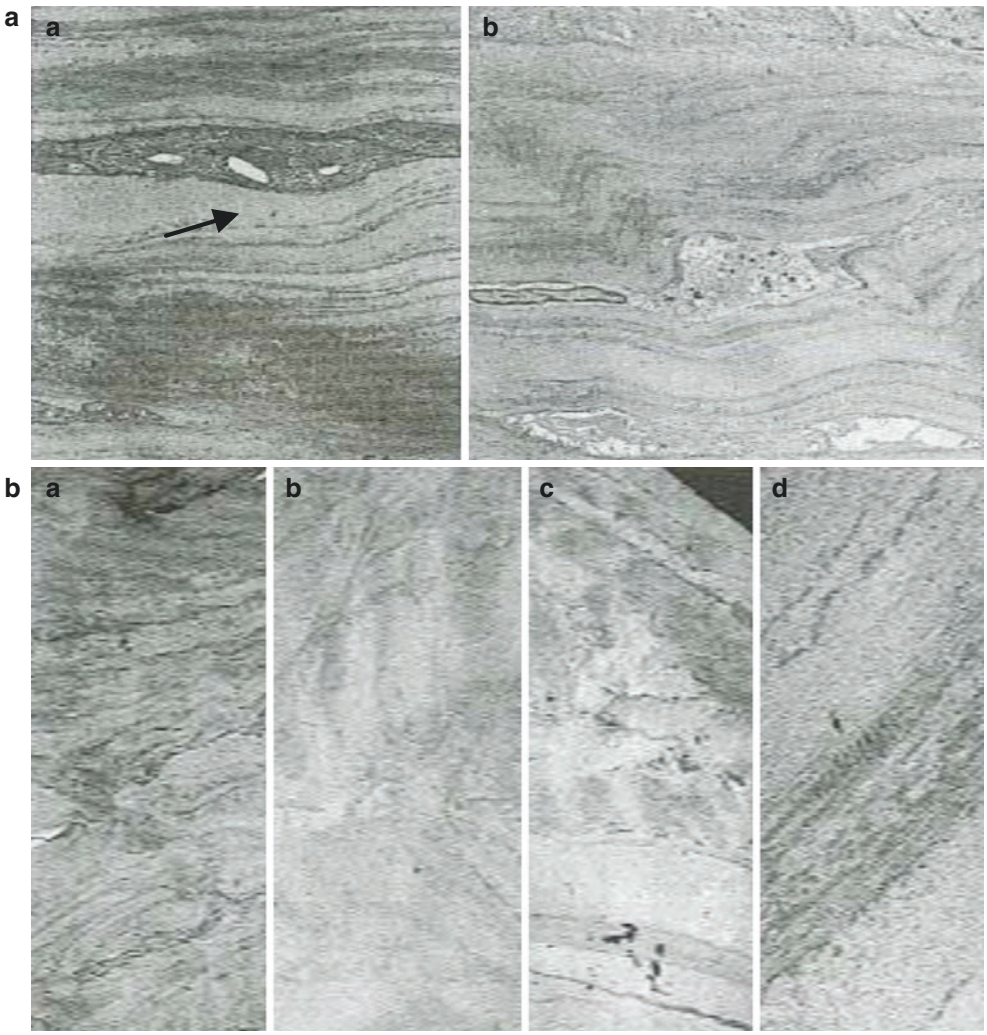

Fig. 6.1 Electron microscopy of lamellar wound area in postmortem human corneas treated with LASIK. Property of Kramer et al. [28]. (**a**) Electron micrograph demonstrates activated keratocytes (*arrow* in *a*) with deposition of electron-dense material in the lamellar wound (×4750) and higher magnification of the same area (*b*) (×72, 500). (**b**) Electron micrograph demonstrates different grades (*a–c*) of collagen lamellar disarray in the lamellar wound (×4750). Wide space collagen (*arrow* in *d*) found around the lamellar wound (×47,500)

philic deposits; PAS-positive, electron-dense granular material interspersed with randomly ordered collagen fibrils; increased spacing between collagen fibrils; and widely spaced banded collagen.

LASIK wound healing after femtosecond laser and mechanical microkeratome surgery was also compared by means of in vivo corneal confocal microscopy [29]. This investigation revealed more fibrotic scarring in the flap margin with the femtosecond laser than with the mechanical microkeratome. The reason is probably that the flap edge produced by tissue ablation with the femtosecond laser leaves an empty space which is filled by an epithelial plug during the first 2 months after surgery. This plug disappears after 2 months, probably by constriction of the wound edges, resulting in a stronger fibrotic response similar to that observed after radial keratotomy (RK). This difference did not offer through any significant benefits of LASIK with femtosecond over LASIK with microkeratomes in regard to safety and efficacy [30].

The low rate of fibrosis observed after LASIK, limited to the flap margin, has been noted by refractive surgeons performing LASIK re-treatment. In order to lift the flap, sometimes several years following the initial surgical procedure, the surgeon has to disrupt epithelial and fibrotic connections that have formed in the flap margin; once this has been done, it is much easier to lift the flap [31].

6.4 Flap Interface

Postmortem studying of human corneas after LASIK [28] showed permanent pathologic changes. These changes were most prevalent in the lamellar interface. Such changes included elongated basal epithelial cells, epithelial hyperplasia, thickening and undulations of the epithelial basement membrane (EBM), and undulations of Bowman's layer (Fig. 6.2a, b).

After LASIK surgery, the flap interface, as observed by slit lamp biomicroscopy, is usually devoid of visible scars. However, histological examination of rabbit eyes [32] revealed a PAS-positive extracellular matrix deposited along the lamellar incision, as late as 9 months after the procedure. Electron microscopy of the lamellar wound area in LASIK treated rabbit eyes demonstrated collagen lamellar disarray

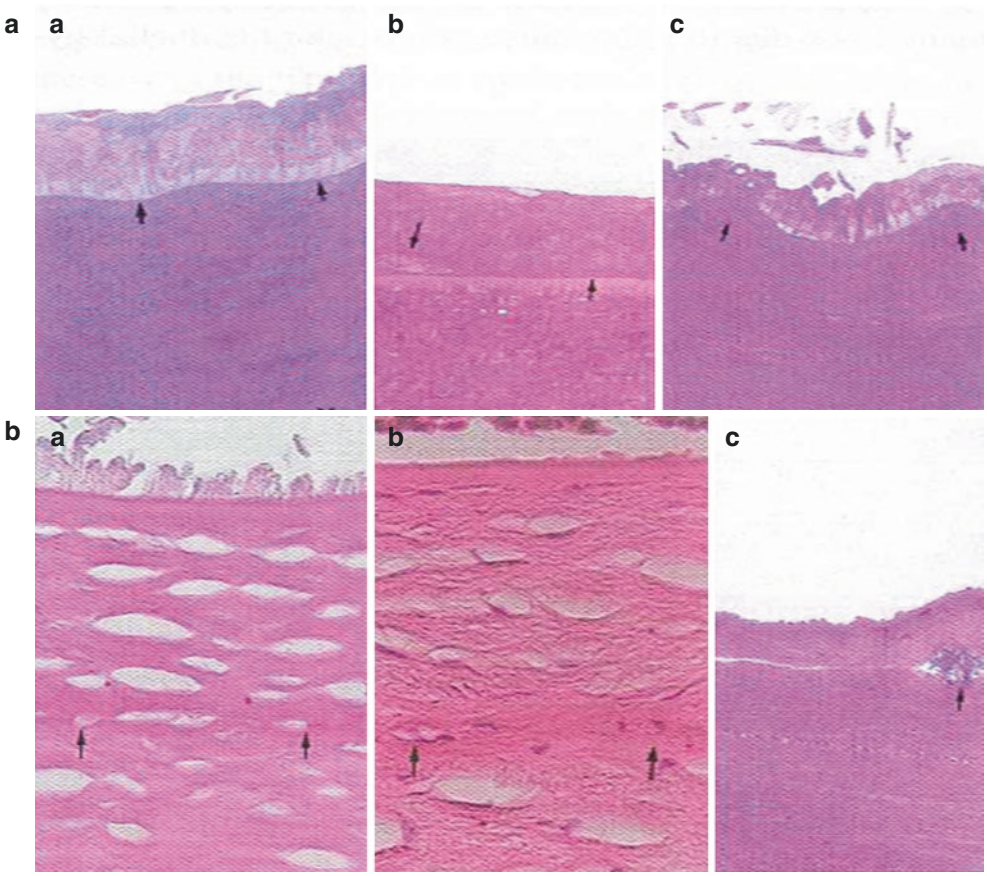

Fig. 6.2 Light microscopy of lamellar wound. Property of Kramer et al. [28]. (**a**) Light micrograph of the thickened epithelium due to elongation of basal epithelial cells (*arrows* in *a*); thickening, wrinkling, and reduplication of the epithelial basement membrane (*arrows* in *b*); and undulations of Bowman's layer (*arrows* in *c*). (**b**) Light micrograph demonstrates PAS-positive material in the wound interface (*arrows* in *a*), deposition of eosinophilic material in the wound interface (*arrows* in *b*), and separation of the flap from the stromal bed with interface debris (*arrows* in *c*)

with activated and quiescent keratocytes containing small vacuoles. Extracellular matrix abnormalities were also detected, including electron-dense granular material interspersed with randomly ordered collagen fibrils, increased spacing between collagen fibrils, and widely spaced banded collagen. These pathologic alterations in post-LASIK corneas may affect corneal function, as regularity is essential for transparency. This also explains the risk of late flap dislocation posttrauma even months after the surgery.

6.5 Scars Linked to Surgical Complications or Postoperative Trauma

6.5.1 Corneal Erosion and Epithelial–Stromal Interaction

Myofibroblast activation is the key factor in haze formation after refractive surgery [2, 3]. Myofibroblasts are relatively opaque in comparison to keratocytes due to their diminished crystallin protein production. Some of the factors that activate myofibroblasts include depth of ablation [33, 34], degree of damage to the epithelial basement membrane [1, 19, 35], irregularity of postoperative stromal surface [5, 36], and time needed for epithelial defect healing [6]. As mentioned previously, basement membrane disruption has been shown to be the key event responsible for myofibroblast activation in the anterior stroma, resulting in fibrosis. These factors might explain why haze formation is encountered more post PRK than post LASIK.

Basement membrane disruption occurs at the site of RK incisions, in the central cornea post PRK, and at the flap margin in LASIK. It induces corneal scarring associated with loss of transparency. Occurrence of large intraoperative epithelium sloughing/defects through the course of LASIK procedure or its postoperative period may be due to excessive dryness [37]. It might also be a diagnostic sign for subclinical epithelial basement membrane dystrophy (EBMD) [38], also known as map-dot-fingerprint or Cogan's microcystic dystrophy, which is the most common corneal dystrophy. Such patients are prone to multiple postoperative complications including scarring formation. It is even recommended not to proceed with LASIK for the second eye if this was observed during performing the procedure for the first eye.

Figure 6.3 shows images of a patient who unfortunately developed multiple recurrent corneal erosions following LASIK treatment; this resulted in the development of central scar. Patient was treated 6 months later with PTK, resulting in a residual faint central scar and a BCVA OS of 0.4 (+0.5/−6.00 × 165).

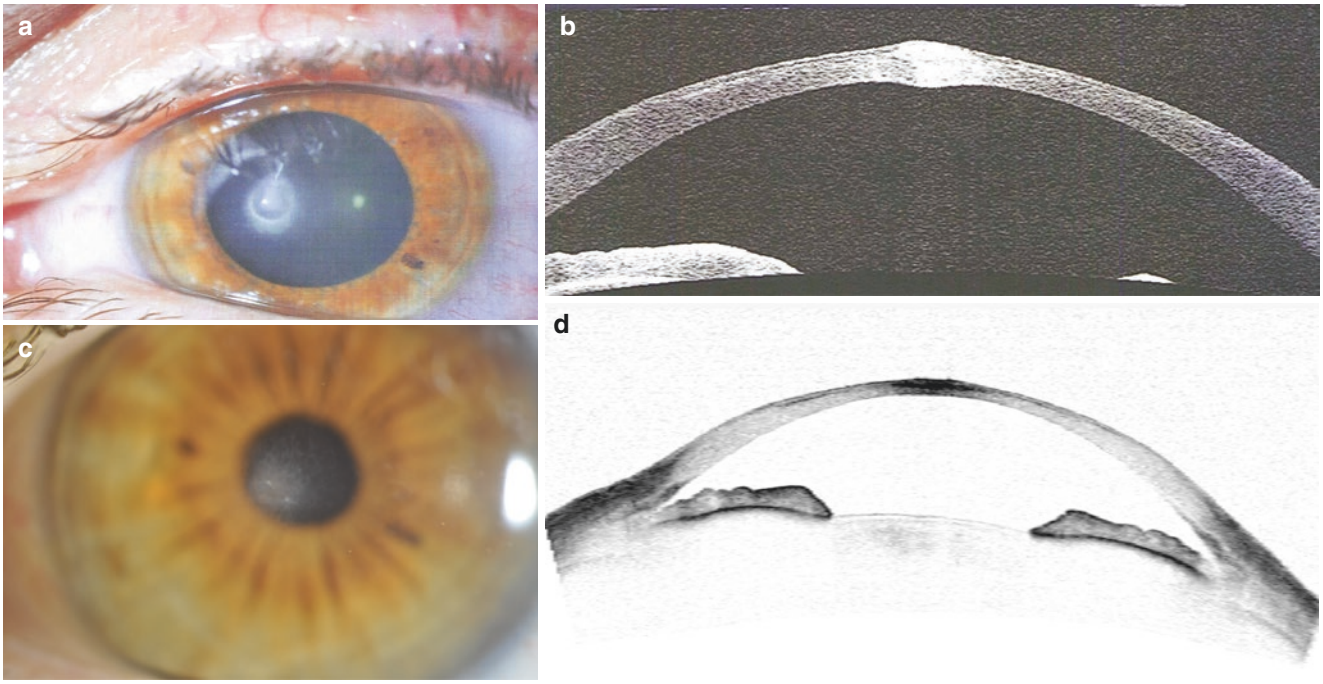

Fig. 6.3 Post-LASIK corneal scar secondary to development of recurrent corneal erosions (**a**) as seen in OCT (**b**). Patient underwent PTK, resulting in mild central scar 6 months postoperatively (**c**) as seen in OCT (**d**)

Epithelial defects may not only alter flap adherence (with a higher threat of displacement or wrinkles) but are also associated with an increased risk of epithelial ingrowth, diffuse lamellar keratitis, and subepithelial fibrosis [39, 40].

Intact epithelium plays a very important role in preventing myofibroblasts proliferation and subsequent haze formation. Many experimental studies evaluated healing post LASIK after epithelial removal. Some studies [15, 41] reported the presence of myofibroblasts and type III collagen in the subepithelial region, corresponding to scar tissue formation. Others, on the other hand [42], observed temporary changes in corneal reflectivity by means of confocal microscopy, but they did not detect accumulation of new collagen nor keratocyte activation. The likely key difference between these studies was probably the status of basement membrane integrity after epithelial removal.

This raises the question of late postoperative epithelial trauma though. Figure 6.4 shows corneal slit lamp and confocal microscopy images of a patient with extensive bilateral corneal de-epithelialization due to tear gas exposure 6 months after myopic LASIK correction. Only transient subepithelial opacification associated with moderate fibroblast activation was observed, in spite of extensive epithelial loss and basement membrane disruption. The visual outcome was excellent, probably because of the relatively long interval between LASIK and the corneal insult.

So defective regeneration of the epithelial basement membrane, after its disruption post epithelial removal, has a critical role in determining whether scarring will occur post LASIK [14].

6.5.2 Flap Misalignment and Folds

In contrast to microstriae, macrostriae are full-thickness folds of the LASIK flap that occur secondary to flap slippage and misalignment. Striae are a frequent cause for post-LASIK patient dissatisfaction. Misplacement of the flap leads to a loss of best visual acuity and must be prevented or treated to avoid abnormal healing and scarring. This may be caused by severe dryness and adhesion of the flap to the tarsal conjunctiva or simply be direct trauma. The altered central convexity of the ablated stroma bed may result in flap redundancy which prevents the flap from being perfectly positioned. This was described as the "tenting effect." The tenting effect of the corneal flap over the altered central convexity of the ablated stromal bed helps in its formation [43].

Macrostriae are best treated immediately [44]. The flap is lifted, either partially or completely, and refloated with balanced salt solution, before being stroked gently and smoothed back to its proper position, taking care to remove any peripheral epithelium that would become trapped in the interface [45]. Flap repositioning, hydration, and stretching may be effective within the first 48 postoperative hours. Once the folds become fixed, epithelial debridement on top of the folds and flap suturing are usually necessary [46].

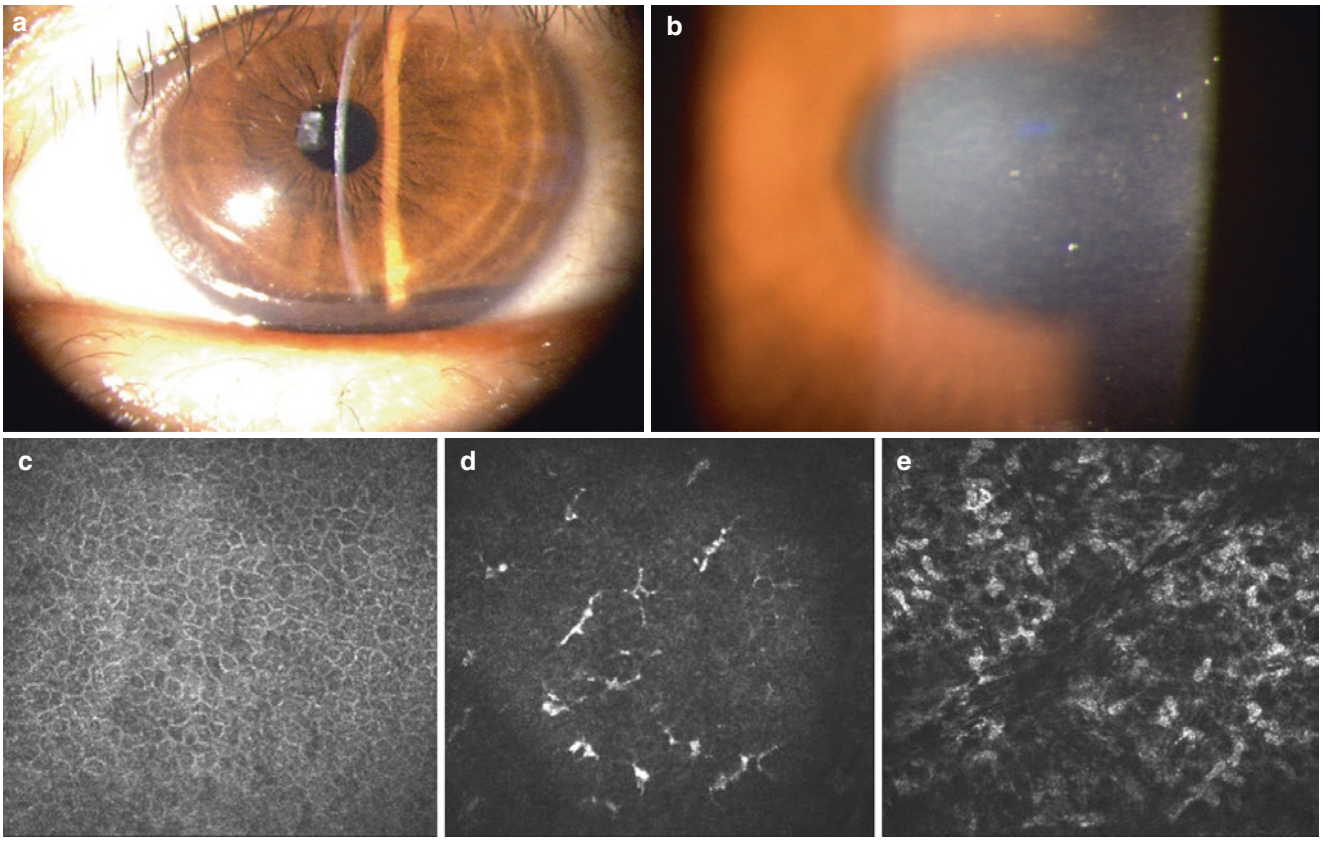

Fig. 6.4 Transient corneal haze after extensive traumatic epithelial abrasion 6 months after LASIK (**a**). Slit lamp examination shows subepithelial haze (**b**), and confocal microscopy shows hypereflective epithelial cells (**c**), inflammatory cell infiltration (**d**), and fibroblast activation (**e**)

These flap-lifting procedures place the patient at an additional risk of infection, epithelial erosion, epithelial ingrowth, and diffuse lamellar keratitis (DLK) and can potentially trigger an inflammatory response which may lead to the loss of the refractive effect [47, 48]. Irregular astigmatism and decrease in best corrected visual acuity (BCVA) may then occur.

Delayed wound healing of the interface after LASIK also places patients at a high risk of traumatic flap displacement. Scarring, persistent folds, DLK, and epithelial ingrowth may result from this latter complication.

6.6 Scars Linked to the Patient's History

6.6.1 Abnormal Local Wound Healing

Salzmann's-like corneal lesions located at the site of LASIK flap margins have been reported to occur during the first postoperative year [49–51]. The pathogenesis of this complication is uncertain; it is possible that tear hyposecretion, decreased blink rate, and the dellen effect that often occur after LASIK could cause the corneal irritation needed to induce Salzmann's nodular degeneration in predisposed patients. Most cases are treated medically. Some cases however might be associated with epithelial ingrowth which might need the use of superficial keratectomy to treat it [52].

Histological analysis of this type of complication reveals an irregular and thickened epithelium overlying the corneal lesions and discontinuity of Bowman's layer, replaced by periodic acid-Schiff (PAS)-positive thickened basement membrane-like material. Underlying this basement membrane is a layer of relatively regular, hypocellular, collagen-like connective tissue, displaying hyalinization on trichrome staining, similar to the initial description of Salzmann's nodular degeneration [50]. It is believed that the subclinical flap elevation contributes to the development of these nodules (Fig. 6.5).

6.6.2 Abnormal General Wound Healing (Keloid Formation)

Keloid is a dermatological problem characterized by proliferation of dense fibrous tissue that extends beyond the boundaries of the original injury or trauma. Keratinocytes and fibroblasts play a major role in keloid formation through increased expression of growth factors. Following refractive

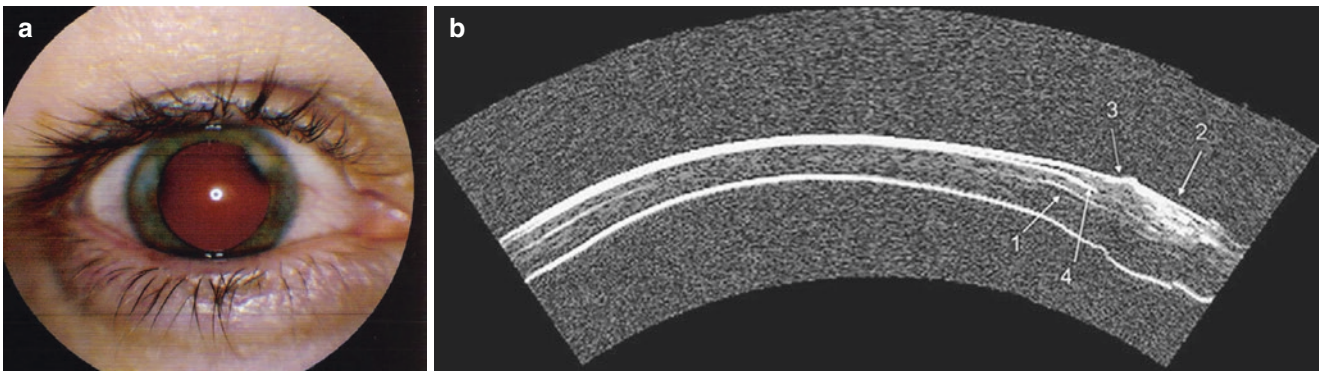

Fig. 6.5 (**a**) Anterior segment photograph demonstrating Salzmann's-like nodule in the midperipheral cornea of the right eye following LASIK. (**b**) High-frequency UBM image of the nodule showing the lamellar flap interface (*1*), the hyperechogenic nodule (*2*), thinned epithelium (*3*), and the abrupt end to Bowman's layer (*4*). Property of VanderBeek et al. [50]

surgery, cytokines and growth factors are released in the tear film [9, 53]. So theoretically, this might increase the risk of subepithelial fibrosis and corneal haze.

The United States Food and Drug Administration (FDA) established a list of absolute and relative contraindications for PRK. This list included patients with antecedent keloid formation. Similar FDA guidelines were subsequently adopted for LASIK. These recommendations are not based on clinical studies and outcomes but rather on the known ocular complications of these disorders as well as the documented outcomes of non-laser ocular surgery in such patients [54].

Conflicting data have been published on the safety and accuracy of LASIK in patients with a past history of dermatological keloids. While a history of keloid formation usually contraindicates PRK, LASIK is generally considered safe in these conditions [55–57]. While the minimal basement membrane disruption associated with LASIK should prevent abnormal scarring in such patients, abnormal bilateral scars have been reported in a patient for whom LASIK was chosen because of intense corneal haze in his first PRK-treated eye [58].

One factor that might play a role in keloid formation is wound tension and stretching [59]. As the corneal tissue is not under this tension, this might prevent formation of haze post LASIK in dermatologic keloid patients. Still the potential risks should be carefully explained to such patients before surgery.

6.6.3 Previous Laser Refractive Surgery

As previously stated, enhanced inflammatory response leading to corneal haze and/or scar formation is linked to epithelial basement membrane disruption. Such disruption occurs following any PRK and to a lesser degree any LASIK procedure. Such concern is present when trying to manage under corrections post previous LASIK. PRK used to enhance under corrected myopic eyes with previous LASIK can induce intense corneal scarring up to 10 months postsurgery [60]. This is associated with myopic regression and loss of BCVA. That is why it is strongly advised not to use PRK to enhance under corrected myopia from previous LASIK. If used though, usage of prophylactic MMC (0.02%) is a safe and effective option for treating myopic regression following LASIK.

On the other side, LASIK appears to be a safe and effective procedure for enhancing eyes with no or minimal haze and residual myopia after PRK [61]. It is less predictable though in eyes with severe haze [62]. LASIK re-treatment in eyes with myopic regression after LASIK might be a good option also [61], provided that corrections are under −2.00 D as attempts to correct residual refractive errors >−2.00 D were associated with a significant rate of haze [63].

So it seems that the enhancement procedure of choice for residual myopia is LASIK after lifting the primary flap. Its effect though might not be as effective in the case of severe haze presence [61, 64].

Mechanical and femtosecond LASIK has been used to treat RK-induced hyperopic shift. Although abnormal stromal scarring is a danger in areas involving both the excimer laser and keratotomy treatment zones, the main complication appears to be the reopening of the RK wound, with a risk of epithelial defects or ingrowth [65]. In such cases, PRK with 0.02% mitomycin application has been proposed to correct the refractive error and to prevent major scarring.

6.6.4 Scars Linked to Abnormal Postoperative Inflammation or Healing

6.6.4.1 Role of Ultraviolet Light

Excimer laser generates pulses in the UV spectrum at a wavelength of 193 nm, which produces ablative photo

destruction of the target tissue. Mutagenicity may be neglected, but thermal effects, although minimal, exist. Thermal denaturation of biological molecules does not usually occur until their temperature reaches 40–60 °C. A major thermal effect such as charring, coagulation, or vaporization is unlikely to occur following excimer laser exposure because the corneal surface experiences a 20 °C rise in temperature (from 18 to 38 °C) [66]. So even though there is a thermal component to 193-nm laser ablation of the cornea, it probably does not have a major contribution to tissue damage. Cooling of the ocular surface or the flap interface has been proposed to reduce corneal collagen damage and fibroblast activation.

UV light has been shown to stimulate wound healing response through corneal fibroblast activation and favors regression of the refractive effect and haze formation after PRK [2]. Its effects are minimal though after LASIK [67].

6.6.4.2 Diffuse Lamellar Keratitis (DLK)

DLK, or "Sands of Sahara" syndrome, is a noninfectious disorder characterized by an inflammatory reaction at the flap interface after LASIK. While most cases happen early (within 1–5 days) post-LASIK treatment, late-onset DLK has also been described [68].

The exact cause of DLK is unknown [69]. Multiple possible causative agents were accused for early-onset DLK. There is usually a specific causative cause for late-onset cases [70]. Diffuse lamellar keratitis is thought to be related to an immunologic or toxic reaction to a contaminant at the lamellar interface, leading to leukocyte migration into the lamellar interface. Predisposing factors include talk from surgical marker pens [71], gloves [72], eyelid debris, meibomian gland secretions [73], povidone–iodine solution, debris or oils derived from the microkeratome, ophthalmic sponges [74], antibiotic agents [75], or even endotoxins derived from gram-negative "biofilms" in sterilizer reservoirs [76]. Other potential factors are problems encountered during [77] or after LASIK surgery, such as epithelial defects [78].

DLK is classified in four stages [79], stage 4 being the most severe. This stage is associated with stromal melting, deep flap folds, central haze, hyperopic shift, irregular astigmatism, and even stromal melting, leading to a severe reduction in visual acuity. Scarring in LASIK, though very uncommon, generally occurs secondary to severe inflammation such as that occurs in advanced cases of DLK. The condition generally improves spontaneously when mild, while topical steroids may be beneficial in more severe cases. During LASIK, DLK appears to be slightly more common when the femtosecond laser is used for flap creation [30]. However, most of these cases appear to be mild and resolve with minimal treatment and little effect on visual acuity. Higher energy level for flap creation and larger flap diameter are associated with an increased risk for DLK development though [39].

Interface scarring on both sides of the lamellar cut and irregular astigmatism may persist after treatment, with a possible decrease in BCVA [80]. DLK might recur in patients with autoimmune disease [81, 82], secondary to an activating event such as viral keratitis, or idiopathically [83]. Interface scarring might present after resolved DLK as a thin scarred stroma. Figure 6.6 shows a case of a 35-year-old female who underwent femto-LASIK for high hyperopic correction. She developed a central toxic keratopathy in one eye after a flap lift was required due to macrofolds seen 24 h after the initial procedure, complicated with an intraoperative large epithelial defect over the flap. As a sequel she

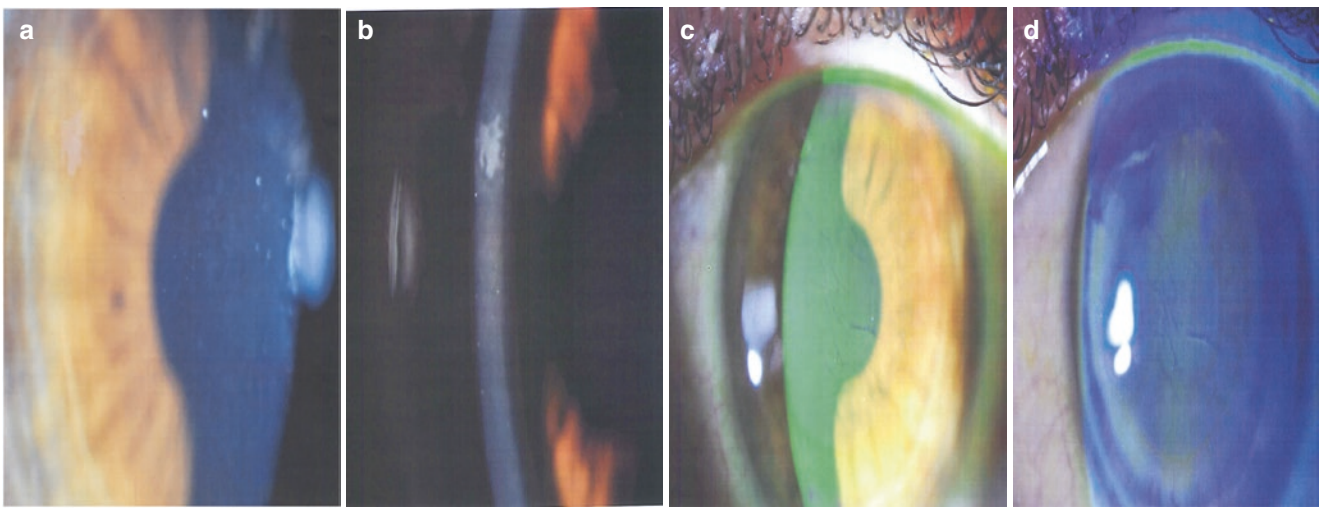

Fig. 6.6 Scarring following central toxic keratopathy after LASIK treatment, presenting a diffuse faint corneal scar (**a**) and mild epithelial ingrowth (**b**). The underlying stroma is scarred, thinned, and shrunk resulting in the appearance of folds in the overlying flap (**c**) which are best seen using the blue filter and fluorescein (**d**)

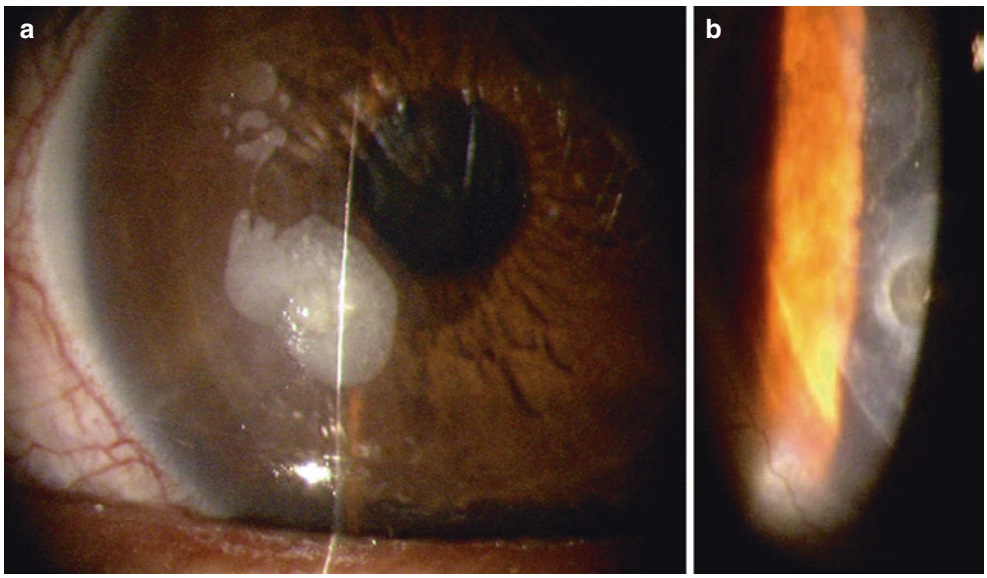

Fig. 6.7 Epithelial ingrowth in the LASIK flap interface. (**a**) Flap melt associated with epithelial ingrowth. (**b**) Fibrotic scar 2 months following epithelial ingrowth removal

developed a diffuse faint scar under the flap (Fig. 6.6a) and a mild nonprogressive epithelial ingrowth (Fig. 6.6b). Residual randomly distributed central microfolds with a radial pattern are usually observed (Fig. 6.6c) which are seen more clearly at the slit lamp using blue filter and fluorescein dye (Fig. 6.6d).

6.6.4.3 Epithelial Ingrowth: Fibrosis

Epithelial ingrowth is a relatively rare complication of LASIK procedures though is a frequent one following re-treatment and flap lift. Its incidence was reported as low as 0.03% [84] and as high as 9.1% [85]. The overall incidence of visually significant epithelial ingrowth has decreased with the use of femtosecond laser for flap creation [84]. Epithelial ingrowth is a normal healing response at the LASIK flap and generally produces no symptoms [86, 87]. Two mechanisms have been described to explain how epithelial cells might reach the interface: (1) intraoperatively during flap creation by deposition of clumps of epithelial cells by the keratome or other instruments and (2) postoperative migration of surface epithelial cells into the flap gutter and across the interface.

If epithelial ingrowth caused focal flap elevation, extension into the edge of the pupil or into visual axis, or induced focal keratolysis and consequently melting, then it needs treatment. It can reduce visual acuity by occluding the visual axis or by inducing irregular astigmatism.

Two forms of epithelial ingrowth, differing in severity, can be distinguished in central areas of the flap interface. While isolated epithelial nests (not connected to the flap edges) resolve within months with no loss of visual acuity and no need for surgical intervention, progressive epithelial ingrowths forming a continuous sheet with limbal stem cells may disturb interface wound healing, produce unequal remodeling, and lead to localized stromal loss. In this latter case, surgical intervention is required to prevent progression or induction of astigmatism and scarring in the area of epithelial ingrowth.

Progressive keratolysis of the flap is the main complication of epithelial ingrowth. The pathogenesis is not completely understood, but epithelial–stromal interactions with protease production may be involved [88]. Figure 6.7 shows epithelial ingrowths associated with flap melting. Treatment consisted of flap lifting and epithelial scraping of the interface. A dense fibrotic scar appeared in the area of epithelial ingrowth, supporting a pathological effect of direct epithelial interaction with the corneal stroma.

Although most epithelial ingrowths in the flap interface occur from the flap margin, they may also arise from the edges of a complicated buttonhole flap. This can lead to a major reduction in visual acuity, particularly because it is close to the visual axis. Transepithelial mitomycin-assisted PRK has been proposed to treat this complication and to prevent intense scarring [89].

Increased epithelial ingrowth incidence post LASIK is associated with older age [90], use of mechanical microkeratomes as compared to femtosecond lasers for creation of the flap [30], hyperopic LASIK treatment [91], epithelial defects during surgery [92], LASIK after RK [93], and LASIK re-treatment [94].

Although refractive surgeons generally consider LASIK to be a scarless procedure, it is nonetheless associated with changes in corneal composition. These changes may lead to a loss of transparency, due to abnormal healing and scar formation, or may be associated with abnormal recovery of corneal biomechanics. Surgeons and their patients must be aware of these changes in order to prevent or minimize their consequences.

Take-Home Pearls

- The popularity of LASIK over PRK relies on its ability to induce minimal scarring.
- Unusual scarring associated with visual loss may occur following LASIK, due to intraoperative or postoperative complications or abnormal wound healing.
- Severe diffuse lamellar keratitis (DLK), epithelial ingrowth, or thin flaps increase the risk of post-LASIK scarring.
- The vast majority of abnormal healing responses following LASIK can be prevented or treated.
- Proper patient selection, limited flap manipulation to prevent erosions, perfect flap positioning to prevent wrinkles and displacement, and proper treatment of all excessive inflammation or abnormal tissue response, such as DLK and epithelial ingrowth, are essential to best optimize the visual outcome.

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Infections After Refractive Surgery

7

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Core Messages

- The incidence of post-laser-assisted in situ keratomileusis (LASIK) infectious keratitis has been declining. However, when infections occur, they remain to cause significant visual loss.
- The use of the femtosecond laser may decrease the risk of postoperative infections by reducing complications, with less epithelial defects and better wound healing.
- Infections presenting early after LASIK (within 1 week) are commonly caused by Gram-positive organisms, whereas delayed-onset infections (presenting 2–3 weeks after LASIK) are commonly caused by atypical *Mycobacterium* and fungi.
- Persistence of interface inflammation or appearance of corneal infiltrate after LASIK should be presumed infectious unless proven otherwise.
- Fungal infections should be considered in those cases lacking improvement after early broad-spectrum therapy, as they are associated with severe visual loss.
- A high index of suspicion and aggressive management which includes early lifting of the flap, scrapings for microbiological investigation, irrigation, and aggressive antibiotic therapy may lead to better outcomes.

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Although LASIK is a relatively safe procedure, infections can be a rare but sight-threatening complication [1–6]. Recent case reports of infections after LASIK are related to unique microorganisms [2–5]. Some descriptive reviews that have been published as part of articles reporting new cases recognize the importance of effective management of this potentially serious complication after LASIK [4–12, 14, 15]. In this chapter, we will first present a general discussion on infections after LASIK, followed by relevant excerpts from our systematic review of published literature.

Infections after LASIK are rare. Although prophylactic postoperative broad-spectrum antibiotics like fluoroquinolones and tobramycin are routinely prescribed after almost every LASIK case, infections still occur. The frequency of LASIK infections reported in case series varies from 0.02 to 1.5% [1]. Several large LASIK case series have reported no infectious complications, and more recent studies focus on reporting infections following a unique or specific circumstance or experimental condition. In a recent retrospective case series review, Ortega-Usobiaga et al. assessed the occurrence of infectious keratitis after LASIK and surface

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ablation when topical moxifloxacin was added to postoperative prophylaxis with tobramycin [5]. Among 108,014 eyes, ten eyes developed post-LASIK infectious keratitis. They reported a decrease of infectious keratitis from 0.025 to 0.011% when topical moxifloxacin was added to postoperative care [6]. Post-LASIK infections have been classically divided into early (within 2 weeks after surgery) and late onset (after 2 weeks of surgery). With the use of fourth-generation fluoroquinolone prophylaxis, early-onset infections are more common and are mainly caused by Gram-positive bacteria (methicillin-resistant *S. aureus*—MRSA—and *streptococcus species* [1, 6, 81]). Later onset infections are on the decline and are mainly caused by atypical mycobacteria (more commonly by *M. chelonae and M. fortuitum and less commonly by M. abscessus*) [1, 13, 81–83] or fungus (*Candida*, *Fusarium*, and *Aspergillus* species) [1, 7, 81–83]. *Acanthamoeba* is an uncommon cause of late-onset keratitis, but the epidemiologic trend, especially in contact lens users, has been increasing since 1999 [1]. Most of the time, this entity is misdiagnosed and frequently requires therapeutic keratoplasty. The exact reason of the risk for *Acanthamoeba* keratitis in post-LASIK patients is not clear and is subject of study. In a few cases, the infections may be polymicrobial, and in others, the microorganism is not identified.

Risk factors associated with development of post-LASIK infections include prior corneal surgery, blepharitis, dry eye, epithelial defects, break in aseptic surgical technique, steroid use, HIV status, and the healthcare environment. The introduction of the femtosecond laser in the construction of the flap results in improvement of flap morphology and predictability of LASIK surgery. Also, replacement of the microkeratome by the femtosecond laser decreased the risk of postoperative infections through the improvement of wound healing and decrease in postoperative epithelial defects.

Patients with infections after LASIK usually complain of pain, decreased or blurry vision, photophobia, irritation, or redness; however, as many as 10% may be asymptomatic. Symptoms and signs such as pain, discharge, flap separation, epithelial defects, and anterior chamber reaction are strongly associated with Gram-positive infections, and redness and tearing are more common with fungal infections. However, symptoms such as pain, photophobia, decreased vision, and irritation are nonspecific indicators of ocular surface disease, therefore may not have specific association with particular infections (bacterial, mycobacterial, or fungal). Infections after LASIK often present with inflammation in the corneal interface, which can mimic diffuse lamellar keratitis (DLK), and is key to differentiate these two entities. Because of the DLK misdiagnosis, many cases may be initially treated with frequent topical corticosteroid therapy, and there may even be a transient improvement in the inflammation. However, unlike DLK, the inflammation associated with infections usually persists despite topical corticosteroids and worsens with corticosteroid tapering. The time of onset of variable infections appears typically between 3 and 21 days post surgery and DLK is usually seen within the first week. The appearance of an interface inflammation more than 1 week after LASIK should be presumed to be of an infectious etiology until proven otherwise. Although the DLK infiltrates may also coalesce, any focal infiltrate surrounded by inflammation should be presumed infectious until proven otherwise. Infections presenting early after LASIK are associated with more severe reductions in visual acuity. However, severe visual acuity reductions are more associated with fungal infections than with Gram-positive or mycobacterial infections. Therefore, in cases of suspected infection, if no response or worsening is observed despite 7 days of broad-spectrum antibiotics, the possibility of a fungal infection should be considered.

Corneal infiltrates are present in almost all cases of infections after LASIK. The infiltrates are most commonly in the flap interface followed by infiltrates within the lamellar flap (Fig. 7.1). Infiltrates in the stromal bed and flap margins are less common. An overlying epithelial defect may be present in a third of the cases. But, in most cases, corneal infiltrates are not accompanied by an epithelial defect. This is contrary to the dogma that an epithelial defect is necessary for the diagnosis of an infectious infiltrate. In other types of refractive surgery, epithelial defects usually serve as a portal for organisms to establish infections in the stroma. However, in LASIK patients, creating the lamellar flap may introduce organisms into the stroma, and an epithelial defect may not be necessary for infection to occur. For this reason, infection should be suspected if infiltrates are seen in LASIK patients, and antibiotic therapy should be commenced before an epithelial defect occurs. In severe infections, anterior chamber

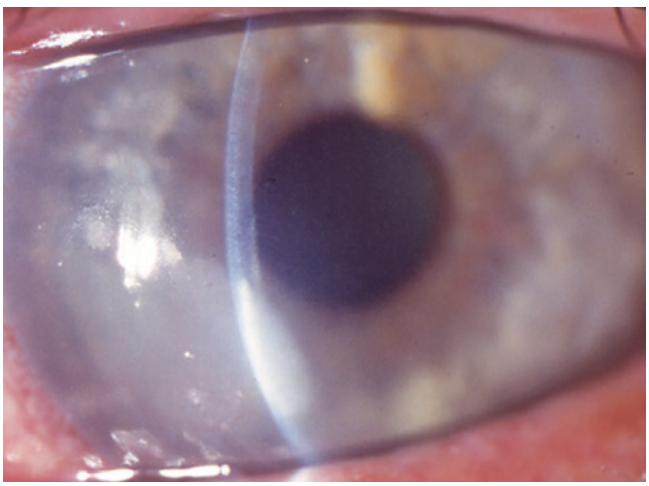

Fig. 7.1 Infiltrate development near LASIK flap

reaction or flap melting may occur. Clinical features that should raise the suspicion of infection with mycobacteria after LASIK include a delayed onset of keratitis and an indolent course. Presenting symptoms can include any of the following: pain, redness, photophobia, decreased vision, a "white spot" in the cornea, a foreign body sensation, and/or mild irritation. Presenting clinical signs include infiltrates in the corneal interface that can be either multiple white granular opacities <0.5 mm in diameter or single white round lesion (0.1–2 mm in diameter).

Due to the sequestered nature of infections following LASIK, it may be difficult to rely solely on topical treatment. Antibiotic penetration, especially antifungal agents, may not be sufficient to reach infections that lie at the interface. There may be an association between early flap lift and identification of the organism with a better outcome. Any focal infiltrate following LASIK should be considered infectious, and the practice of empirical antibiotic treatment without culturing should be discouraged. We recommend lifting and repositioning of the flap early after symptom onset for culture, scraping, and irrigation of the stromal bed, especially when the infiltrate involves the interface (Fig. 7.2). This allows greater antibiotic penetration and removes the sequestered nidus of infection. Culture media should include blood agar, chocolate agar, Sabouraud's agar, and thioglycolate broth. Cultures for fungus and mycobacteria should not be neglected. Corneal scrapings should be cultured on Lowenstein–Jensen media or Middlebrook 7H-9 agar. Smear stains should include Ziehl–Neelsen or fluorochrome stains for acid-fast bacilli (Fig. 7.3). Gram stains, Giemsa stains, and KOH preparations at the time of scraping may provide valuable insight into the proper antibiotic therapy before culture results become available (Fig. 7.4). Infiltrates confined to the flap, or those associated with full-thickness ulcers, may not benefit greatly from early flap lift, although scrapings for culture should still be taken. Biopsy may be considered in those circumstances, especially if there is no improvement with medical treatment. Although flap amputation for therapeutic reasons may limit the amount of vision regained after resolution of infection, it can halt the extent and progression of the infectious process and help in greater penetration of antimicrobials. Cultures can be performed identifying the cause of infection.

Figure 7.5 outlines steps for treatment. The first step in the treatment of infections after LASIK is to lift the corneal flap and culture as described above. Treatment recommendations that are described herein are based on the

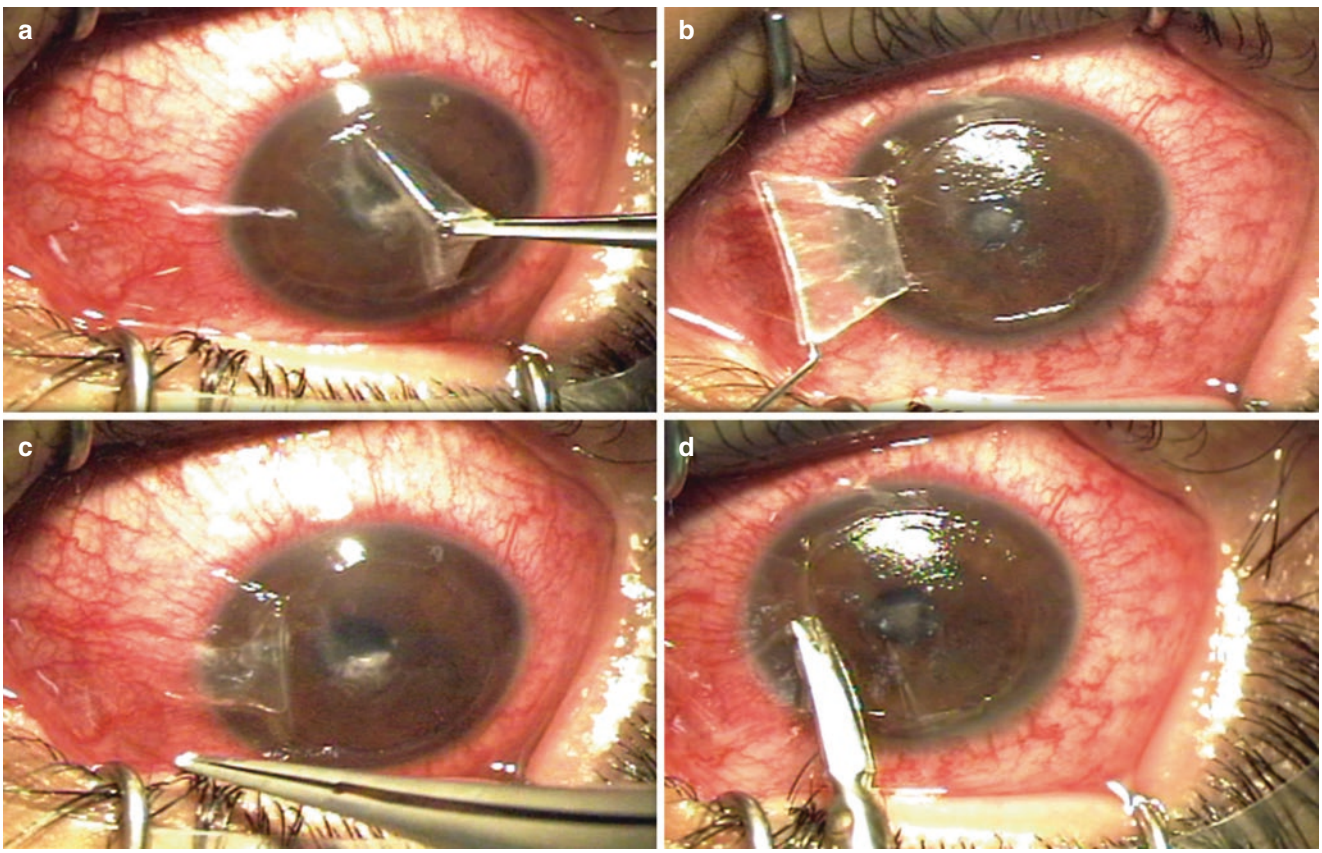

Fig. 7.2 (**a**) Presence of the infiltrate in the flap, which is lifted (**b**) and amputated (**c**). Scraping of the stromal bed (**d**)

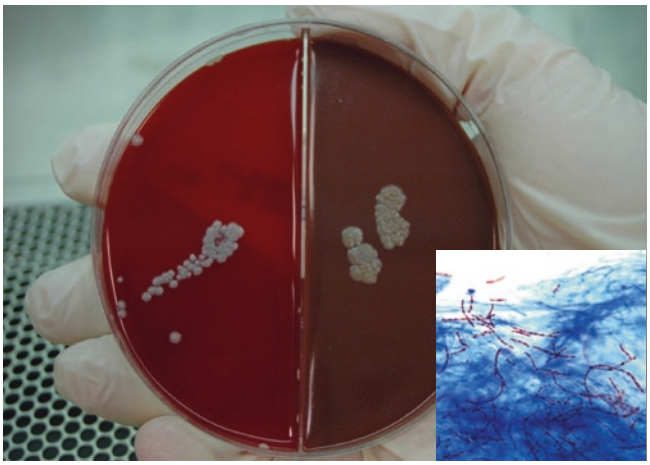

Fig. 7.3 The culture plate shows mycobacterial colonies and acid-fast bacilli

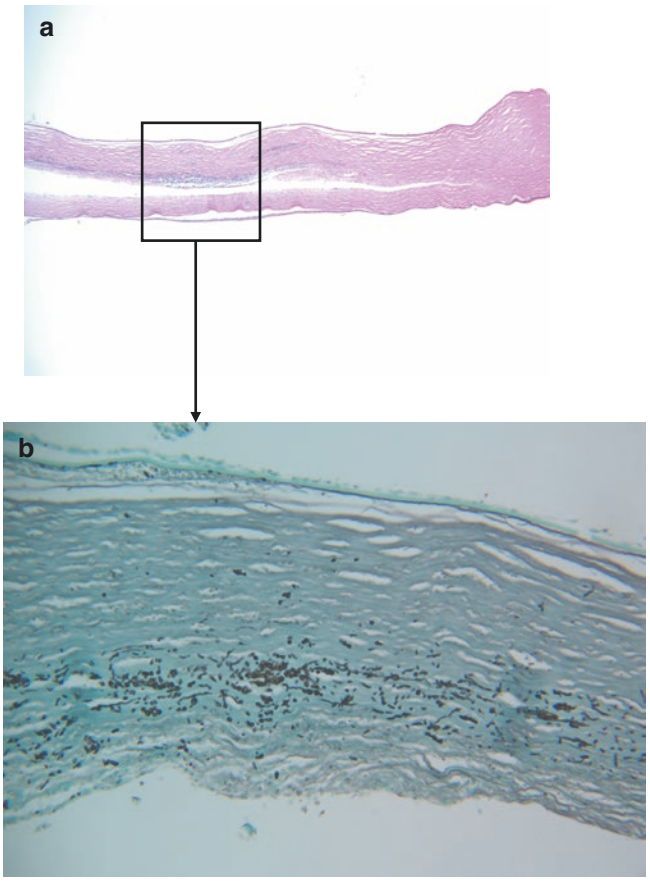

Fig. 7.4 (**a**) PAS stain of LASIK flap. (**b**) GMS stain with evidence of intrastromal hyphae. Courtesy of Dr. Douglas Buxton. New York Eye and Ear Infirmary

recommendations in the ASCRS white paper on infections after LASIK [81]. Initial treatment in all cases (described below) should be modified based on culture and scraping results and clinical response to therapy. Irrigation of the flap interface with an appropriate antibiotic solution (fortified vancomycin 50 mg/mL for rapid-onset keratitis and fortified amikacin 35 mg/mL for delayed-onset keratitis) may be helpful. For rapid-onset keratitis, the recommendation is to use a fourth-generation topical fluoroquinolone such as gatifloxacin 0.3% or moxifloxacin 0.5% given in a loading dose every 5 min for three doses and then every 30 min, alternating with an antimicrobial that is rapidly bactericidal and has increased activity against Gram-positive organisms, such as fortified cefazolin 50 mg/mL every 30 min. In patients who work in a hospital environment, there is an added risk for methicillin-resistant *Staphylococcus aureus* (MRSA). In these patients, the recommendation is to substitute fortified vancomycin 50 mg/mL for cefazolin every 30 min to provide more effective therapy against MRSA. In addition, the use of oral doxycycline 100 mg twice a day to inhibit collagenase production and also discontinuation of corticosteroids is advocated. For delayed-onset keratitis, the recommendation is to begin therapy with amikacin 35 mg/mL every 30 min, alternating with a fourth-generation fluoroquinolone (gatifloxacin 0.3% or moxifloxacin 0.5%) every 30 min, starting oral doxycycline 100 mg twice a day, and discontinuing corticosteroids [81]. It should be noted that the recommended initial treatment is ineffective against fungal infections. The treatment for fungal infections is initiated after positive smears or cultures. Topical voriconazole has recently been reported to be an effective treatment for both post-LASIK *Acanthamoeba* and fungal keratitis [1]. Also note that medical treatment of atypical mycobacterial keratitis is often difficult. Treatment for atypical mycobacteria may include topical or oral antibiotic clarithromycin and must be changed according to the specific antibiotic sensitivity for each case [1, 13].

Several steps may help prevent infectious keratitis following LASIK. Meibomian gland disease should be treated before LASIK. Proper sterilization of instruments and intraoperative sterile techniques should be used, including sterile gloves and drapes, and disinfection of the skin and eyelids with povidone iodine. During the procedure, instruments should be sterile. Efforts should be made to avoid irrigating Meibomian secretions into the flap interface (use of a Chayet LASIK drainage ring is helpful). Suction lid specula may be helpful in removing excessive fluids and debris. Postoperatively, patients should be instructed to wear plastic protective shields and not to rub the eye. Prophylactic antibiotics are likely helpful and should be used for a few days

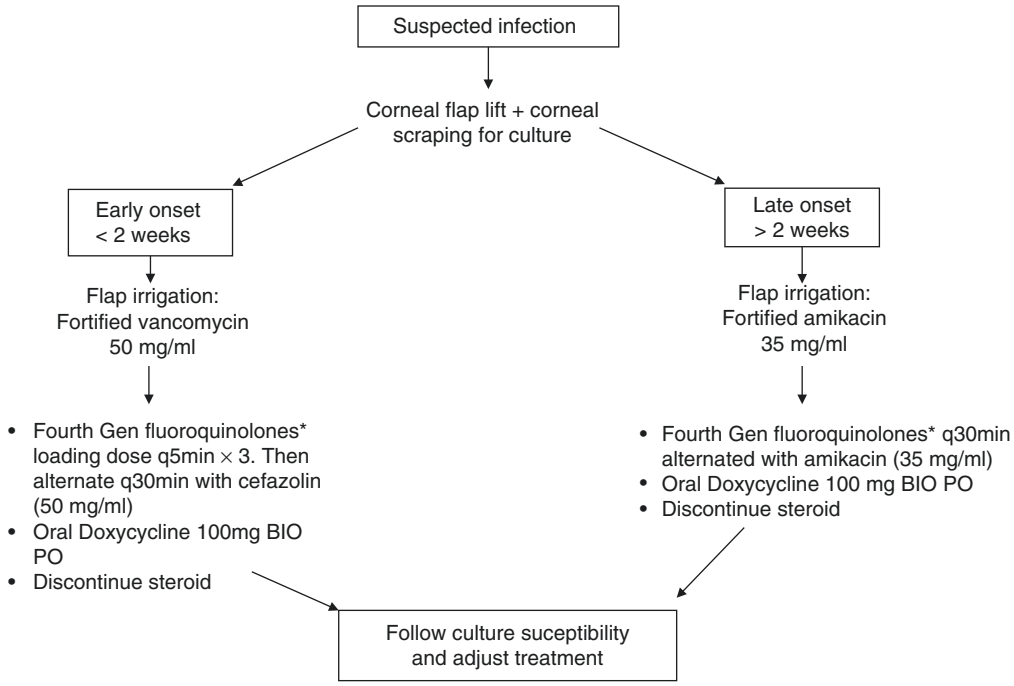

Fig. 7.5 Initial management of infections after refractive surgery. *Fourth-generation fluoroquinolones (gatifloxacin 0.3% and moxifloxacin 0.5%)

postoperatively. Patients should be instructed to avoid sleeping with pets and do gardening or swimming in the perioperative and early postoperative period. Patients with dry eyes should be instructed to use frequent artificial tears, or, if indicated, punctal plugs may be placed.

7.1 Review of Published Literature

We have systematically reviewed published case reports of infection occurring after LASIK and examined the associations between the microbiologic profile of the infection, risk factors for infection, presentation of symptoms and signs, treatment strategies, and the severity of reduction in visual acuity. An original article was published by Chang et al. in Survey of Ophthalmology [20]. We update and reproduce relevant details below. A total of 179 infections involving 167 patients were described in 60 articles analyzed. Of all 167 patients, 76 were referrals. Twenty-eight patients had bilateral infection, and unilateral infection occurred in 139 patients. Ninety percent of infections occurred after primary LASIK.

7.1.1 Onset and Frequency of Infection

Out of the reported cases, identified from the literature, on infectious keratitis after refractive surgery [16–81], 32% had symptom onset within 7 days of the last refractive procedure. The mean time of presentation in this early-onset group was 2.7 ± 4.2 days (range, 0–7 days). Gram-positive bacteria were cultured in 53.7% of the infections. Of which during this time period, the predominant reason for infection was of bacterial origin, Gram positive being one of the highest percentage (53.7%), *S. aureus*, *S. pneumoniae*, *S. viridans*, *S. epidermidis*, *Rhodococcus*, and *Nocardia*. Other infections identified at similar time periods, but with lower incidence rates, were *Candida* and atypical mycobacteria (10% and 5%, respectively).

As time from the onset of symptoms extends, slower organisms find an encouraging environment for growth, changing the infectious etiology. For cases that lasted for more than 10 days, atypical mycobacteria appeared in more than half of them. The majority of ocular infections caused by mycobacteria are from the atypical mycobacteria group. Of this group, only six species have been reported to cause LASIK-related infectious keratitis. Four of the six mycobacteria that have been involved in LASIK infections are rapid growers, *M. chelonae* and *M. fortuitum* (both Runyon type IV) being the two most common. The other two, *M. terrae* and *M. szulgai*, are slow growers. The variation of clinical symptoms is significant when comparing slow-growing versus fast-growing mycobacterium. Hence, this underscores the importance of late-onset symptoms after LASIK with atypical mycobacteria and its wide range period of presentation from 2 to 14 weeks after surgery. This is in contrast to the shorter period of time to clinical onset of symptoms for bacteria and even fungus. In the case of fungal keratitis, even

Table 7.1 Frequency of infection after LASIK

	Frequency of infection (number of cases/total)
Miller et al. (ARVO abstract) [22]	1.50% (1/1679)
Pirzada et al. [23]	1.20% (1/83)
Dada et al. [24]	0.20% (1/500)
Stulting et al. [25]	0.19% (2/1062)
Perez-Santonja et al. [26]	0.12% (1/801)
Lin and Maloney [27]	0.10% (1/1019)
Seedor et al. (ARVO abstract) [28]	0.02% (1/6312)
Gimbel et al. [29]	0 (0/2142)
Kawesch and Kezirian [30]	0 (0/290)
Price et al. [31]	0 (0/1747)

though it presents with an indolent course, it most often manifests itself clinically within 24–36 h after trauma as with bacterial etiologies.

The frequency of LASIK infection reported in several case series varied from 0.02 to 1.5% [1, 24–29]. Several large LASIK case series have reported no infectious complications (Table 7.1) [22–31].

7.1.1.1 Characteristics of Infection

The presenting signs and symptoms of infectious keratitis in the setting of refractive surgery are pain, blurred vision, photophobia, redness, foreign body sensation, and discharge. Information about specific presenting symptoms was available for 130 of the eyes infected after LASIK. Fifty-eight of the 130 eyes presented with redness (44.6%), 49 (37.7%) had pain, 41 (31.5%) had decreased or blurry vision, 31 (23.8%) had photophobia, 22 (17%) presented with irritation, 9 (7%) complained of discharge, and 12 (9.2%) were asymptomatic.

Corneal infiltrate was present in 173 of 179 (96.6%) eyes. Of the eyes without infiltrate, pain, photophobia, and discharge were the presenting symptoms. Twelve (6.94%) infiltrates were entirely within the lamellar flap; 140 (80.9%) were found in the interface; 3 (1.73%) were located in the stroma; 8 (4.6%) are involved the flap, interface, and stroma; and 6 (3.47%) are involved the flap margin and adjacent cornea (data missing for 6 eyes). Thirteen of 173 (7.5%) eyes were noted to have ulcers, and 5 (2.8%) had abscesses. Anterior chamber (AC) reactions were documented in 38 (22%) eyes, and 51 (29.5%) new-onset epithelial defects were found on initial presentation. Infiltrates were present in all eyes without epithelial defects. Flap separation was noted in 11 (6.3%) eyes, and 8 (4.6%) had epithelial ingrowth on presentation. One case of endophthalmitis was reported. In 12 (6.9%) cases, the lamellar flap melted due to the infection.

Gram-positive infections are more likely to be present with pain and discharge than other microorganisms. They are also more strongly associated with epithelial defects, flap separation, and anterior chamber reactions. Fungal infections are significantly more likely than others to present with redness and tearing. Mycobacterial infections were not significantly associated with a particular symptom or sign, but some reports have described the crack windshield appearance of these infiltrates (Fig. 7.6.). Decreased vision, photophobia, and irritation were nonspecific symptoms of infection that were not associated with any particular microorganism.

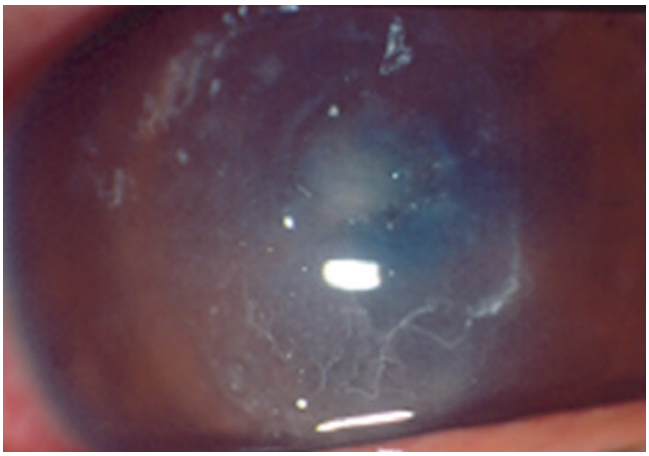

Fig. 7.6 Cracked windshield appearance of corneal infiltrate in atypical mycobacterial infection

7.1.2 Microbiological Profile

Infections caused by a single Gram-positive organism were found in 29 (17.16%) of the 169 eyes that were cultured and included *S. aureus*, *S. pneumoniae*, *S. viridans*, *S. epidermidis*, *Rhodococcus*, and *Nocardia* (Table 7.2). Fungus, such as *Fusarium*, *Aspergillus*, *Curvularia*, and *Scedosporium*, was the sole cause of infection in 25 eyes (five were not further classified). Seventy-four mycobacterial infections that were due to *M. chelonae*, *M. abscessus*, *M. szulgai*, *M. fortuitum*, and *M. mucogenicum* were found. There were four polymicrobial infections. One of the patients had a viral infection, due to *herpes virus simplex*. Twenty-seven cultures were sterile.

7.1.2.1 Outcomes and Sequelae

Final visual acuity was available in 164 of the 179 eyes. Clinically nonsignificant reductions in visual acuity occurred in 100 (55.8%) eyes, 31 (17.3%) had moderate reductions, and 33 (18.4%) suffered severe reductions in visual acuity. Thirty-seven percent of infections resulting in nonsignificant reductions in acuity were caused by Gram-positive bacteria, 47% by mycobacterium, and 4.0% by fungus, and 4.0% were polymicrobial and 8% were culture-negative.

Of the eyes with moderate visual acuity reduction, 29.0% infections were due to Gram-positives, mycobacterium was

Table 7.2 Microbiological profile

Organism type	Number of eyes
Gram-positive bacteria	29
S. aureus	19
S. pneumonia	3
S. viridans	2
S. epidermidis	2
Nocardia	2
Rhodococcus	1
Fungus	25
Fusarium	5
Aspergillus	6
Curvularia	2
Scedosporium	1
F. oxysporum and Galactomyces geotrichum	1
Candida	5
Not specified	5
Mycobacterium	74
M. chelonae	45
M. abscessus	8
M. szulgai	5
M. fortuitum	2
M. mucogenicum	2
M. aurum	1
not specify	11
Pseudomonas aeruginosa	4
Acanthamoeba	1
Polymicrobial	4
S. epidermidis and Fusarium solani	1
S. epidermidis and Aspergillus	1
S. epidermidis/Curvularia/AFB	1
Staphylococcus and M. chelonae	1
Herpes virus simplex	1
Others	2
Negative culture	27

found in 48.4% eyes, 9.7% were culture-negative, 9.7% was fungal, and 3.2% were not cultured. Gram-positives caused 3 (9.1%) infections in the severe reduction group, 6 (18.18%) were due to fungus, 14 (42.42%) were mycobacterial, 3 (9.1%) were caused by pseudomona, 2 (6.1%) were polymicrobial, 3 (9.1%) eye was culture-negative, and 2 (6.0%) eyes were not cultured.

Of the 32 Gram-positive infections for which information was available, including polymicrobial infections involving Gram-positive organisms, the mean final Snellen VA was 20/45. The mean visual acuity of eyes after fungal infections was 20/297, and after mycobacterial infections, the mean acuity was 20/55. Fungus was significantly associated with severe reductions in visual acuity ($p = 0.002$).

Twenty-three total keratoplasties, including 2 lamellar keratoplasty and 21 penetrating keratoplasties, were performed. Fourteen were performed for therapeutic reasons, and 9 were performed for optical reasons (scarring and irregular astigmatism). Eight of the 14 therapeutic keratoplasties were performed for persistent, worsening infiltrate despite 2–12 weeks of intensive medical therapy, 3 keratoplasties were performed after perforation after 3–4 weeks of medical therapy, 1 was performed for corneal thinning and progression of infection after 7 months, and there was no indication available for 2 keratoplasties.

Four percent of the eyes were noted to develop epithelial ingrowth after resolution of infection. Information about scarring and irregular astigmatism was available for 81 eyes, after excluding those with therapeutic penetrating keratoplasty.

Conclusion

Although infection after LASIK is a rare complication, serious consequences such as moderate or severe reductions in visual acuity are common after infection. It may be difficult in some cases to distinguish between infection and diffuse lamellar keratitis. However, we emphasize that a high index of suspicion must be maintained whenever inflammation persists after LASIK surgery or a corneal infiltrate develops. Treatment should not be empirical. Cultures and smears should be performed after flap lifting and aggressive topical antibiotic therapy initiated. The initial treatment should be modified based on culture and scraping results and clinical response to therapy.

Take-Home Pearls

- A high index of suspicion for infections must be maintained whenever interface inflammation persists or a corneal infiltrate develops after LASIK.
- Early-onset (<2 week after LASIK) infections are usually due to Gram-positive bacteria. Late-onset infections are usually due to atypical mycobacteria.
- *Acanthamoeba* keratitis is often misdiagnosed in post-LASIK infections and more often requires therapeutic keratoplasty.
- Clinical examination is key to differentiate infectious keratitis from DLK after LASIK surgery.
- Early lifting of corneal flap for microbiological tests (smear and cultures) precedes aggressive topical antibiotic therapy.
- Cultures for fungus and atypical mycobacteria should not be neglected.
- Initial therapy may be modified based on culture results and clinical response.
- The most important factor within our control is prevention of infection.

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Diffuse Lamellar Keratitis (DLK)

8

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Core Messages

- DLK is an early postoperative complication appearing as an inflammatory response initially in the corneal stroma followed by the flap interface.
- Occurrence is infrequent.
- Postoperative examination at 1 day after the LASIK procedure is usually diagnostic.
- Careful cleaning techniques and avoidance of contaminants may reduce outbreaks.
- Treatment of stages 1 and 2 includes aggressive topical steroids and careful daily monitoring.
- Treatment of stage 3 includes lifting the flap, gentle rinsing, and careful daily monitoring thereafter.

8.1 Background

LASIK surgery continues to be a popular and effective refractive surgery option for patients. LASIK is a safe and effective alternative to spectacle and contact lens correction of refractive error, but eye care providers must be familiar with potential complications. Diffuse lamellar keratitis (DLK) is an uncommon complication that can occur in the early postoperative period. This complication can cause scarring and an adverse visual outcome. Once considered a mystery, much more is now understood regarding the etiology and treatment of this disease. Understanding the time course of the disease, along with proper identification, staging, and intervention, can help eliminate visual loss associated with this condition.

This early post-LASIK inflammatory syndrome was first reported at the October 1997 American Academy of Ophthalmology (AAO) meeting by Smith and Maloney. Their findings were later published in the March 1998 issue of *Ophthalmology* [1]. This condition was characterized by a whitish, granular, diffuse, culture-negative lamellar keratitis occurring in the first few days after surgery. In some patients' eyes, the inflammation would disappear spontaneously, while in some the condition worsened, followed by flap melt, scarring, and adverse visual outcome. This initial report documented 13 eyes with this condition, which the authors termed "diffuse lamellar keratitis."

Other early reports at the 1998 ASCRS meeting also described cases of this peculiar inflammatory reaction occurring in the lamellar interface shortly after LASIK. Names such as "shifting sands," "sands of the Sahara," "PLIK (post-LASIK interface keratitis)," "NSDIK (nonspecific diffuse intra lamellar keratitis)", and "DIK (diffuse intralamellar keratitis)" were applied to the condition [2, 3]. Some of these names like the shifting sands and sands of the Sahara tried to describe the appearance of the condition, which was whitish, granular, with the appearance of waves of increased density.

DLK can still be a troublesome complication after LASIK. It can occur after uneventful surgery and progress quickly. Patients with this rare complication can develop the typical cascade of problems despite treatment.

8.2 Etiology and Prevalence

DLK is an inflammatory response in the corneal lamella. Its typical pathologic characteristic is inflammatory cell infiltration in the lamella. There has been considerable focus on the etiology of DLK. Contaminants in the lamellar interface introduced at the time of surgery may stimulate the condition in some patients. Oil, wax, metallic, and other foreign particles in the LASIK interface have been documented by investigators using scanning and confocal and electron microscopy and liquid chromatography [3]. Other cases seemed to be associated with epithelial defects at the time of surgery [4]. It has also been proposed that DLK represents a hypersensitiv-

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ity reaction to bacterial cell proteins that have accumulated on the autoclaved instruments. The bacteria multiply on the wet instruments or the autoclave overnight [5]. While the sterilization kills the bacteria, the cell walls persist on the instruments, and this material is transferred to the corneal interface. Avoiding the use of stagnant fluids in instrument cleaning and sterilizing protocols has been shown to minimize the occurrence of DLK [6]. Wiping the microkeratome blades with alcohol before mounting may also reduce the occurrence of DLK. One study showed that wiping 100% alcohol on the blade with a merocell spear and then rinsing with balanced salt solution (BSS) before mounting may remove unwanted substances from the manufacturing or sterilization process [7].

When the LASIK flap is created with the femtosecond laser versus a microkeratome, there may be greater inflammation. A study comparing corneal flaps made with a femtosecond laser with those made with a mechanical microkeratome in rabbits measured early postoperative inflammation [8]. Inflammatory cell infiltration in the central cornea and at the peripheral interface was significantly greater in the femtosecond group than the microkeratome group at 4 and 24 h postoperatively. This DLK-like inflammation may require stronger anti-inflammatory drugs to be used postoperatively. However, recent biomechanical studies show improved healing and improved outcomes in vision in general with the femtosecond laser flap creation compared with blade-assisted flap created [9].

It is also known that epithelial defects, either intraoperatively or postoperatively, can cause acute or late-onset DLK. One study evaluated six DLK cases after an epithelial defect and showed alterations in the keratocyte phenotype. Not all cases showed inflammatory cells in the flap interface and may have originated from sterile epithelial stromal or inflammatory cell-stromal cell interactions [10].

Other proposed sources that may cause DLK include betadine, BSS, environmental agents, lubricant, topical medications, benzene, contaminants from eyelids such as meibomian gland secretions, laser thermal effect, or talc. What is clear only is that no one source is responsible for the condition.

Confocal microscopy has been used to try to identify the pathogenesis of DLK [11]. In this evaluation, in stage 1 and 2 DLK, the epithelium, posterior stroma, and endothelium were found to be normal. In the lamella in front of the incision, many round-or oval-shaped cells with diameters approximately 12–20 μm were detected. The number of cells varied between the eyes with stage 1. Corneas with stage 2 DLK had dense infiltrates. The cells had eccentric, highly reflective nuclei and less reflective intracellular structures, were mostly mononuclear, and were distributed diffusely or arranged in lines. In the lamella, clusters and lines of small, highly reflective, irregular-shaped cells 8–10 μm in diameter were reportedly seen. They were similar to granulocytes of lymphocytes. Seven days postoperatively, these cells almost disappeared. If stage 3 DLK developed, it appeared from 3 to 5 days postoperatively, and more dense infiltration and more highly reflective shape materials showed in the lamella. One microscopist stated this appeared as an aggregation of decayed cells, most likely granulocytes and was noticed clinically and by confocal microscopy [12].

In those rare corneas that went on to stage 4 DLK, it developed 5–7 days postoperatively. Anterior stromal structure was unclear at this level of inflammation, with highly reflective and folded corneal flaps seen and highly reflective scarring in some.

The prevalence of DLK has been minimally studied. One study out of Canada over a 2-year period of time reported DLK incidence of 0.67 cases per 100 procedures ($n = 72{,}000$ procedures), with 64% occurring in outbreaks. The outbreaks decreased dramatically from the first year to the end of the second year (72–40%), indicating perhaps that reporting and following prevention and control measures that were recommended may have helped reduce the outbreaks [13]. DLK can also occur in patients undergoing small-incision lenticule extraction [14].

8.3 Identification and Appearance

Examining the patient at day 1 is critical in identifying DLK. The cellular reaction will almost always be apparent in the first 24 h. It will appear as a fine white granular reaction in the lamellar interface and on the first day is most often in the periphery. It is important to differentiate DLK from punctate epithelial keratopathy (PEK) which can appear on day 1 as well. Swelling of the LASIK flap (flap edema) or epithelial edema may look similar. Using a small amount of fluorescein and paying close attention to where the slit lamp is focusing should help eliminate confusion. It also may be confused with meibomian gland debris and/or tear film debris which occasionally may get trapped under the patients' flaps. Meibomian gland debris looks more grayish in color and may shine more than the flat-white granular appearance of DLK.

It is uncommon to see DLK after the first 24 h without a causative agent. Causes of late-onset DLK have been reported. One case described onset of DLK 3 years after uneventful bilateral LASIK in one eye of a 56-year-old woman. There was no epithelial defect, no trauma, and no other apparent cause, suggesting that DLK can occur several years after LASIK without obvious cause. This particular case was identified as stage 3 and responded well to topical steroids [15]. Another case reported a 58-year-old male Caucasian who developed delayed-onset diffuse lamellar keratitis, seemingly in the absence of an epithelial defect,

25 days following an enhancement LASIK procedure to his right eye. In this case, treatment was complicated by the fact that the patient was a steroid responder and experienced an intraocular pressure rise that had to be managed with pressure-lowering drops [16]. It has also been shown that DLK can be associated with viral pseudomembranous keratoconjunctivitis. One case of a 47-year-old woman developing DLK 2 years after uneventful LASIK indicates that the plane created by the microkeratome remains unhealed for a long time. Aggressive treatment with topical steroids resolved the inflammation; corneal clarity and visual acuity were completely restored in this case [17].

8.4 Staging

Four stages have been used to categorize diffuse lamellar keratitis. Once DLK is identified, a staging of severity and location can then be made. The following staging system has proven helpful [18].

Stage 1: Stage 1 is defined by the presence of white, granular cells in the periphery of the lamellar flap, with sparing of the visual axis. This is the most common presentation of DLK at day 1 and, with careful inspection, may be present in as many as 1 in 25–50 cases (Figs. 8.1 and 8.2).

Stage 2: Stage 2 is defined by the presence of white, granular cells in the center of the flap, involving the visual axis. This appearance, occasionally present at day 1, is more frequently seen on day 2 or 3, the result of central migration of cells along the path of least resistance, giving it the so-called shifting-sands appearance. This occurs in approximately 1 in 200 cases (Figs. 8.3 and 8.4).

Stage 3: Stage 3 DLK appears as the aggregation of more dense, white, clumped cells in the central visual axis, with relative clearing in the periphery. This is often, but not always, associated with a subtle decline in visual acuity by one or two lines. Often, but not always, this is accompanied by a subjective description of haze by the patient. The cellular reaction collects in the center of the ablation and may settle slightly inferior to the visual axis with gravity. The frequency of Stage 3 DLK may be as high as 1 in 500 cases (Figs. 8.5 and 8.6).

Identification of this stage 3, a more intense, central accumulation of cells, is important to reducing occurrence of an unwanted outcome. If left untreated, a significant portion of these eyes will go on to develop permanent scarring. We have found that lifting the LASIK flap soon following the

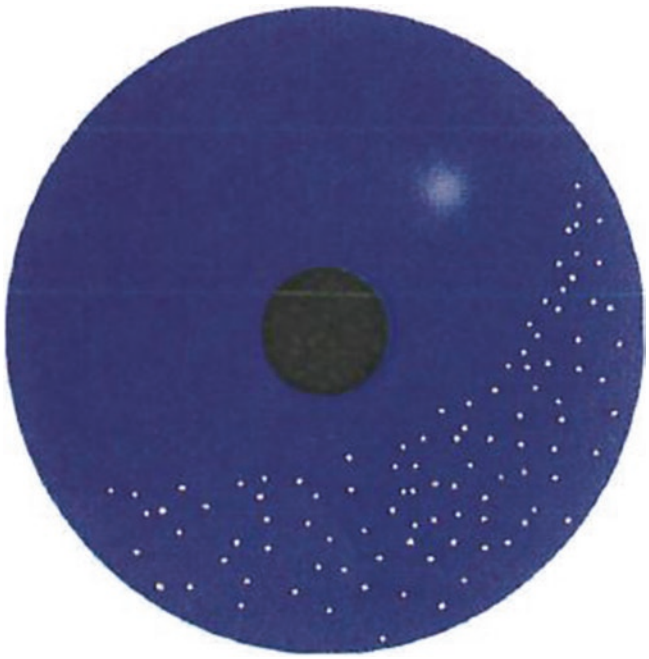

Fig. 8.2 Cells are mainly in the periphery and in the stroma in stage 1 DLK

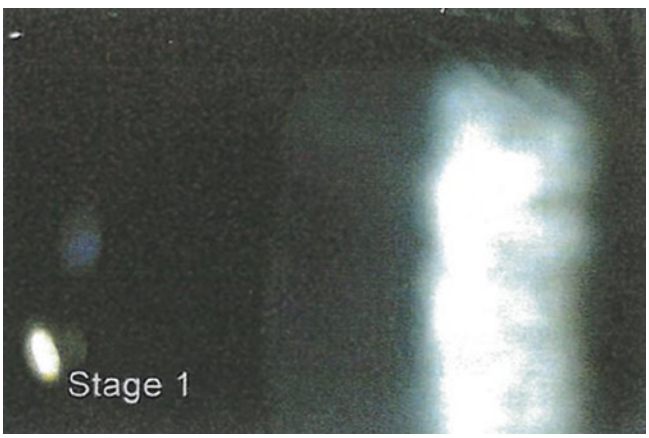

Fig. 8.1 Stage 1 DLK is characterized by fine white cells in the stroma, usually in the inferior periphery. No clumping of cells in the interface or cells in the central portion of the cornea is present

Fig. 8.3 Stage 2 DLK is characterized by fine white cells in the stroma that now extend to the center of the cornea. No clumping of cells in the interface of the cornea is present

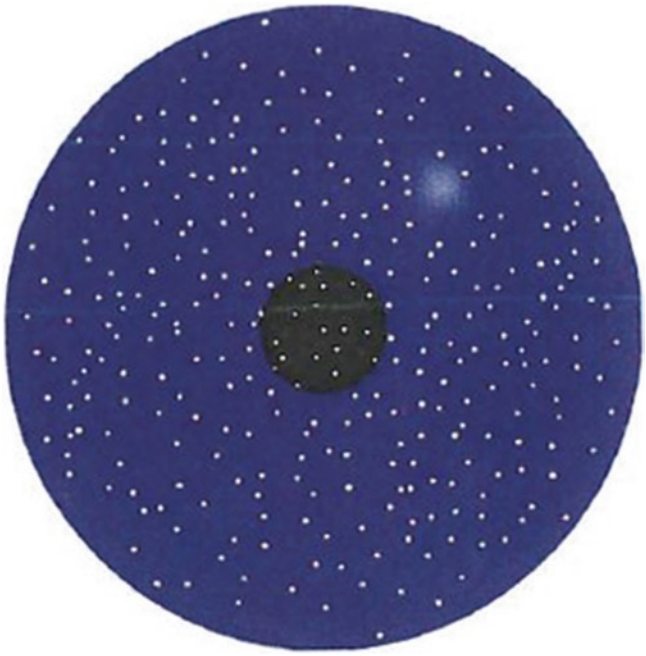

Fig. 8.4 Cells are distributed throughout the cornea, even centrally and yet are still in the stroma in stage 2 DLK

Fig. 8.6 Cells are clumping paracentrally and are now in the LASIK flap interface in Stage 3 DLK

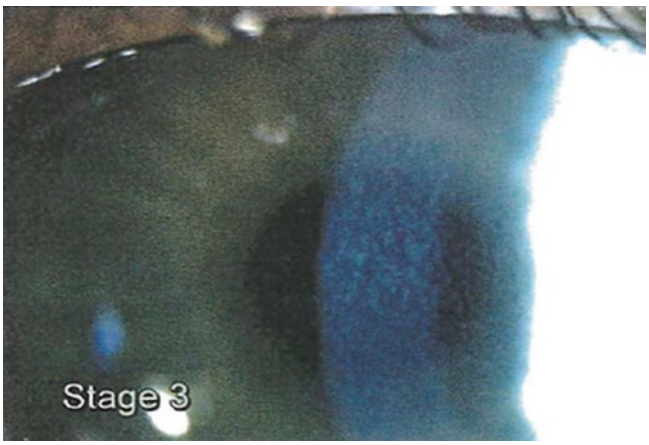

Fig. 8.5 Stage 3 DLK is characterized by fine white cells that have now clumped slightly centrally or just inferior to the center of the cornea. They are no longer only in the stroma but have now layered slightly in the LASIK interface. At this stage, they may actually start to clear in the periphery. This is the most important stage of DLK to recognize

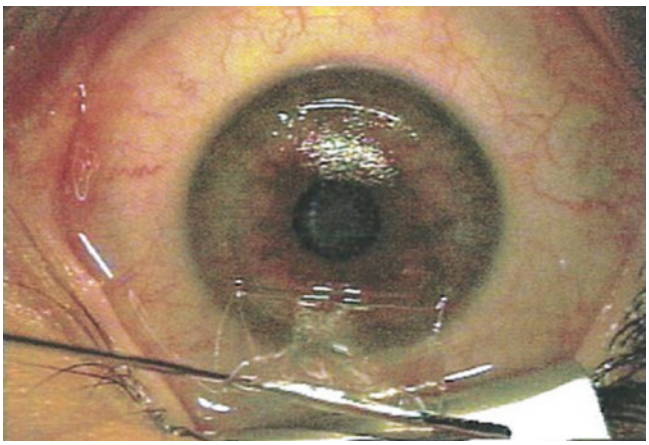

Fig. 8.7 Lifting of the LASIK flap and gentle irrigation is helpful in stage 3 DLK

appearance of stage 3, or when threshold DLK is present, can effectively blunt the inflammatory response and prevent permanent scarring from occurring (Fig. 8.7). No eyes in the series of this group of surgeons' 10,000 patients had any loss of best-corrected visual acuity (BCVA) attributable to DLK when the interface was irrigated promptly at the identification of stage 3 [18].

Stage 4: Stage 4 DLK is the rare result of a severe lamellar keratitis with stromal melting, permanent scarring, and associated visual morbidity. The aggregation of inflammatory cells and release of collagenases results in fluid collection in the central lamellae, with overlying bullae formation and stromal volume loss. A hyperopic shift with irregular astigmatism due to central and paracentral tissue loss, along with the appearance of corrugated mud cracks, is an ominous sign. Lifting and irrigation at this point is of little benefit and may actually be harmful. Lifting and irrigation at stage 4 may result in additional stromal volume loss if aggressive tissue manipulation is performed. Proper identification, grading, and appropriate intervention may prevent this from occurring. The incidence of a severe stage 4 DLK is approximately 1 in 5000 (Figs. 8.8 and 8.9).

Fig. 8.8 Stage 4 DLK is characterized by scarring and loss of stromal volume

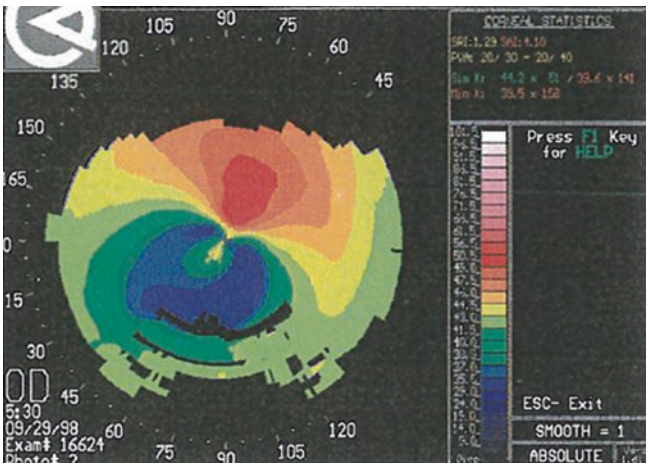

Fig. 8.9 Topography from stage 4 DLK can often show irregular astigmatism from extra flattening in the area of stromal volume loss. Often this will improve over a year after the DLK episode

8.5 Intervention and Treatment

Although each case may show a different level of severity or inflammation, the time course of diffuse lamellar keratitis is consistent. The experience of these authors has shown that the cellular reaction is nearly always present at postoperative day 1 and peaks at approximately day 5. DLK can best be thought of as a threshold disease; after a certain level of inflammation is reached, it is likely that there will be permanent scarring.

Stage 1 and 2 DLK will follow a self-limited course, resolving in 7–10 days. We manage both stage 1 and stage 2 by using an aggressive course of topical steroid drops, usually prednisolone acetate 1%, one drop administered every hour while awake, and by using a steroid ointment applied to the eye at bedtime. Of note is that no randomized study has concluded that this is of benefit. Prompt follow-up of the patient in 24 and 48 h will identify the small number of cases that will progress to stage 3.

If stage 3 is identified, management becomes more aggressive. Management involves either more aggressive topical and oral steroids [19] or, as we prefer, lifting the flap and debulking the inflammatory reaction by careful irrigation of the bed and undersurface of the cap. This should be done when stage 3 is identified, which is usually at postoperative day 2 or 3 (48–72 h post operatively). This should blunt the inflammatory response and it is hoped that this will prevent permanent scarring. If the flap is lifted too soon, then the cells are still in the stroma, and lifting will not debulk the cells.

Lifting the flap is performed by the following methods. First, delineate the edges of the flap with a blunt spatula. Lift and retract the flap peripherally to its hinge. This usually is relatively easy in the first 72 h. Once the flap is retracted, gently but thoroughly rinse the bed and undersurface of the cap with balanced saline solution (BSS) on a blunt-tipped cannula (Fig. 8.7). Gently cleanse the bed and cap with a lightly moistened Merocel sponge. Aggressive scraping of the flap or stromal bed and using bladed instruments should be avoided. After gentle rinsing and cleansing, carefully reflect and float the flap back into position and allow the flap to dry in place. Maintain the patient on the aggressive topical steroid use (the authors recommend one drop of prednisolone acetate every hour while awake) while closely monitoring over the next several days. Often the clinical picture at 24 h after this flap lift shows significant flap edema and not much change in the level of inflammation. As the cellular reaction resolves, this may be tapered.

Lifting the flaps of those eyes showing any stage of DLK at day 1 may be tempting but should be avoided. This would miss the peak inflammatory reaction and would most likely be overtreatment of the majority of stage 1 and 2 cases that would have been self-limited or responsive to topical treatment. However, waiting until day 5 or 6 will risk the development of stage 4 DLK, which may result in permanent scarring. Thus, lifting stage 3 DLK at 48–72 h after the procedure is most effective.

If the rarest and more severe stage 4 DLK has occurred, then lifting the LASIK flap is of little benefit. It may actually add to stromal volume loss as the collagenolytic enzymes have begun to digest the collagen, and lifting the flap may remove more of the soggy, boggy collagen.

Some cases of DLK may be atypical such as the aforementioned late-onset DLK or those cases associated with pain, decreased vision, or more dense infiltrates. Be aware that these cases may not be true DLK or may be infectious in etiology. When in doubt, appropriate culture of the LASIK flap, undersurface, and bed, as well as prompt institution of antibiotic therapy is important.

8.6 GAPP Syndrome

The GAPP syndrome (good acuity plus photophobia) is a characteristic and transient complication of femtosecond LASIK [20]. This is not DLK but should be mentioned here as an early complication to LASIK performed with the femtosecond laser. This has also been referred to as transient light sensitivity. It is bilateral and appears 6–8 weeks after femtosecond LASIK. Its only symptom is an extreme sensitivity to light without loss of visual acuity. Some patients report pain on upgaze. One study reported an incidence of 1.1% ($n = 5667$) of this transient light sensitivity after LASIK performed with femtosecond flap creation. The average age of patient in this study was 41 and about ½ were women. Onset of symptoms was from 2 to 6 weeks after uneventful LASIK. Most patients' symptoms resolved within 1 week of beginning topical steroid treatment. Patients' symptoms were prolonged if there was a delay in treatment. This study also indicated that reducing raster and side-cut energy settings by an average of 24–33% significantly reduced the incidence of this syndrome [20].

8.7 Steroid-Induced Glaucoma After LASIK

Another complication associated with DLK and its treatment is steroid-induced glaucoma after LASIK. Since treatment of DLK involves aggressive and frequent use of steroid, the possibility of steroid response including elevated IOP should be considered. While treating the DLK must be primary, steroid-induced glaucoma must be considered a possible secondary unwanted effect. In a study reported in 2002, six eyes of four patients who had DLK develop after uneventful LASIK were treated with aggressive corticosteroids. All six eyes had a pocket of fluid develop in the lamellar interface associated with a steroid-induced rise in intraocular pressure. The increase in pressure caused transudation of aqueous fluid across the stroma that accumulated in the flap interface. However, because of the interface fluid, IOP was normal or low measured by central corneal Goldmann applanation tonometry. Only by measuring the pressure peripherally several months later was a high IOP noted. All six of these eyes developed visual field defects, and three eyes had severe glaucomatous optic neuropathy and decreased visual acuity [21].

8.8 Infectious Keratitis Versus Noninfectious Keratitis

It is important to differentiate microbial keratitis from DLK. Microbial keratitis is a serious complication after LASIK. DLK is also serious, but is noninfectious and not treated with antimicrobial drugs. The most common signs of microbial keratitis after LASIK include ciliary and conjunctival hyperemia and whitish stromal infiltrates in the interface. These infiltrates are usually dense and grayish-white, with indistinct edges that may extend into the surrounding stroma. Corneal flap and epithelium are commonly involved, causing an epithelial defect that stains with fluorescein. This is not common in diffuse lamellar keratitis as there is no epithelial defect with DLK. In DLK any aggregate of cells occurs in the interface, despite the diffuse cells in the stroma. They are diffuse and scattered through a large area of the interface, not extending anteriorly into the flap nor posteriorly into the stroma. Symptoms of microbial keratitis after LASIK include foreign body sensation, decreased vision, pain, photophobia, redness, and tearing. It is uncommon for the patient with DLK to have any of these symptoms, especially in the early stages of the condition. When a lesion is suspected of being microbial keratitis, the corneal flap can be lifted and the stromal bed scraped for culture and laboratory diagnosis. Prompt management with appropriate antibiotics is critical with microbial keratitis as this is one of the most vision-threatening complications after LASIK. DLK can be distinguished from infectious infiltrates by clinical presentation and close follow-up [22].

Conclusion

In conclusion, eye care providers must be familiar with potential complications of LASIK surgery. DLK is an uncommon complication that can occur in the early postoperative period. Undetected or untreated, it can cause scarring and an adverse visual outcome. Increased awareness of potential contaminants as well as proper maintenance and cleaning of sterilizer water reservoirs have decreased but not eliminated the frequency of occurrence of DLK. Educating patients to the importance of early follow-up despite lack of symptoms, technical staff, and those who follow LASIK patients postoperatively is critical to identifying and treating DLK appropriately. However, occasional cases still occur, and understanding the time course of the disease, along with proper identification, staging, and intervention, can help reduce visual loss associated with this condition.

Take-Home Pearls

Staging of DLK

- Stage 1
  - Usually identified at 1 day postoperatively
  - White, granular cells in the periphery of the cornea
- Stage 2
  - May be present at 1 day postoperatively, more commonly seen 48–72 h postoperatively
  - White, granular cells in the center of the cornea
  - Shifting-sands appearance

- Stage 3
  - If present, usually seen at 48–72 h postoperatively
  - Dense, white, clumped cells in the central visual axis in the flap
  - Requires flap lifting to reduce incidence of permanent scarring
- Stage 4
  - Rare end result of a severe lamellar keratitis.
  - Stromal melting, permanent scarring, and visual morbidity.
  - Hyperopic shift, mud cracks.
  - Treatment may be of little help.

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9 Pressure-Induced Interlamellar Stromal Keratitis and Persistent Epithelial Defect (PED) Masquerade Syndrome

Sadeer B. Hannush, Michael W. Belin, and Dimitri Azar

Core Messages

- The reader must recognize that not all flap interface haze appearing after LASIK represents DLK or infection.
- Interface fluid is usually the result of elevated IOP, frequently steroid induced. The fluid may be space occupying, resulting in falsely low IOP measurements on applanation tonometry, or non-space occupying, allowing accurate pressure measurement.
- If presumed DLK does not respond to a regimen of frequent topical steroids, then consider elevated IOP as the etiology (pressure-induced interlamellar stromal keratitis).
- Management consists of discontinuation of the topical steroid and lowering of the IOP.

9.1 Introduction

DLK, or sands of the Sahara (SOS), is post-LASIK corneal flap infiltration or inflammation that was first described in 1998 by Smith and Maloney [1] in a series of 12 patients. The infiltrates typically present on postoperative days 1–3 and may be diffuse, focal, or multifocal. Another condition that may mimic DLK has been described as resulting from the accumulation of interface fluid. Slit lamp examination of these patients reveals a clear zone between the stromal bed and flap that represents a pocket of interface fluid [2–4]. In this entity, central applanation tonometry is very low as can be expected when applanating over a pocket of fluid, while more reliable methods of measuring intraocular pressure such as peripheral applanation or pneumotonometry reveal markedly elevated pressure inside the eye. In 2002, Belin et al. [5] reported a series of four patients in whom a clinical picture almost identical to classic DLK developed. All patients described onset of decreased visual acuity after the first postoperative week, all failed to improve with frequent topical steroid drops, and all had clinically significant elevated IOP. No patient exhibited any frank interface fluid or clear zone. Each patient responded with both improvement in visual acuity and decrease in interface haze, with the lowering of intraocular pressure and discontinuation of topical steroids. To describe this condition, they coined the term elevated intraocular pressure-induced interlamellar stromal keratitis (PISK) (Figs. 9.1, 9.2, 9.3, and 9.4).

The differential diagnosis to PISK includes DLK. In contrast to PISK, DLK doesn't present with interface fluid. Four clinical stages of DLK have been described, ranging from

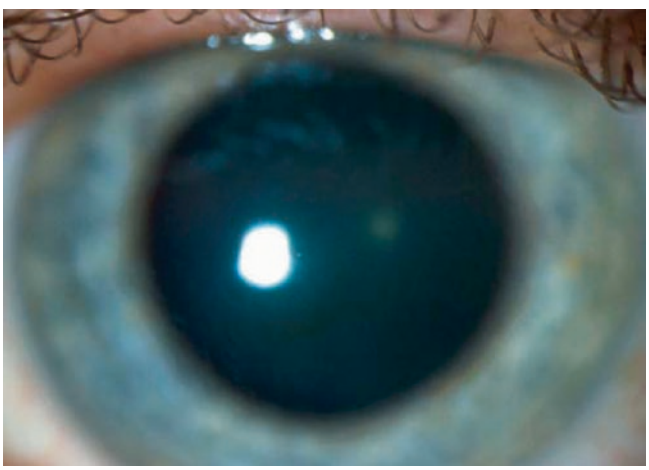

Fig. 9.1 Patient with PISK, showing mild diffuse haze

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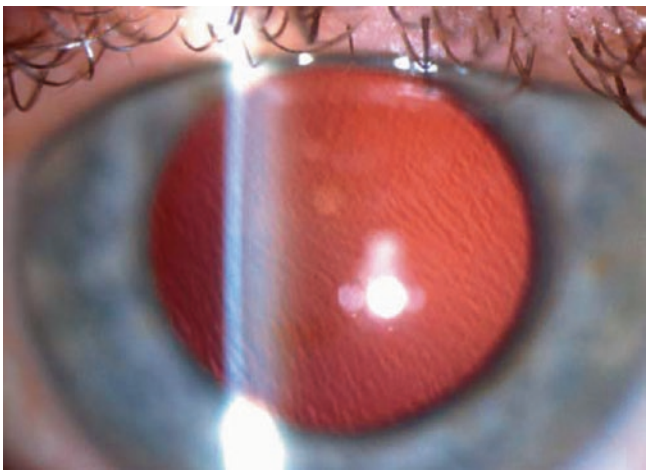

Fig. 9.2 Same patient seen with retroillumination: wavy, granular pattern mimics sands of the Sahara (SOS) in diffuse lamellar keratitis (DLK)

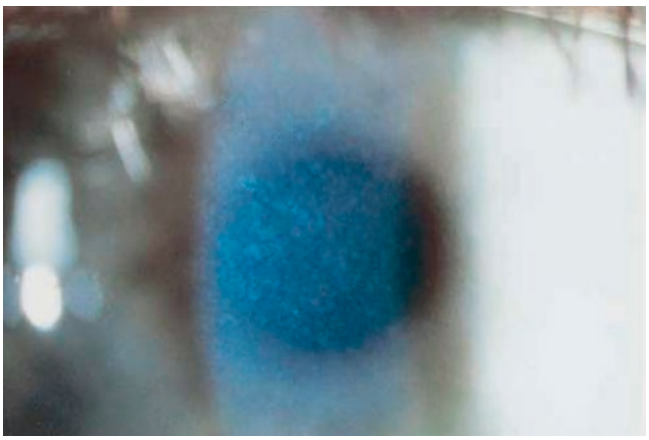

Fig. 9.3 Slit lamp photography of a patient with PISK, showing diffuse interface haze similar to mild-to-moderate DLK

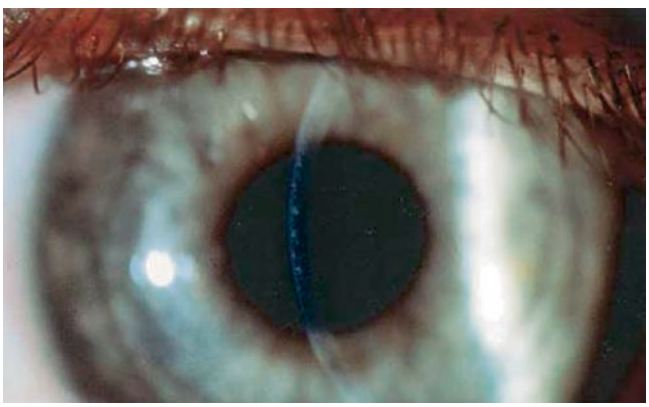

Fig. 9.4 Slit lamp photograph of same patient: narrow slit shows haze limited to the interface

nonvisually significant interface haze to severe dense infiltration associated with stromal necrosis [6]. Most cases are mild, asymptomatic, and self-limited or responsive to topical steroids. Slit lamp examination typically shows a fine granular infiltrate confined to the flap interface, often in the periphery of the stromal bed. Moderate cases are often accompanied by a decrease in visual axis. Severe cases are associated with significant interface haze, cellular aggregation, and pain. Severe cases not responding to hourly topical steroid drops may require surgical intervention to irrigate the interface, washing off the inflammatory cells and other potential inflammatory agents. Untreated, severe DLK can lead to flap melting and necrosis [7]. The incidence of DLK has been reported to range from 1 to 4%, but this almost certainly underestimates the true incidence, because very mild cases are often missed or underreported [8]. Suspected cases included metallic debris from the microkeratome or blade, sterilizer reservoir biofilms, meibomian gland secretions, bacterial endotoxins, glove talc, cleaning or disinfecting solutions, debris from surgical sponges, and epithelial debris. Rather than being caused by a single agent, DLK probably represents a common inflammatory response in the lamellar interface to a variety of stimuli.

9.2 Pressure-Induced Interlamellar Keratitis (PISK)

Since the initial report, several reports have appeared in the ophthalmic literature describing the same phenomenon. In 2009, Moya Calleja et al. described four eyes of three patients with steroid-induced interface fluid syndrome after LASIK. Slit lamp microscopy revealed in these patients an optically clear fluid-filled space between the flap and stromal bed. They also observed that pain is not a universal feature in patients with PISK [9]. In 2007, Frucht-Pery et al. [10] attributed early transient visual acuity loss after LASIK to steroid-induced elevation of IOP. The same phenomenon was described in 13 eyes by Galal et al. [11] in 2006. They concluded that what they described as interface corneal edema was secondary to elevation of IOP, which developed in steroid responders. In 2004, Norduland et al. [12] described ten eyes of six patients with late-onset interface inflammation and increased IOP where the lamellar inflammation did not resolve until the pressure was controlled. Also in 2006, Kurian et al. [13] observed swollen and enlarged cellular structures, as well as the presence of microlacunae separating the stromal collagen lamellae. Confocal microscopic examination did not show mononuclear cells and granulocytes typically seen in patients with classic DLK. The same phenomenon was previously observed by Cheng et al. in 2004 [14] in the

in vivo confocal microscopic findings of two patients with steroid-induced glaucoma after LASIK. Again, inflammatory mononuclear cells and granulocytes, seen in patients with DLK, were absent at that time. In 2003, Davidson et al. [15] described the case of a 53-year-old patient with a history of treated ocular hypertension who underwent uncomplicated LASIK surgery. The postoperative course was complicated by markedly elevated IOP induced by topical corticosteroid drops used to treat what appeared to be diffuse lamellar keratitis. Once the topical steroids were discontinued, the intraocular pressure returned to normal range with complete resolution of the corneal findings.

A late-onset DLK picture has been reported in LASIK patients, weeks, or months after surgery, in the setting of trauma, recurrent erosions, or epithelial abrasions [16–18]. PISK, on the other hand, has been reported even years after surgery. In 2012, Lee et al. [19] reported a case of PISK 9 years after LASIK in the setting of anterior uveitis, with symptoms of diffuse interface haze limited to the flap with elevated IOP and a worsening condition with topical steroids. More recently, Wong et al. wrote a case of PISK, 3 weeks after vitreoretinal surgery for rhegmatogenous retinal detachment, which in turn occurred 7 years after LASIK. An anterior segment OCT exposed a fluid layer between the residual stromal bed and the LASIK flap. It was accompanied by the well-known diffuse corneal stromal haze and raised intraocular pressure, associated with PISK [20].

The possible cause-and-effect relationship between DLK and PISK is less clear. Steroid-induced pressure elevation in nonoperated eyes is typically clinically silent and not associated with an inflammatory component. It may be that lamellar keratitis after LASIK represents a common clinical presentation for both inflammatory and noninflammatory insults to the post-LASIK eye. Alternatively, the DLK-like picture in PISK may represent a mild form of non-space-occupying interface fluid collection (microlacunae) with measureable elevated pressure. This is in contrast to space-occupying interface fluid with falsely low or normal intraocular pressure previously described in the literature. Slit lamp optical coherence tomography (SL-OCT) can be used to differentiate between space-occupying interface fluid collection and non-space-occupying interface fluid collection (Fig. 9.5) [21].

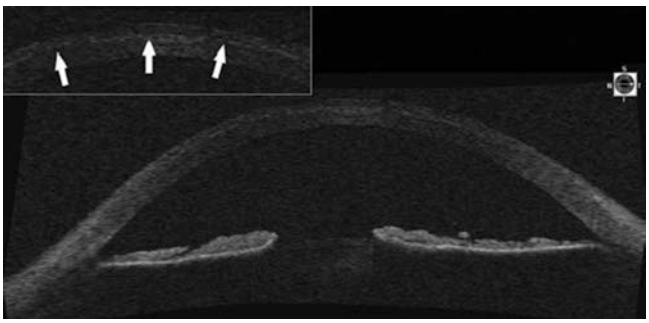

Fig. 9.5 SL-OCT image of the left eye of a patient with PISK showing exclusion of a space-occupying fluid accumulation in the interface (*arrows*) [21]

9.3 Persistent Epithelial Defect (PED) Masquerade Syndrome

Azar et al. [22] first described the case of PED masquerade syndrome in which the LASIK operated eyes exhibit epithelial defect of the LASIK flaps, extending to their edges (Fig. 9.6a,b). Four cases were reported by the team where the LASIK-induced epithelial ingrowth resembled stromal edema associated with persistent epithelial defect. PED masquerade syndrome is usually a rare complication of LASIK; however, if not diagnosed and treated in time, it can lead to irreversible vision loss. The delayed diagnosis often results from the concealment of usually subtle, epithelial ingrowth sheets by the presence of stromal edema and DLK.

Some of the clinical features present in PED masquerade syndrome include microkeratome-related flap margin involving epithelial defect that are convex shaped at the periphery, delayed reepithelialization, stromal edema, DLK and/or ulceration of the flap, comprehensive epithelial scraping, early flap lifting, flap repositioning, ironing, and possible suturing (Fig. 9.6). Fluorescein pooling is seen at the flap edge overlying epithelial growth, and confocal microscopy shows cells present on the flap interface (Fig. 9.6c). In addition to the stromal edema and superficial epithelial defect, all the four cases presented by Azar et al. also had a deep orthogonal stromal edge (>80 μm, from ablation) in which the central stroma was elevated relative to the periphery, which corresponded to their experimental rabbit model of epithelial cell migration into the stroma. Two of the patients fared similar outcomes to those of rabbits, who experienced slow melting of the stromal edema (in long term), caused by the epithelial cell-produced MMP9.

The most effective treatment for PED masquerade syndrome involves flap lifting and mechanical debridement of the ingrown cell sheets from under the flap and from the stromal bed surface, with or without the use of contact lens bandage. To prevent the regrowth of the epithelial sheets resulting from stromal hydration, the epithelial defect should not be extended to the flap margin, and the remnants of the ingrowth should be redirected toward the flap surface. Suturing is also helpful to this end.

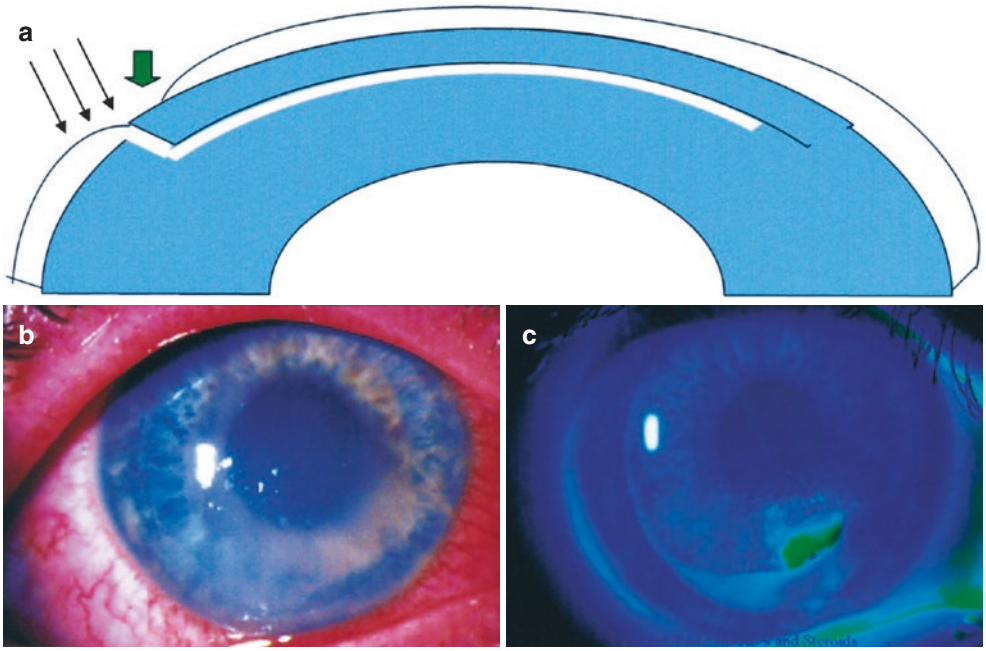

Fig. 9.6 **(a)** Diagrammatic illustration of epithelial-defect-masquerade syndrome after LASIK showing the characteristic epithelial convexity adjacent to the stromal edema in the inferior half of the LASIK flap. **(b)** Clinical appearance of epithelial-defect-masquerade syndrome. **(c)** Fluorescein staining showing an epithelial defect at the edge of the flap and arcuate fluorescein pooling below the defect corresponding to the peripheral region of the epithelial ingrowth

Conclusion

It is important to recognize that PISK occurs beyond the typical immediate postoperative period and is associated with a significantly elevated IOP. All cases respond not to topical steroid therapy, but to lowering of the IOP and a reduction or discontinuation of the topical steroids. Patients may or may not have a history of ocular hypertension. The IOP elevations may occur in some patients earlier than is traditionally associated with steroid-induced IOP elevation.

It is customary for refractive surgeons not to measure IOP on the first postoperative day for fear of causing a flap displacement. It has become too commonplace, however, not to measure IOP on later routine postoperative visits because the refractive populations tend to be a younger, healthier group that is at lower risk for ocular disease. The importance of IOP measurement and of maintaining a high level of suspicion when a DLK-like picture occurs after the first postoperative week, unassociated with other causative events (e.g., epithelial defect), and showing recalcitrant character to an increase in topical steroids, cannot be overemphasized. IOP measurement in cases of suspected DLK appearing after the first week after LASIK is strongly recommended. If elevated, lowering the pressure and discontinuing the topical steroids frequently result in resolution of the interface changes, paralleled by improvement in vision. Further, the space-occupying and non-space-occupying interface fluid collection should be discriminated with SL-OCT to avoid falsely low or normal IOP.

In the rare case of persistent epithelial defect and delayed reepithelialization after LASIK, PED masquerade syndrome must be considered in order to avoid delay in diagnosis leading to irreversible vision damage. An astute observation and early surgical intervention can save someone's world.

Take-Home Pearls

- A DLK-like picture appearing a week or more after LASIK may not be inflammatory in nature. It may represent interface fluid that may or may not be space occupying.
- PISK should be considered in the differential diagnosis of LASIK patients who develop corneal haze, even years after surgery.
- It is important to measure IOP and to maintain a high level of suspicion when a DLK-like picture occurs after the first postoperative week, is not associated with other causative events (e.g., epithelial defect), and does not readily respond to an increase in topical steroids.
- If IOP is indeed elevated, consider PISK as the etiology.
- Management consists of lowering the pressure and discontinuation of the topical steroids.
- Delayed reepithelialization with persistent epithelial defect after LASIK can lead to irreversible vision damage with delayed diagnosis. It can be subtle to detect due to the presence of stromal edema and DLK-like symptoms.

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Prevention and Management of Flap Striae After LASIK

10

Roger F. Steinert and Jorge L. Alio del Barrio

Core Messages

- Prevention measurements of flap striae should be known by the refractive surgeon.
- It is critical to differentiate between macrostriae and microstriae as their clinical implications and management are different.
- We will review the medical and surgical management of visually significant flap striae.
- Phototherapeutic keratectomy (PTK) offers an alternative approach for long-standing striae.

10.1 Introduction

An optically smooth and clear flap is critical for recovery of vision after LASIK. The anterior flap is the principal optical interface of the eye, dominating the factors influencing the recovery of vision. A smooth surface also leads to patient comfort and overall patient satisfaction with the procedure.

The preoperative assessment must include accurate assessment of the status of meibomian gland and tear production. The presence of external ocular or systemic diseases that influence the stability of the LASIK flap surface must be determined. If the tear film is not optimal, aggressive preoperative measures must be taken, including lid hygiene, tear supplementation, anti-inflammatory agents, and possibly placement of punctal plugs prior to the LASIK procedure. Prophylaxis is more effective than remedial therapy once the LASIK flap is in difficulty postoperatively.

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Operative factors can also influence the difficulties in a smooth LASIK flap postoperatively. Anesthetic drop administration should be minimized. When anesthetic is applied, following an artificial tear, instructing the patient to close the eyelids, in order to prevent drying due to lack of blinking, is advisable. Administration of vasoconstrictive agents such as phenylephrine and brimonidine (Alphagan, Allergan, Irvine CA) has been associated with flap irregularities, possibly due to effects on dryness and mucin in the tear film. If alignment marks are made with ink, they should be irrigated immediately, as most inks have an alcohol base which also disrupts the epithelium. If it is compatible with the manufacturer's recommendations, the use of a non-preserved medium viscosity artificial tear immediately prior to the passage of a microkeratome can reduce some of the frictional damage to the epithelium. In addition, minimizing the duration of elevation of the flap will reduce the potential for induced damage to the surface. Likewise, it is advisable to avoid prolonged irrigation under the flap once it is replaced, as the duration of irrigation is related to the amount of induced flap edema with subsequent striae. Likewise, excessive stroking of the flap may contribute to the development of both surface defects and striae. It is important not to let the flap surface dry at any time. Once the flap is repositioned, immediate administration of a high viscosity artificial agent such as Celluvisc (Allergan) is helpful.

The flap should also be protected against physical injury with a shield or goggles. It is important to educate the patient about the proper administration of eye drops in order to avoid disrupting the flap by pressure on the eyelids or direct trauma from an eye drop bottle tip. For the first day, in addition to the pharmacologic medications, frequent administration of an artificial tear maintains lubricity. In the hours immediately following LASIK surgery, naps longer than 1 h should be interrupted with the administration of artificial tears in order to avoid drying and adhesion of the flap to the underside of the eyelid during sleep. Most patients will have a reduction in tear film quality and/or volume for several months postoperatively, and frequent administration of artificial tears is usually

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advisable, as well as more aggressive surface treatment if deterioration of the surface is detected.

10.2 Flap Striae

Flap striae, or wrinkles, have two general types of configuration. *Macrostriae* consist of broad undulations of parallel or semi-parallel lines. This appearance is similar to a "washboard" or windswept sand (Fig. 10.1). Macrostriae are usually caused by dislocation of the flap. Careful inspection at the slit lamp will typically show a widened gutter (Fig. 10.2). Because the epithelium may have rapidly filled in this area, application of fluorescein will help show the presence of a widened gutter as the fluorescein pools. *Microstriae* have a more random pattern of fine irregularities easier seen on retroillumination. The appearance is similar to dried cracked mud or the dry cracks on a salt lake (Fig. 10.3). Microstriae have an appearance somewhat similar to prominent corneal nerves.

Fig. 10.1 Macrostriae have broad undulations similar to windswept sand

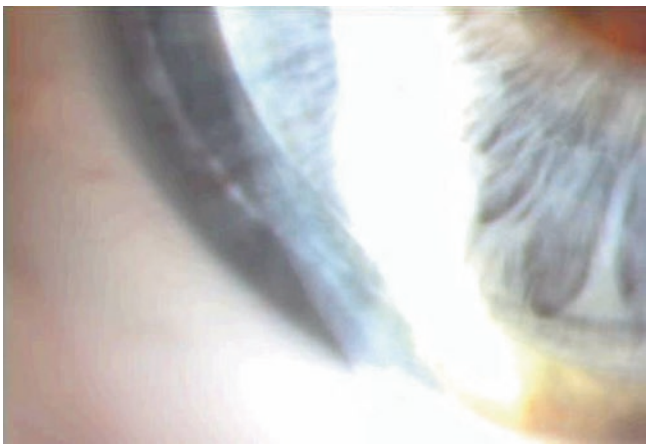

Fig. 10.2 Macrostriae are usually due to the flap slippage, which will result in a widened gutter in one area as well as the flap wrinkles

Fig. 10.3 Microstriae resemble random fine cracks seen in a dried salt lake bed

In many cases, flap slippage that results in macrostriae has no identifiable cause. However, some patients will note acute onset of unusual pain if the flap slippage occurs due to drying with subsequent traction on the flap.

10.3 Treatment of Macrostriae

If macrostriae are detected soon after occurrence, ideally within the first 24 h, the surgeon has the opportunity to resolve the problem with immediate treatment. The flap should be lifted, epithelium cleaned from the gutter in order to avoid subsequent epithelial ingrowth into the interface, the flap floated with balance salt solution, and gently stroked and smoothed back into position (Fig. 10.4). Application of bandage soft contact lens for 1 day helps stabilize the flap and may reduce the potential for epithelial ingrowth.

When macrostriae are undetected and untreated for 1 or more days, the folds tend to become fixed. This occurs due to a filling in effect of the epithelium, followed by contracture of the collagen. Based on the severity and duration of the folds, a sequence of increasingly aggressive interventions may be needed to eliminate the folds. These include de-epithelialization followed by swelling of the flap with hypotonic solution, stretching with forceps, and suturing with interrupted or running sutures.

De-epithelialization is important in releasing fixed macrostriae, because the epithelium has remodeled around the macrostriae and will prevent the folds from relaxing (Fig. 10.5). Epithelium can be debrided directly with a spatula or similar

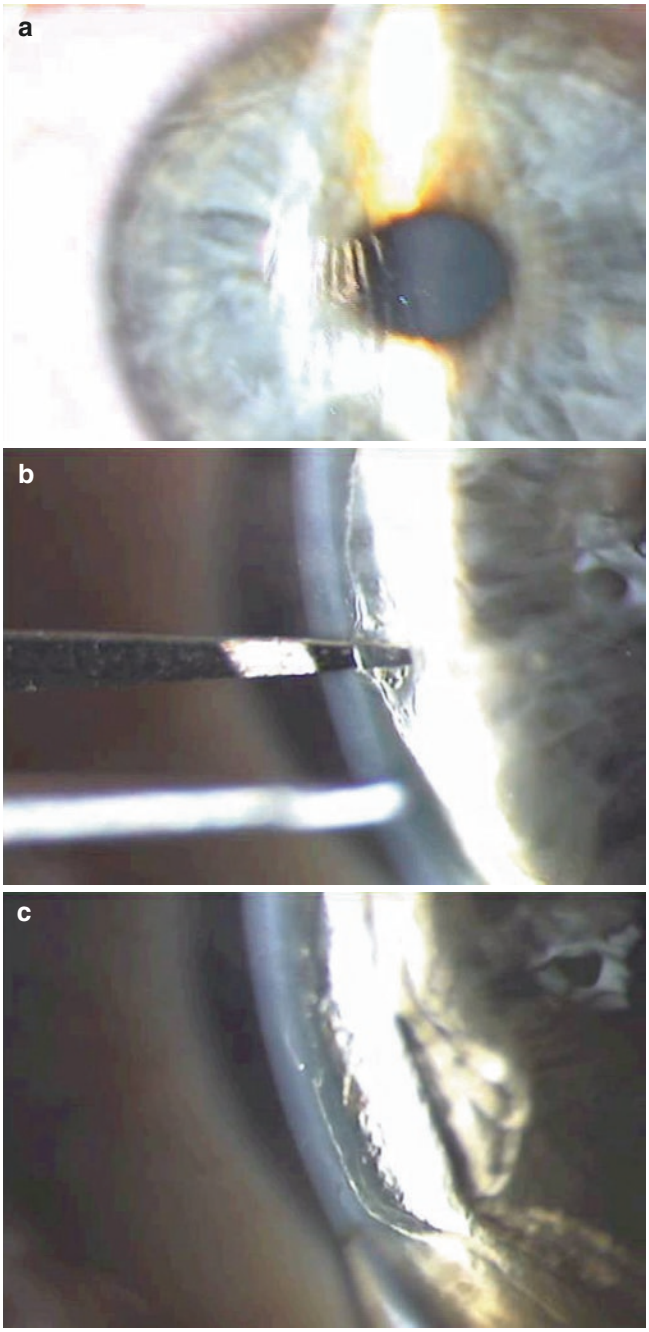

Fig. 10.4 Macrostriae. (**a**) Macrostriae visible in a LASIK flap on the first postoperative day; (**b**) lifting the edge of a flap with the tip of a jeweler's forceps; (**c**) the flap gutter has been cleaned of an ingrowth of epithelium; the edge is visible near the limbus

instrument, but a gentle and effective way of both debriding epithelium and beginning a swelling of the flap is to drip sterile distilled water over the central cornea for several minutes. This will cause the epithelium to swell and the cell membranes to rupture, following which gentle debridement with a surgical spear sponge will be possible. Further drops of sterile distilled water on the surface will lead to more flap

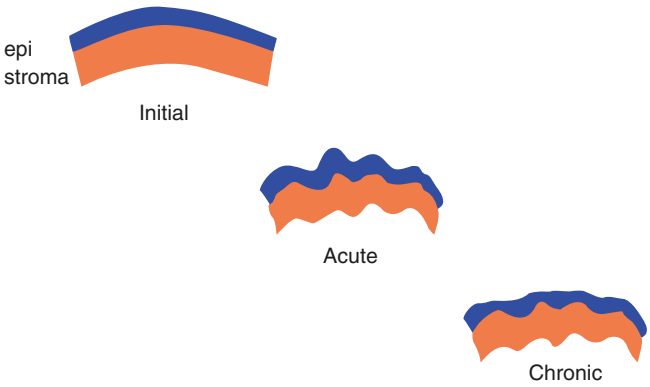

Fig. 10.5 Schematic illustration of establishment of macrostriae with epithelial remodeling and collagen contracture

edema anteriorly, which will help relax the fixed macrostriae. The flap itself is refloated with balanced salt solution, not the hypotonic distilled water, because the swelling is desired anteriorly in the flap, but not in the region of the interface. If excessive hydration of the flap occurs, there is the possibility that swelling in the anteroposterior direction will result in a mechanical contracture of the flap diameter. Initially the flap striae will appear to have been resolved. However, when the flap is repositioned and then subsequently dehydrates due to endothelial pump function, the reduced flap diameter will be fixed in place and then new striae may occur as a result.

After hydration as described above, the macrostriae may not be fully resolved but should appear improved. By the next day, when the bandage soft contact lens is slipped aside, the macrostriae should be resolved. If the macrostriae appears severe despite the initial hydration, or they have not resolved the next day, then the patient can be instructed to apply drops of sterile distilled water with the bandage contact lens in place on an hourly basis for 1 day. Because these drops are not preserved, it is important that they are discarded after no more than 1 day's use. In addition, prophylactic antibiotic drops and steroid drops are important. These corneas have increased vulnerability to an inflammatory reaction (diffuse lamellar keratitis).

If macrostriae persist despite the hydration treatment, then traction may be necessary. In some cases traction with one or more forceps will be successful. If simple traction with forceps is unsuccessful, then the flap may be sutured with multiple interrupted 10-0 nylon sutures or a tight running circumferential suture. Sutures can be removed within several days or weeks; there is no firm guideline on the timing of suture removal [1, 2]. The surgeon should make the patient aware that the suturing of the flap may create new striae or induce regular or irregular astigmatism. In severe cases of recalcitrant striae, amputating and discarding the flap have been advocated [3].

10.4 Treatment of Microstriae

Before instituting treatment of microstriae, the surgeon must determine whether microstriae are optically significant and responsible for a patient's visual symptoms. Because microstriae are smaller in both elevation and width, compared with macrostriae, the epithelium may be able to mask the presence and reduce the optical impact of microstriae. Most LASIK flaps, in fact, have microstriae that are invisible.

Optically significant microstriae are usually not detected on color corneal topography maps but can be seen disrupting the mires on the Placido image. In addition, optically significant microstriae will typically exhibit "negative staining" of the fluorescein pattern, as well as being visible on retroillumination (Fig. 10.6) [4].

Microstriae pathologically represent fine wrinkles in the Bowman layer. This in turn causes disruption of the tear film and the anterior optical surface. Risk factors for optically significant microstriae include thin flaps and high myopia, where the flattening of the surface of the cornea by the myopic correction causes anterior compression of the flap [5]. However, troublesome microstriae have occurred with no known risk factors.

The initial treatment should be medical, encouraging surface epithelial healing. This includes treatment of any external eyelid disease, frequent administration of non-preserved artificial tears, and, where needed, punctal plugs or treatment for several weeks with an extended wear bandage soft contact lens.

Numerous treatments have been advocated for persistent optically significant microstriae, including the treatments listed above for macrostriae (hydration, stretching, and suturing) [6]. In addition, heating of the flap and pressure with a cotton-tip applicator have been advocated [7–13].

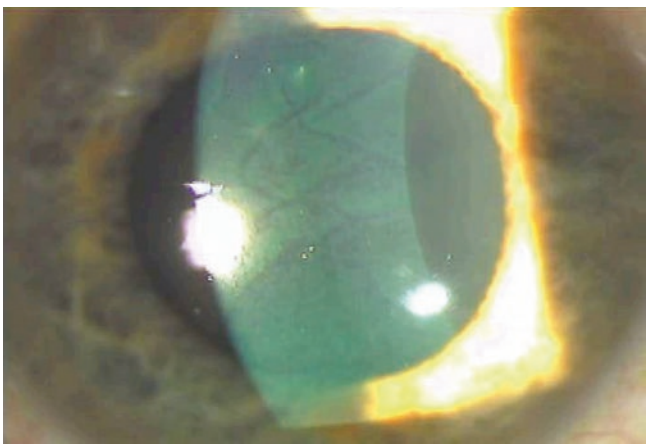

Fig. 10.6 Microstriae seen by "negative staining" of fluorescein in the tear film, caused by the disruption of the tear film by the elevated surface over the microstriae, disrupting the tear film

10.5 Phototherapeutic Keratectomy

In my experience, the most reliable and predictable results in treating microstriae and persistent macrostriae occur with use of the technique of excimer laser phototherapeutic keratectomy (PTK) [14, 15].

The protocol for PTK with a broad-beam laser (Visx S4, Advanced Medical Optics, Santa Clara, CA) is as follows: Three hundred pulses are programmed at a diameter of 6.0 mm. In the first phase of the treatment, 200 pulses are applied to perform transepithelial ablation utilizing the pupil tracker. The epithelium acts as a masking agent, as it is thinner over the striae and thicker in areas between the striae. After the initial 200 pulses, the surgeon then turns off the pupil tracker and applies a maximum of 100 further pulses utilizing masking fluid. A medium viscosity preservative-free artificial tear (e.g., Refresh Plus, Allergan) is applied with a debris-free microsurgical spear sponge. Ideally, a moderate amount of moisture is applied, such that the cornea appears to glisten, but where the fluid layer is not so thick as to fully obscure the microstriae. If the fluid layer is too thick, the laser pulses will have a dull "thud" sound rather than a sharper "snap" sound, and bubbling may be seen in the fluid. Five to eight pulses are delivered, followed by re-wiping and repeating the process, with the surgeon controlling the pulse delivery with the foot pedal of the laser. Setting the laser repetition rate as low as possible (6 Hz) facilitates the repeat wiping and brief firing of the laser. The PTK is judged to be completed when the appearance of the striae is markedly reduced but not necessarily eliminated or when the maximum number of 300 pulses is reached, whichever comes first.

Postoperatively, a bandage soft contact lens is applied, and antibiotic and steroid drops at a rate of at least four times daily are used until reepithelialization occurs, typically around the fourth postoperative day.

We have now analyzed and published the results from 44 patients with the mean follow-up after PTK of 297 days (ranging from 70 to 931 days). Mean uncorrected visual acuity improved from 20/43 to 20/33, and mean best spectacle improved from 20/29 to 20/23 at the last follow-up visit. Figure 10.7 shows the change in acuity in PTK. Overall there was an average shift in refractive error of +0.80 D after PTK (Fig. 10.8).

Refractive stability after PTK could be assessed in 24 eyes that were available at both 1 month and 1 year later (Fig. 10.9). The shift in mean refraction from the 1 month to the 12 month later was less than 0.5 D.

The PTK treatment did not result in optically significant haze in the LASIK flaps. Only five eyes (1.6%) reached a haze level of 1+; 14 eyes (7.8%) had trace haze at any interval, and 28 eyes (59.6%) had no detectable haze at any interval. No instances of late-onset haze occurred.

10.6 Role of Anterior Segment Optical Coherence Tomography (AS-OCT)

AS-OCT has been gaining popularity in the last few years due to its increasing usefulness for precise corneal imaging. It can efficiently visualize corneal structural changes associated with LASIK flap dislocation including flap micro- and macrofolds and epithelial hyperplasia between the striae and identify a widened gutter even in those cases where it has not been previously detected by careful slit lamp examination [16, 17]. In a recent study it was shown that OCT can detect microdistortions in Bowman's layer in 88.5% of patients 1 day after SMILE (small incision lenticule extraction) and 42.1% 1 day after LASIK, even when no clinically significant corneal striae are detected under slit lamp examination [18]. These microdistortions had no significant impact on long-term visual outcomes or wave front aberrometry.

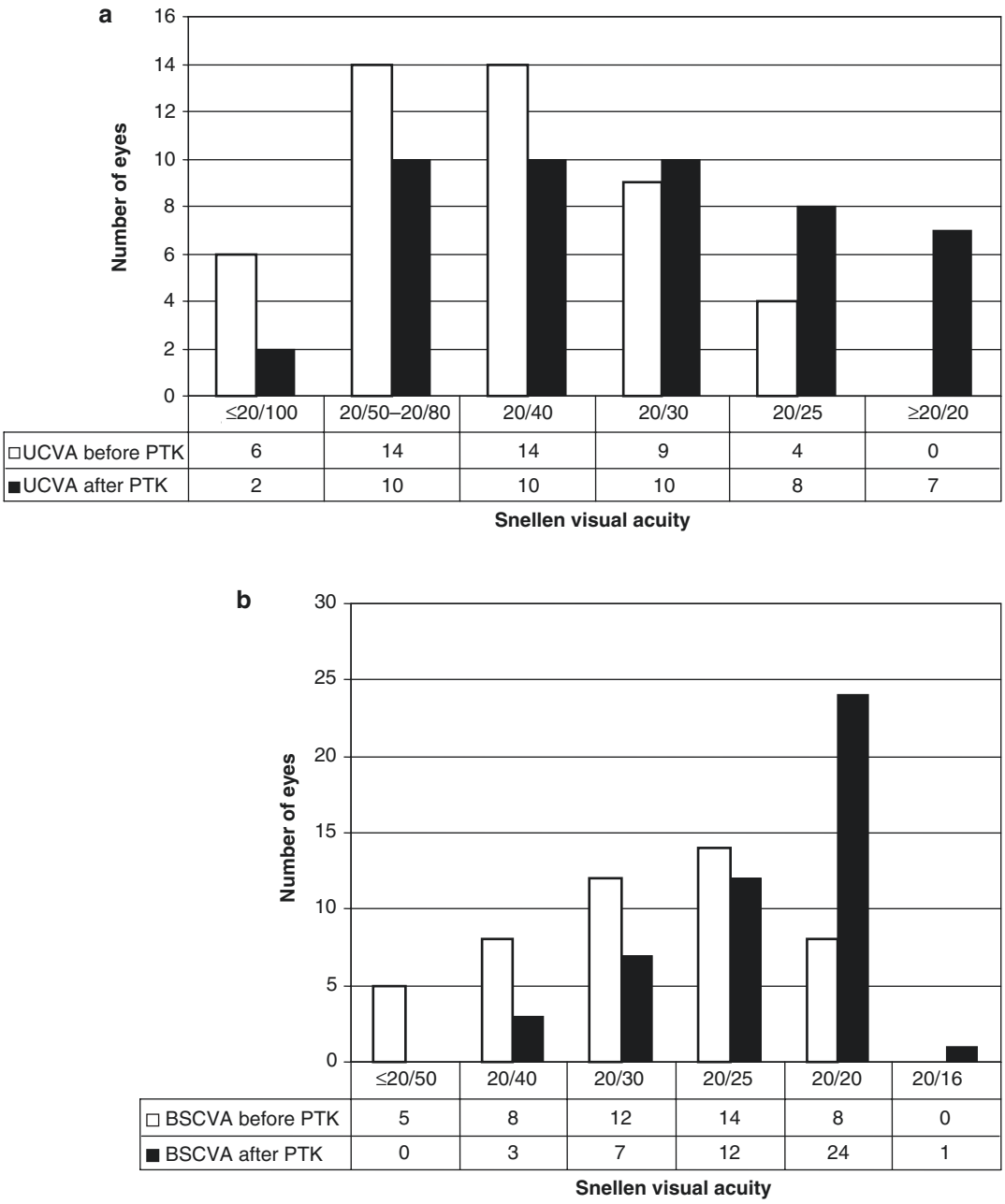

Fig. 10.7 (**a**) Distribution of uncorrected visual acuity before and after phototherapeutic keratectomy. (**b**) Distribution of BSCVA before and after phototherapeutic keratectomy. (**c**) Change in BSCVA (From [15], reproduced with permission)

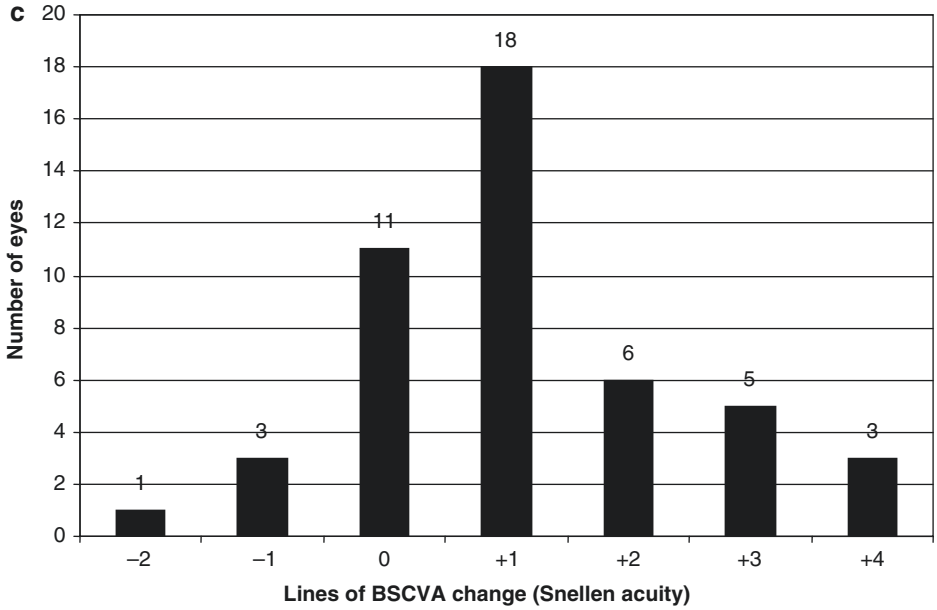

Fig. 10.7 (continued)

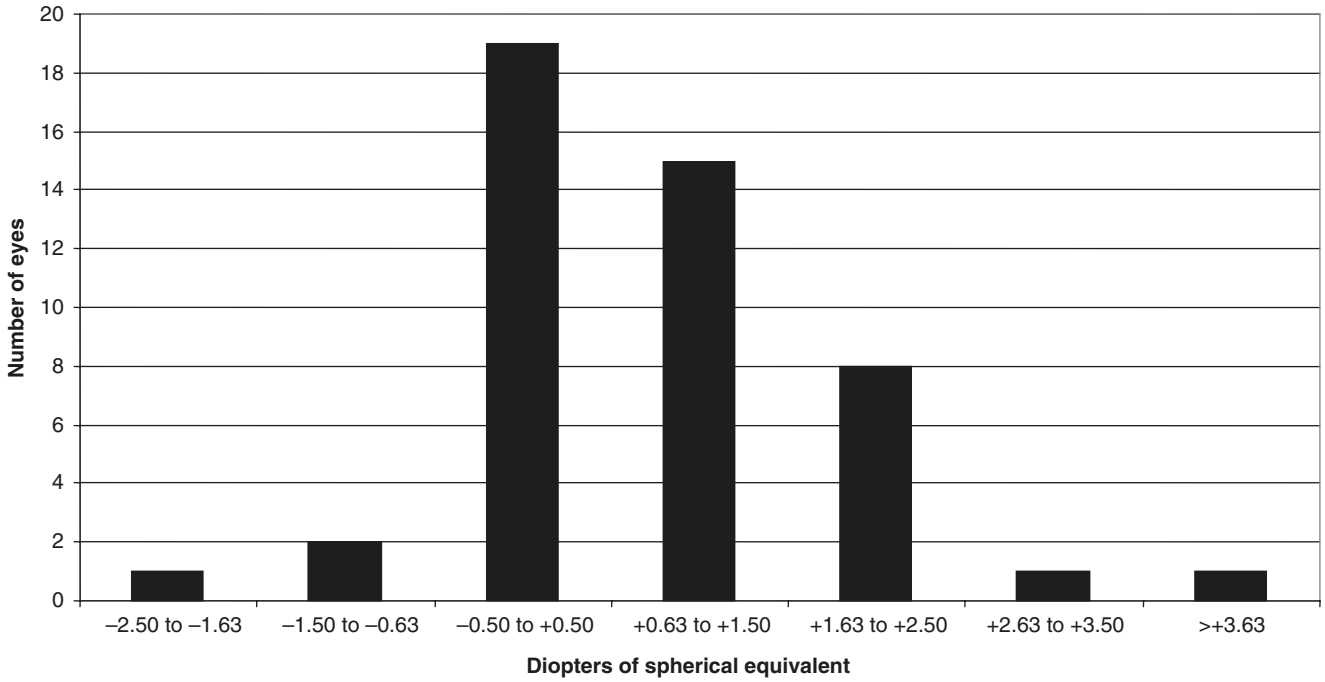

Fig. 10.8 Distribution of net change in spherical equivalent refractive error after phototherapeutic keratectomy (From [15], reproduced with permission)

Take-Home Pearls

- Careful attention to preoperative risk factors, external disease, and proper patient education and training postoperatively can reduce the frequency of macrostriae and microstriae in the LASIK flap.
- If flap slippage occurs with optically significant macrostriae, treatment should be prompt and definitive, utilizing increasingly aggressive measures as needed. If macrostriae are detected and treated within 24 h, refloating the flap, accompanied by debridement of the epithelium and hydration, is usually successful.

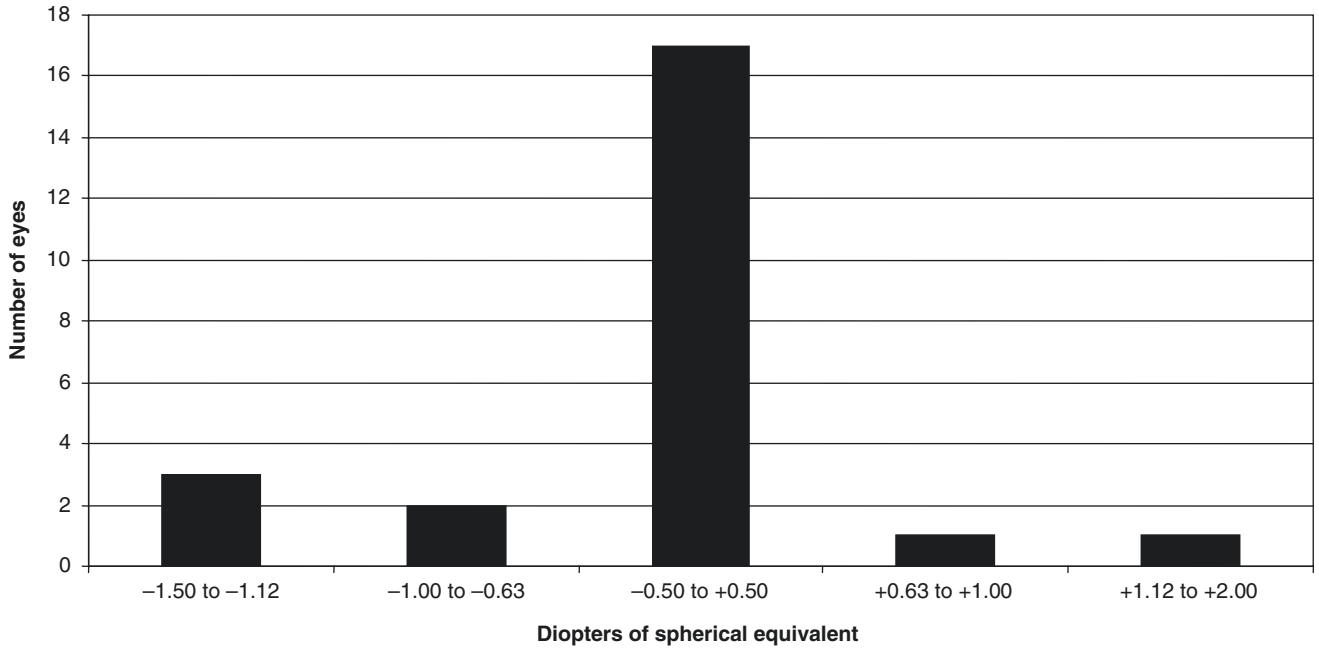

Fig. 10.9 Change in refraction from 1-month post phototherapeutic keratectomy to the last visit at 12 months or later (From [15], reproduced with permission)

- In more severe or prolonged cases, aggressive stretching or suturing of the flap may be necessary. In contrast, visually significant microstriae may improve by support of the epithelium medically.
- Phototherapeutic keratectomy (PTK) following a standardized protocol has been proven to be safe and effective in improving acuity in cases of established flap striae.

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Marginal Sterile Corneal Infiltrates After LASIK and Corneal Procedures

11

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Core Messages

- Sterile infiltrates represent a rare condition that starts within 1–5 days after LASIK.

11.1 Introduction

Currently, there are three key techniques to correct refractive defects in the cornea: LASIK, PRK, and SMILE. Laser in situ keratomileusis (LASIK) remains as the first choice for the correction of refractive errors in the majority of patients [1]. Clinical advantages of LASIK over surface ablation techniques are related to the maintenance of an intact healthy epithelium over the central cornea after the lamellar cut is performed to expose the corneal stroma for laser ablation. This technique leads to a faster visual rehabilitation, less postoperative discomfort, and less healing response, which trends towards more stability, especially for eyes with higher corrections [2]. Nevertheless, the LASIK technique has limitations and associated complications related to the creation of a hinged flap or to its presence on the cornea after surgery [3, 4]. These complications extend from mere annoyance to catastrophic consequences for the eye that threaten vision. Early recognition and prompt appropriate treatment of such possible complications are critical to maximize the success rates of the procedure (efficiency), and to minimize the chances of visual loss (safety). In addition, it is important to be alert to identify, in the preoperative process, cases at higher risk for complications. This would enable the surgeon to develop strategies to prevent or minimize the impact of such problems on the patients' recovery.

The very high popularity of LASIK over the past decade had motivated basic science and clinical research, which led to a significant evolution in the technique and in understanding its pathophysiology. New complications inherently related to the LASIK flap have been described. The potential space created by the lamellar dissection creates a corneal environment susceptible to specific inflammatory conditions. The flap interface is a path of least resistance to cell migration that determines the particular presentation of inflammatory processes as diffuse lamellar keratitis (DLK) [5, 6]. It is also a determinant of potential lamellar opportunistic infections [6, 7] and other forms of culture-negative keratitis [8–12]. In addition, understanding the mechanisms related to specific LASIK complications has an impact on similar conditions not necessarily related to the procedure. For example, the neurotrophic mechanisms related to LASIK-associated dry eye [13, 14] have provided important insights that have been also relevant to other forms of dry eye [15]. Even though the clinical aspects and pathophysiology of these complications are very different, they all have in common some relation with the lamellar corneal dissection. Peripheral sterile infiltrates can also occur after other common corneal procedures, such as collagen cross-linking [16, 17]. This procedure does not have a primary refractive purpose but certainly revolutionized

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the management of corneal ectatic diseases. In this chapter, we review peripheral or marginal sterile infiltrates that follow LASIK, their pathophysiology, clinical aspects, diagnosis, prevention, and treatment.

11.2 Defining Sterile Corneal Infiltrates

Marginal or peripheral sterile corneal infiltrates are localized, noninfectious, inflammatory processes of the ocular surface that can be associated with a number of etiologies. Classically, this type of peripheral keratitis is also called marginal catarrhal infiltrates or ulcers because of the host's antibody hypersensitivity response to the antigen of bacteria related to chronic blepharoconjunctivitis, usually *Staphylococcus* species [18]. However, beta-hemolytic streptococcus and other bacteria, as well as other conditions such as collagen vascular disease, may also cause peripheral sterile corneal ulcers.

There are reports of sterile corneal infiltrates after various refractive procedures [9–12, 19–22]. Sterile infiltrates have been described after photorefractive keratectomy (PRK) [19–22] and collagen cross-linking [16, 17]. Corneal infiltrates can also occur in association with topical nonsteroidal anti-inflammatory drugs (NSAIDs) without concurrent steroids [19, 20], as well as with patching the eye with bandage contact lenses causing hypoxia [19, 20] and topical anesthetic [21] abuse. In this situation, the typical clinical presentation is from the first to third postoperative day, with moderate to severe pain, decreased visual acuity, ciliary injection of the globe, and subepithelial white infiltrates in the treated area, often in the shape of an immune ring, with or without peripheral infiltrates [19, 20]. There is a high risk of permanent scarring accompanied by irregular astigmatism and reduced one to two lines of the best spectacle-corrected visual acuity [19–21]. The incidence has been reported to be about one case for every 300 PRK procedures [20]. The most accepted mechanism for the development of these infiltrates is related to the use of topical NSAIDs without concomitant use of topical steroids. As NSAIDs block only the cyclooxygenase pathway of arachidonic acid metabolism, there is a shift of arachidonic acid metabolism through the alternative lipooxygenase pathway. The resulting leukotriene accumulation results in neutrophil chemotaxis and sterile corneal infiltrates [22]. In addition, a Wessely-type peripheral immune ring has also been described after phototherapeutic keratectomy (PTK) for corneal scarring in a patient who was also treated with diclofenac eyedrops and a bandage contact lens after the surgery [23]. In this case, corneal biopsy was performed, which demonstrated infiltration by neutrophils and the presence of an active fibroblastic reaction, without lymphocytes or plasma cells [23]. This case clearly illustrates the role of neutrophil chemotaxis by leukotrienes. The understanding about this causative mechanism and the use of topical steroids, along with NSAIDs, have significantly reduced the occurrence of this entity [24].

However, sterile corneal infiltrates after surface ablation are not exclusively related to topical nonsteroidal anti-inflammatory drugs (NSAIDs) without concurrent steroids and tight contact lens. Rao and coworkers reported a patient who developed bilateral, marginal-inferior, subepithelial infiltrates of presumed noninfectious etiology after myopic PRK in whom NSAIDs and a soft contact lens were not used postoperatively [25]. In addition, a case of peripheral sterile corneal infiltrates after LASEK has been reported without the use of topical NSAIDs [12]. In this situation, the mechanisms are likely to be different from sterile corneal infiltrates after surface ablation that were caused by the use of topical NSAIDs or tight contact lens wear. There is a high similarity of this condition to marginal catarrhal infiltrates related to staphylococcal lid margin disease. In addition, clinical presentation is also less intense, as usually it does not affect the final outcome.

Peripheral sterile catarrhal infiltrates have been reported after LASIK (Table 11.1) with nasal and superior hinge types of mechanical microkeratome [8–12, 26] and with the femtosecond laser [12]. The mechanism of this type of sterile corneal infiltrates after refractive procedures is likely related to immune reactions.

11.3 Pathophysiology

Local immune reactions, along with mixture effects of the flap creation and laser ablation on the cornea, associated with other ocular surface and/or systemic factors can trigger this complication [8–12, 26].

Classic marginal catarrhal keratitis resembles sterile peripheral infiltrates very highly. The clinical findings, clinical courses, and responses to corticosteroid treatment suggest a similar pathophysiologic mechanism. In the case of classic marginal catarrhal infiltrates, the pathogenesis has been attributed to a localized corneal hypersensitivity reaction to toxins produced by bacteria colonizing the eyelid margins. These lesions represent sterile local deposition of antigen-antibody complexes in the peripheral corneal stroma (Gell & Coombs types II and/or III) [27]. The antigen is most likely an exotoxin elaborated by local bacteria, usually *Staphylococcus aureus*. However, several other organisms have been implicated in marginal keratitis [27].

Mondino and coworkers created an experimental animal model of catarrhal infiltrates by applying exotoxins from *Staphylococcus* species onto the eyes of rabbits previously sensitized to the cell wall antigens [28]. They demonstrated that immunized rabbits expressed humoral immunity against

Table 11.1 Reported cases of peripheral sterile catarrhal infiltrates after LASIK

	Reference/Article	Eyes	Beginning of symptoms	Associated conditions	Visual outcome	Culture	Treatment
CASE 1	Haw WW, Manche EE. [10] J Refract Surg. 1999;15:61–3.	Unilateral OS	DAY 1	History of dry eye and chalazion excision	20/20	Culture was obtained	Topical antibiotics and corticosteroids
CASE 2	Yu et al. [11] J Cataract Refract Surg. 2002;28:891–4.	Bilateral	DAY 1	Superior corneal pannus	20/25	Not performed	Topical antibiotics and corticosteroids
CASE 3	Ambrosio et al. [12] J Refract Surg. 2003;19:154–8.	Bilateral	DAY 6	Meibomian gland dysfunction and blepharitis	20/20	Bacterial and fungal culture were obtained	Topical antibiotics and corticosteroids
CASE 4	Ambrosio et al. [12] J Refract Surg. 2003;19:154–8.	Bilateral	DAY 1	Meibomian gland dysfunction and blepharitis	20/25	Bacterial and fungal culture were obtained	Topical antibiotics and corticosteroids
CASE 5	Lahners WJ, Hardten DR, Lindstrom RL. [13] J Refract Surg. 2003 Nov–Dec;19(6):671–5.	Bilateral	DAY 1	Small exotropia associated with mild amblyopia and an atypical pterygium.	20/25	Cultured by scraping the areas of the infiltrates associated with epithelial defects. Flaps not lifted.	Antibiotic and topical corticosteroid. Blood work-up ruled out systemic autoimmune/ inflammatory etiologies.
CASE 6	Lahners WJ, Hardten DR, Lindstrom RL. [13] J Refract Surg. 2003 Nov–Dec;19(6):671–5.	Bilateral	DAY 5	History of rheumatoid arthritis well controlled. Mild meybomian gland disease and superficial stromal scarring, mild pannus, trace stromal thinning.	20/20	Not performed	Antibiotic and corticosteroid
CASE 7	Lifshitz et al. [14] J Cataract Refract Surg. 2005;31:1392–5.	Bilateral	DAY 3	No identifiable	20/25	Not performed	Topical antibiotics and corticosteroids
CASE 8	Lifshitz et al. [14] J Cataract Refract Surg. 2005;31:1392–5.	Unilateral OD	DAY 1	No identifiable	20/20	Not performed	Topical antibiotics and corticosteroids
CASE 9	Singhal S, Sridhar MS, Garg P. [28] J Refract Surg. 2005;21:402–4.	Bilateral	DAY 1	No identifiable	20/20	Not performed	Topical antibiotics and corticosteroids

ribitol teichoic acid (RTA), a major antigen of *Staphylococcus aureus*. IgG and IgA antibody levels against RTA were measured in the serum, tears, and cornea over a 5-month period using enzyme-linked immunosorbent assay. Antibody levels were correlated with the development of the lesions [28]. Histologically, polymorphonuclear leukocytes and mononuclear cells were found. Immune complex deposition activates the classic complement pathway, and this was thought to trigger polymorphonuclear leukocyte infiltration, proteolytic enzyme release, and subsequent ulceration.

The clinical findings, clinical courses, and responses to corticosteroid treatment suggest a similar pathophysiologic mechanism for peripheral sterile infiltrates after LASIK and marginal catarrhal keratitis from hypersensitivity reaction to toxins produced by bacteria. However, it is not clear how humoral immunity plays a role into this mechanism.

The corneal wound healing response after refractive surgery implicates a complex sequence of events involving cytokine-mediated interactions between epithelial cells, keratocytes, corneal nerves, lacrimal gland, tear film, and cells of the immune system [29–31]. Epithelial injury that is associated with LASIK flap formation and flap lifting triggers cytokine release, including interleukin (IL)-1α and tumor necrosis factor (TNF)-α [29, 30], which bind to specific receptors in the keratocyte cells. The subsequent effects include production of pro-inflammatory chemokines, such as monocyte chemotactic and activating factor (MCAF), granulocyte colony-stimulating factor (G-CSF), interleukin-4 (IL-4), neutrophil-activating peptide (ENA-78), and monocyte-derived neutrophil chemotactic factor (MDNCF). These chemokines attract inflammatory cells into the cornea from the limbal blood vessels and the tear film [32]. It has been hypothesized that in ocular surface

inflammatory conditions, such as blepharitis or meibomian gland dysfunction, patients have an inflammatory milieu that predisposes them to increased cellular migration into the peripheral cornea following the production of cytokines IL1-α and TNF-α during the LASIK procedure [10]. It is also possible that lid manipulation during surgery contribute to an increase of the meibomian secretions containing bacterial toxins into the ocular surface [12, 33].

The appearance of corneal infiltrates after cross-linking was also reported in previous studies. Corneal thickness less than 425 μm and corneal curvature greater than 60 diopters were pointed as risk factors. In the presence of both features, the patient would have an increased risk of 26.5% for developing corneal infiltrates after the cross-linking procedure. Endothelial toxicity induced by the UV exposure is enhanced in thinner corneas. Interestingly, the authors hypothesized that steeper corneas may retain less riboflavin drops. This fact would induce less corneal soaking and consequently less endothelial UV protection provided by the riboflavin [16, 17].

11.4 Clinical Diagnosis and Differential Diagnosis

Patients typically have a sluggish onset of the clinical signs with mild to lack of symptoms because of the gradual evolution of the infiltrates. Usually, the condition presents from the first to the fifth day after the surgery, visual acuity is not severely affected, and the condition affects both eyes if they were operated on the same day. The typical presentation is a localized or circumferential stromal infiltrate peripheral to the flap edge with intact overlying epithelium and an intervening clear zone between the peripheral corneal infiltrate and the limbus (Fig. 11.1a, b) [10–12, 26]. There is mild to moderate redness, and there is no anterior chamber reaction. Blepharitis, meibomian gland dysfunction, or seborrhea is usually found. Usually there are no prominent symptoms, and patients may complain of mild pain, foreign body sensation, and tearing.

In post-LASIK patients, cellular infiltration under the flap as diffuse lamellar keratitis (DLK) might also occur in the presence of peripheral infiltrates [10, 12, 26]. These cases are likely to have more aggressive healing and develop refractive regression and undercorrection, which can be observed in corneal topography (Fig. 11.2).

Sterile infiltrates can also occur after cross-linking procedures [16, 17]. The presentation can be modified if an intracorneal ring segment (ICRS) had been implanted (Fig. 11.3).

Proper differentiation from infectious keratitis is essential for the management of these patients. It is important to maintain a high degree of suspicion for infectious keratitis because the management is very different and the prognosis could be disastrous if the infection is not properly treated.

Herpes simplex keratitis is also in the differential diagnosis of marginal keratitis [34]. The ultraviolet exposure associated with the excimer laser might trigger for HSV-1 reactivation [35, 36]. Even patients without history of herpetic eye disease can present with this complication. Accordingly, it should always be considered for patients with infiltrates or persistent corneal epithelial defects after excimer laser procedures.

11.5 Clinical Management and Preventive Measurements

Topical steroids represent as the mainstream for the treatment of peripheral infiltrates after LASIK. We typically use prednisolone acetate 1% every 1–2 h while awake and recommend reevaluating the patient every day, until the

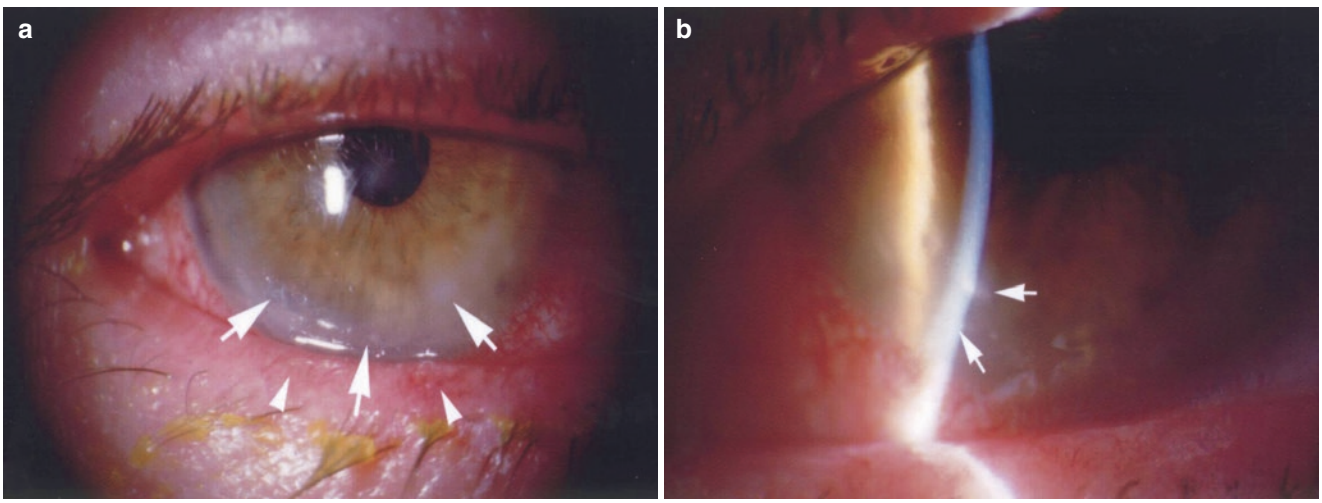

Fig. 11.1 (**a**) Numerous peripheral infiltrates located just outside the flap edge on the first day after LASIK. (**b**) Direct slit illumination under high magnification demonstrates the clear zone (also called lucid interval) between the infiltrates and the limbus (*arrows* - marginal infiltrates; *arrowheads* - eyelid telangiectasia)

condition is under control. Short doses of systemic steroids are to be considered (i.e., prednisone 0.5–1 mg/kg/day for 5 days) if the inflammation is not responsive to topical intense treatment.

In situations where the clinical presentation is more severe, it is advised to get material for microbiological cultures and laboratory work-up, as well as to treat these cases empirically as bacterial infections until the cultures come back negative. We typically use fourth-generation fluoroquinolones, but if there is a high suspicion of infective etiology, fortified topical antibiotics are recommended (i.e., amikacin 20 mg/ml and vancomycin 50 mg/ml). However, in the absence of discharge, epithelial ulceration, and anterior chamber reaction, the surgeon might decide not to proceed with invasive investigations such as corneal scraping and increasing topical steroids with a close monitoring of the patients' signs and symptoms.

If DLK is grade III or if there is aggregation of cells clumped in the visual axis associated with haze and reduced vision, the center flap lift and irrigation are advised [3–5]. Typically, this maneuver is very effective when combined with intense topical steroids.

During preoperative screening, the surgeon should be alert to identify patients with moderate blepharitis and/or meibomian gland dysfunction to start prophylactic treatment prior to surgery. Acne rosacea and hypercholesterolemia are possible important risk factors [10]. Classically, lid scrubs, hygiene, and tetracycline and its derivatives treatment (i.e., doxycycline 100 mg BID) should be considered. Alternatively, omega-3-type essential fatty acid (EFA) nutritional supplementation with flaxseed or fish oil has been shown to be effective in up to 75% of patients with blepharitis and dry eye symptoms (Boerner, Honan, Ambrósio, Stelzner, McIntyre; unpublished data, 2001) [37]. Higher dietary intake of n-3 EFA is associated with a decreased incidence of dry eye in women [38]. However, the use of n-3 EFA oral supplementation to optimize ocular surface prior to LASIK and surface ablation is anecdotal, and controlled trials are needed to confirm efficacy. Preoperative optimization with topical cyclosporine A is an alternative for patients with chronic dry eye and blepharitis. This medication has been demonstrated to be effective in masked, controlled clinical trials for dry eye [39]. We recommend this approach for cases identified as moderate dry eye that are candidates for LASIK as a possible maneuver to turn these candidates into good candidates for LASIK, minimizing the occurrence of LASIK-associated dry eye. Interestingly, patients with keratoconus have also problems related with dry eye and allergic eye disease. Preoperative diagnosis and ocular surface optimization (with fatty acid supplements, cyclosporine drops, and lubricants) may also reduce the risk to develop sterile infiltrates or epithelial wound healing problems after collagen cross-linking.

Epithelial defects can be present which augments the complexity and severity of the case. Infectious disease, including viral, should be carefully considered. In some cases, oral antiviral coverage should be taken depending on the response to intense steroid treatment. Autologous serum 20% along with preserved free topical lubricants should be considered [40].

If a refractive enhancement is to be performed for a patient that had sterile infiltrates after the first LASIK

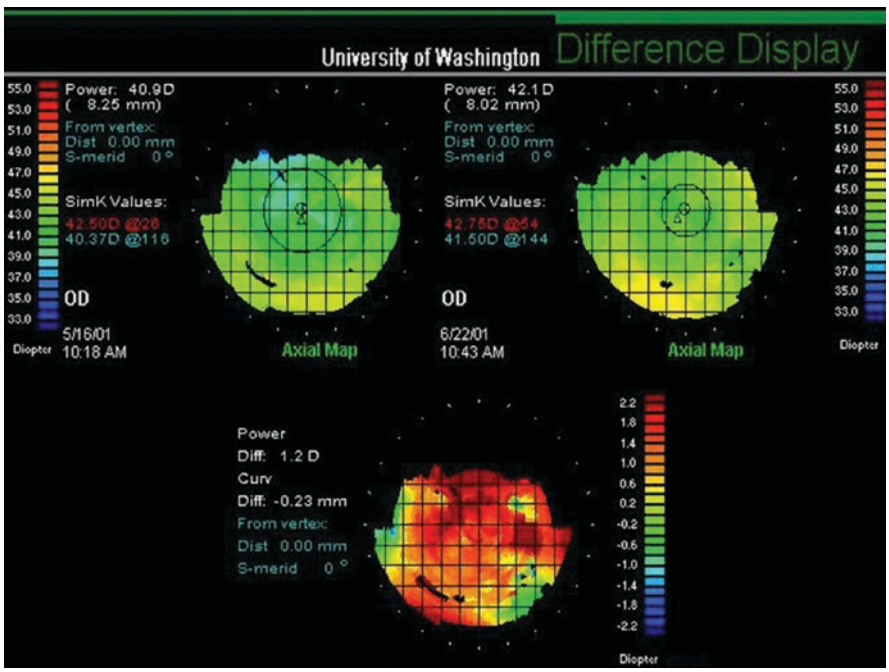

Fig. 11.2 Axial corneal topography subtraction maps demonstrating myopic regression between the first and third month after LASIK. Interestingly, the coefficient of irregularity (CIM) decreased from 3.70 to 1.43

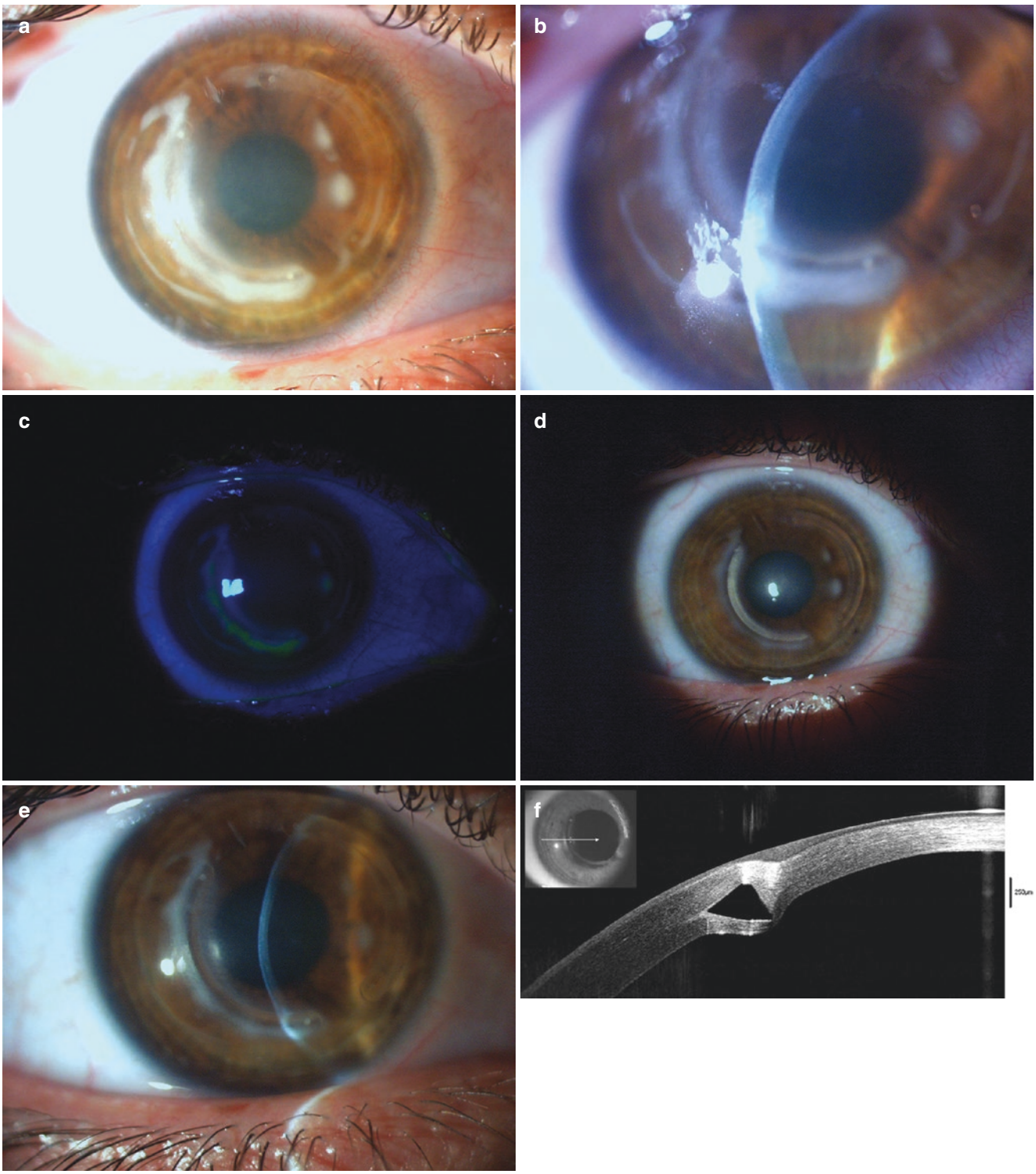

Fig. 11.3 Sterile (culture-negative) infiltrates associated with epithelial defect 1 month after collagen cross-linking in the right eye of a patient referred for second opinion with previous intracorneal ring segments (**a**–**c**) and 1 week after intense topical steroid treatment and autologous serum 20% (**d**–**f**). (**a**) Intense infiltrate around the temporal ring segment and two smaller infiltrates with a lucid interval between the infiltrate and the nasal segment. (**b**) Slit view of the infiltrates, demonstrating epithelial irregularity, confirmed as a defect with fluorescein under cobalt blue light. (**d**) Significant reduction of the infiltration was noted 1 week after treatment under diffuse light and (**e**) slit view. (**f**) High magnification of the demarcation line observed after cross-linking

procedure, prophylactic pretreatment with high-penetration corticosteroids for 2–3 days prior to LASIK may be helpful in preventing recurrence of the marginal sterile infiltrates. It is also an alternative for eyes with residual signs of blepharitis and meibomian gland dysfunction despite lid hygiene and doxycycline [33]. The surgeon can anticipate the susceptibility for such patients, so that they would be monitored more carefully following surgery.

Oral antiviral prophylaxis and treatment may be appropriate when performing LASIK in patients with a history of ocular or systemic HSV infection. We typically keep these cases with prophylactic dose of acyclovir 800 mg a day or valacyclovir 500 g a day for 6 months to 1 year but currently recommend full dose (acyclovir 400 mg five times a day or valacyclovir 500 mg twice a day) for 10 days, starting 2 days prior to surgery. HSV cultures may be necessary for definitive diagnosis, and antiviral treatment may be considered for cases that have negative bacterial and fungal cultures with poor response to topical corticosteroid treatment, especially if there are corneal epithelial defects associated [10].

Confocal microscopy is a powerful diagnostic tool as it provides a noninvasive recognition of several pathologic conditions at the cellular level [41]. We believe there is clinical potential for the confocal microscopy exam to clinically differentiate sterile and infectious keratitis after LASIK, as well as for helping in identifying the microorganism. This would be a major improvement for managing such complications after refractive surgery. However, it has not been demonstrated yet.

Conclusion

Surgeons must be aware of sterile infiltrates, which is a distinct complication from corneal infiltrates of infectious etiology after corneal refractive and therapeutic procedures. Its treatment and outcomes are quite different from those of infectious keratitis, so we advocate for a high degree of suspicion in cases of peripheral infiltrates and for a careful evaluation of the patient with daily visits if necessary, to rule out bacterial or HSV infection. Intense treatment to optimize ocular surface should be considered, and autologous serum 20% may be needed in the case of epithelial defect.

Although the exact mechanism of this complication remains unclear, recognition of postoperative peripheral sterile infiltrates is essential for the management of these patients. Appropriate and early management with intense topical steroids usually results in rapid disappearance of the infiltrates without affecting the final outcome [8–12, 26]. It is also important to identify cases at higher risk for this complication, so that preoperative treatment would avoid or minimize its development.

Take-Home Pearls

- In patients undergoing LASIK surgery, sterile infiltrates can occur with mechanical microkeratomes and with femtosecond lasers.
- Typical presentation is multiple lesions with intact epithelium, but they can also occur with an epithelial defect.
- There is an intervening clear zone between peripheral cornea and the limbus (similar to catarrhal infiltrates).
- Sterile infiltrates can be complicated by DLK, when flap lift for interface cleaning may be necessary.
- Negative smears and cultures (sterile inflammation) and response to steroid therapy confirm the diagnosis.
- Blepharitis is often associated with this complication.
- It usually resolves with intensive high-penetration topical corticosteroids.
- Myopic regression is often seen after proper treatment.
- Recurrence is likely with LASIK enhancement (consider prophylactic pretreatment with high-penetration steroids).
- Identification of cases at higher risk (blepharitis, ocular rosacea) is important to enable preoperative treatment for prevention of this complication.
- Differential diagnosis includes DLK, infectious keratitis, and herpes simplex keratitis.

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Melting

12

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Core Messages

- The cornea experiences a limited number of responses to a wide variety of aggressions.
- Stromal melting, also known as keratolysis or stromal necrosis, is an end-stage response of potentially serious consequences.
- The wounded area is optically dense after experiencing melting. It rarely returns to its normal tensile strength, mainly because the corneal thickness is reduced.
- The therapeutic approach must be directed toward the underlying disease or "trigger" phenomenon and it will depend on the aggressivity of the melt.
- Although stromal melting most frequently occurs after LASIK, it has occasionally been observed after other corneal refractive procedures.
- Both epithelial ingrowth and melting of the flap edge are more common in LASIK re-treatments involving flap relift and after hyperopic re-treatments. Melting is commonly associated with inflammatory disorders of the interface, such as diffuse lamellar keratitis (DLK).

12.1 Introduction

Corneal melting, also known as keratolysis or sterile necrosis of the cornea, is a potentially severe phenomenon that may result in severe corneal thinning and perforation. Postoperative corneal melts may be associated with infectious, inflammatory, or trophic causes [1]. In order to better understand the mechanisms involved and the appropriate therapeutic strategies, basic concepts about stromal physiology and healing are reviewed herein.

12.2 Basic Concepts

The corneal stroma accounts for 90% of the corneal thickness and it is composed almost entirely of extracellular material. Two zones of tissue are recognized: (1) Bowman's layer, a homogeneous acellular sheet of randomly oriented collagenous fibers, and (2) the lamellar stroma, which is organized in obliquely oriented bundles of collagen that surround spindle-shaped cells named keratocytes.

Bowman's layer represents approximately 2% of the corneal thickness. It is composed of an irregular meshwork of filaments made up of collagen types I, III, V, and VI, and possibly type IV.

Stromal fibroblasts or keratocytes are neural crest-derived spindle-shaped cells and produce the majority of the extracellular matrix, including collagen fibers and proteoglycans. Under physiological conditions, keratocytes exhibit minimal mitotic activity and serve mainly to maintain the slow turnover of extracellular components. Normal keratocytes decrease in density from anterior to posterior to increase slightly in the area anterior to Descemet's membrane.

The lamellar stroma is composed of approximately 200 layers of type I collagen, the most abundant in the adult cornea, which are oriented parallel to the corneal surface. The noncollagenous intercellular component of the stroma is composed of glycosaminoglycans (GAGs). Proteoglycans are acidic macromolecules that are formed of at least one sulfated glycosaminoglycan bound to a protein core and associated with collagen fibrils at specific axial locations. As these molecules are extremely hydrophilic, most of the water present in the intercellular stroma is associated with GAG molecules. The proteoglycans are located between collagen

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fibrils and may be regulators of collagen fibril spacing and diameter. Intralamellar adhesive strength of the stroma depends on the relationship between the collagen lamellae and the proteoglycans. Adhesive strength is greater near the periphery, where there is considerably more collagen interweaving.

The main stimulus to corneal stromal reaction is keratocyte death. If minimal, as in the case of superficial foreign bodies of the cornea, keratocyte response is also minimal or none. In these cases, the defect may be permanently filled with epithelial cells that thicken the epithelial cell layer focally and reestablish the surface contour, with no loss of corneal transparency or thickness.

After corneal damage, keratocytes become activated and start synthesizing collagen and proteoglycans, leaving their maintenance status. Moreover, the number of keratocytes increase by mitotic division, and other keratocyte-like fibroblasts may also enter the area. After an intact epithelial cover is re-established, keratocytes migrate from their point of origin to the site of injury and begin to produce collagen. However, although the reparative collagen is the same as native collagen, type I, its diameter is generally larger and more variable. As a result, the homogeneity that preserves the transparency of the cornea and allows light transmission is lost, and a visible scar is observed clinically.

Similarly, the newly synthesized proteoglycans bind water molecules more tightly, which results in chronic, hyperhydration of the scarred tissue. The difference in the nature of the newly formed proteoglycans results in the irregular spacing of the new collagen fibers and, consequently, opacification of the stromal tissue.

In the latter stages of wound healing, stromal keratocytes develop intracytoplasmic actin-myosin contractile elements, similar to those present in muscle cells (myofibroblasts or fibromyoblasts). Fibromyoblasts are responsible for the "contraction" of the corneal wound, which may lead to irregular corneal astigmatism. The initial extracellular matrix of the scar produced is not the same as the final or resting scar. Under the influence of poorly defined stimuli, including mechanically generated forces from surrounding tissues, collagen and proteoglycans are selectively catabolized by specific proteases. New collagen and proteoglycans are then selectively synthesized in a more advantageous orientation, quantity, or proportion. Myofibroblasts revert back to cells with maintenance characteristics similar to the native keratocytes. Hypercellularity may be a permanent feature of the scar tissue. The degree of transparency of the scar tissue may be improved but not to the point of functional rehabilitation.

Although the wounded area is optically dense and hypercellular, corneal scar tissue seldom returns to its normal tensile strength. It is estimated that the maximum recovery is 70% of native tensile strength.

Several agents that inhibit matrix metalloproteinases (MMP) activities in vitro have been tested as topical agents in vivo using the rabbit model of alkali burns. Some MMP inhibitors appear to act by nonspecifically chelating the zinc cation present at the active site of MMP. These agents include sodium ethylenediaminetetraacetic acid (EDTA), tetracycline, cysteine, and acetylcysteine. Thiol-containing synthetic inhibitors of collagenase have been developed that are substantially more potent than the first-generation collagenase inhibitors.

Tissue inhibitor of metalloproteinases type I (TIMP-1) is a protein that is synthesized and secreted by many types of cells and acts endogenously to inhibit the matrix metalloproteinases, collagenase, gelatinase, and stromelysin. Topical application of purified recombinant TIMP-1 significantly reduced the progression of corneal ulceration in rabbits after severe alkali burn. TIMP-1 has not been evaluated in patients affected of corneal burns.

Although much more basic and clinical investigations are needed, treatment of infectious corneal ulcers with a combination of antibiotics and MMP inhibitors may reduce the risk of extensive necrosis.

Topical anti-inflammatory agents such as corticosteroids or nonsteroidal anti-inflammatory agents (NSAIDs) are often associated with delayed stromal healing and acceleration of corneal ulceration. Part of this effect is probably attributable to decreasing DNA synthesis in regenerating stromal fibroblasts. In addition, corticosteroids reduce the synthesis of collagen by cultured fibroblasts. Addition of insulin growth factor (IGF) or epidermal growth factor (EGF), however, may partially preserve the detrimental effect of corticosteroids on wound strength.

12.3 Stromal Melting Classification

Table 12.1 describes stromal melting classification based on its physiopathology.

Table 12.1 Classification of stromal melting based on physiopathology

Active	• Infectious keratitis • Culture-negative ulcerative keratitis [2] • Caustication (alkali, acid, burn-induced) • Immunological diseases (rheumatoid arthritis, primary Sjögren's syndrome [3], Vogt-Koyanagi-Harada's syndrome [4]) • Vitamin A deficiency [5] • Diffuse lamellar keratitis (DLK) or epithelial ingrowth [6] • Other diseases: paraneoplastic pemphigus [7]
Trophic (Dellen phenomenon)	• Pterygium or pingueculae • Molteno shunt plate avulsion [7]
Neurotrophic keratopathy	• Trigeminal nerve damage [8]

12.4 Stromal Melting After Excimer Laser Refractive Surgery

12.4.1 Epidemiology and Etiopathogenesis

Stromal melting after corneal refractive surgery is, fortunately, very rare. It most frequently occurs after laser-assisted in situ keratomileusis (LASIK), especially after LASIK retreatments involving flap lift or after hyperopic treatments. Systemic inflammatory or autoimmune diseases (e.g., thyroiditis, systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, skin eczema-erythema) are significant risk factors that are present in about 50% of the cases of corneal melting. While active disease is an absolute contraindication for corneal ablation procedures, both LASIK and PRK, if the systemic disease is appropriately controlled and no signs of activity are present, the incidence of melting after corneal refractive surgery is extremely low [9–12].

The typical clinical presentation is unilateral corneal melt of the flap edge, which begins 2–5 weeks after the procedure [13]. In the vast majority of cases, melting is seen in conjunction with other complications of the immediate postoperative period, including epithelial defects, thin and/or irregular flaps, buttonholes, epithelial ingrowth, diffuse lamellar keratitis (DLK), infectious keratitis, or dislocated flaps (Fig. 12.1) [6, 14–17]. By induction of apoptosis of the surrounding stromal keratocytes by the implanted epithelial cells on the lamellar interface, epithelial ingrowth is the most frequent trigger of flap melt [18]. Severe DLK (grades III and IV) present a high risk of both flap and stromal melting, which may lead to severe corneal thinning (Fig. 12.2) [19].

Corneal melt is usually a self-limited phenomenon that resolves between 21 and 45 days after onset. Despite the use of topical steroids and/or cyclosporine A, variable degrees of corneal opacification (leukoma) and/or regular and irregular astigmatism are not unusual sequelae.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have proved useful for the treatment of pain, inflammation, and photophobia after photorefractive keratectomy (PRK). Due to their antiproliferative effect on keratocytes, NSAIDs have also been used for the long-term treatment of haze after PRK, and as an attempt to modulate regression after both LASIK and PRK [20–23]. On the other hand, topical NSAIDs may potentiate other risk factors such as dry eye and/or autoimmune diseases. Corneal melting after excimer laser refractive surgery associated with the use of NSAIDs has previously been reported, being the overexpression of MMP-1 and MMP-8 by epithelial cells a possible mechanism [24–27]. A few cases evolved to acute or late corneal perforation. In our opinion, the use of NSAIDs should be limited to the first hours or few days after LASIK or surface techniques aiming for an analgesic effect. Longer-term use is not recommended.

12.5 Treatment of Corneal Melting

12.5.1 General Concepts

Stromal melting after LASIK is usually a self-limited phenomenon that does not require treatment in most cases. If needed, treatment should be directed toward the underlying cause or trigger phenomenon. The use of cyanoacrylate glue and a therapeutic soft or hard contact lens [28, 29], or partial keratectomy and amniotic membrane transplantation may be effective [30–33]. The use of oral tetracyclines (Doxycycline) has also proved effective due to their antimetalloproteinase action, even in cases of infectious *Pseudomonas* keratitis (Fig. 12.3) [34].

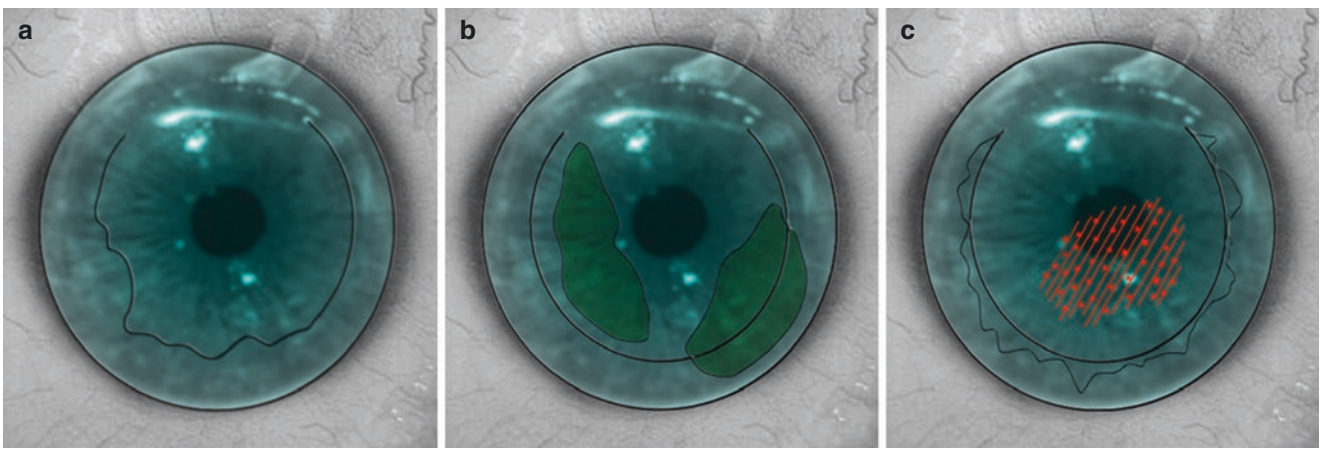

Fig. 12.1 High-risk situations of epithelial ingrowth and melting after LASIK. (**a**) Irregular lenticule. (**b**) Epithelial defect, especially over the flap edge. (**c**) Irregular epithelial edges (reoperations) and DLK

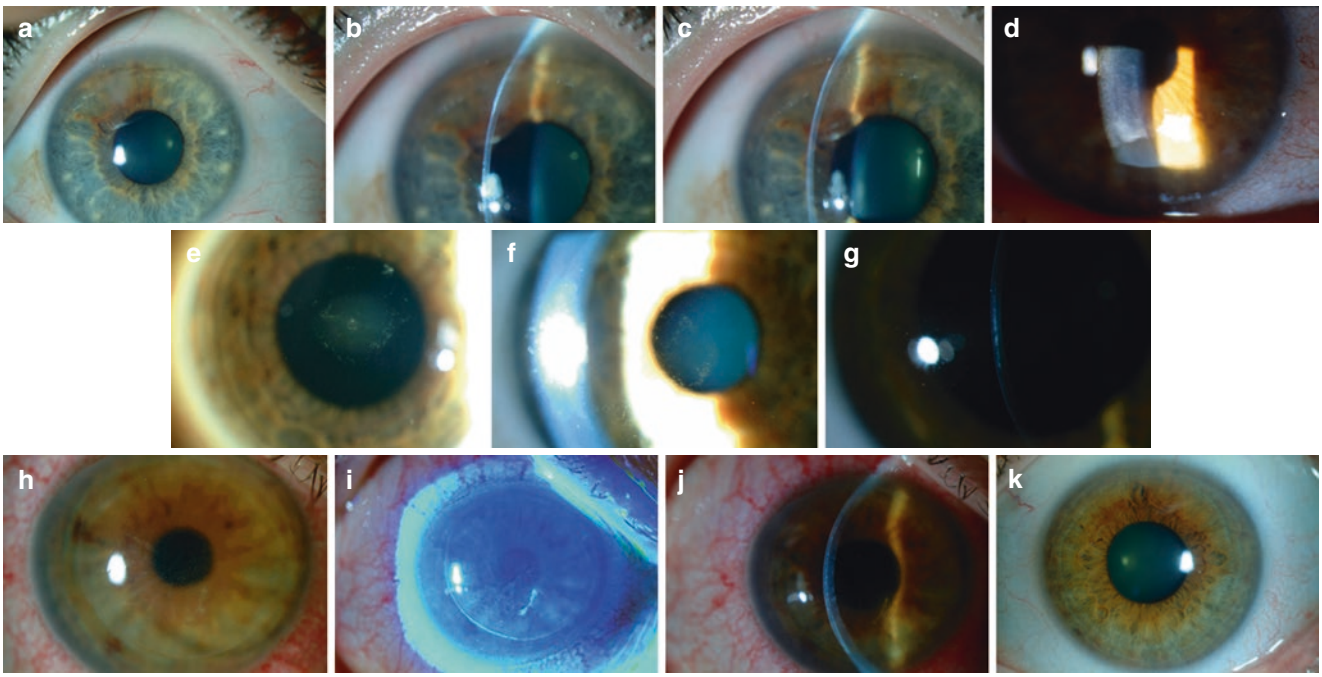

Fig. 12.2 (**a**–**d**) Clinical photographs of peripheral stromal lysis after epithelial ingrowth. (**e**–**g**) Central stromal lysis after end-stage DLK. (**h**–**k**) Stage IV DLK. Stromal lysis may be avoided if intense treatment with oral and topical corticosteroids is urgently started. (**k**) Six months after DLK, no stromal lysis is observed

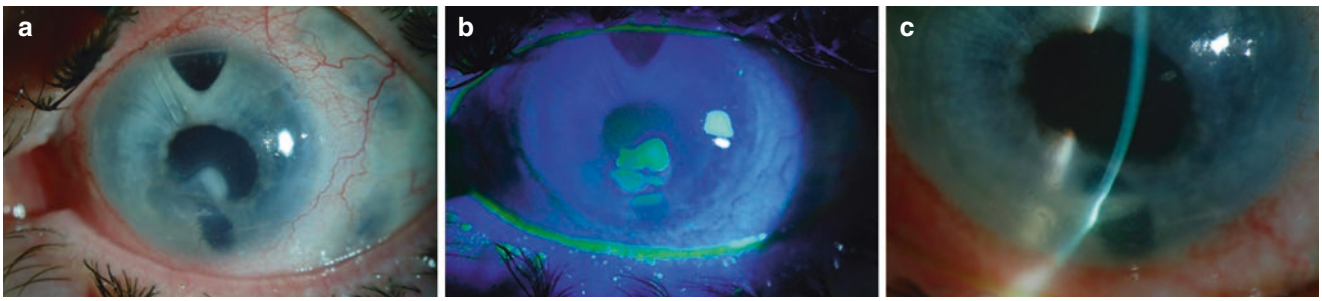

Fig. 12.3 (**a**–**c**) Infectious keratitis may be associated with a certain degree of focal or diffuse stromal lysis. Clinical photographs showing a case of *Pseudomonas* keratitis with focal stromal melting

Corneal melting is an extremely severe complication in patients with keratoprosthesis. Other risk factors are frequently present, specifically herpes simplex virus (HSV) or immunological disorders [35]. An ability to suppress collagenase enzymes has been attributed to topical medroxyprogesterone (MPG), and although it may not have an impact on the incidence of melting in patients with keratoprosthesis, MPG may have a protective effect on the onset and severity of stromal melting [36].

Platelet-activating factor (PAF) delays corneal epithelial wound healing by inhibiting the adhesion of epithelial cells, increasing apoptosis of stromal cells, and inducing MMP-9 activation. PAF-receptor antagonists, LAUO9O1 (2,4,6-trimethyl 1-4-dihydropyridine-3-5-dicarboxylic acid ester), were developed to treat alkali-induced stromal melting and DLK, but they did not reach first-in-human status [37].

12.5.2 Epithelial Ingrowth and Flap Melt

With an incidence ranging between 0.03% and 9.1%, epithelial ingrowth is one of the most common postoperative complications of LASIK [38–40]. Letko et al. reported that eyes with femtosecond laser-created flaps may be less likely to develop significant epithelial ingrowth after LASIK retreatments when compared with eyes in which the flap was created using a mechanical microkeratome [41].

Large intraoperative epithelium sloughing or epithelial defects during LASIK may trigger several postoperative complications after LASIK, including DLK, flap microfolds, epithelial ingrowth, and flap melt. Patients with epithelial basement membrane dystrophy (EBMD) present a high risk of epithelial sloughing, and should not be operated on with LASIK [42]. Similarly, if a patient experiences epithelial

sloughing in the first eye, LASIK should not be performed in the second eye because the risk of bilateral damage is very high (Fig. 12.4).

Epithelial ingrowth and, hence, flap edge melting are more common after LASIK re-treatments, especially those that involve relifting the flap [43, 44]. Some series report that hyperopic re-treatments may experience epithelial ingrowth in up to 30% of cases and flap melt in up to 2% of cases. Therefore, a cautious flap relift technique that preserves the epithelial edges is essential to prevent this potentially severe complication. In our experience, creating a circular flap rhexis has proved very useful in preventing epithelial ingrowth (Fig. 12.5) [45]. Alternatively, we have described a technique of femtosecond laser-assisted enhancements after primary LASIK using a mechanical microkeratome-created flap. The vertical side-cut incision is created by the femtosecond laser (VisuMax, Carl Zeiss Meditec, Jena, Germany), which creates a wound configuration that decreases mechanical trauma to the epithelium and prevents epithelial cell migration. These factors may decrease the risk for post-LASIK enhancement epithelial ingrowth [46].

Moderate-to-mild cases of epithelial ingrowth after LASIK tend to regress spontaneously. Therefore, minimal corneal melt is not likely to induce irregular astigmatism or

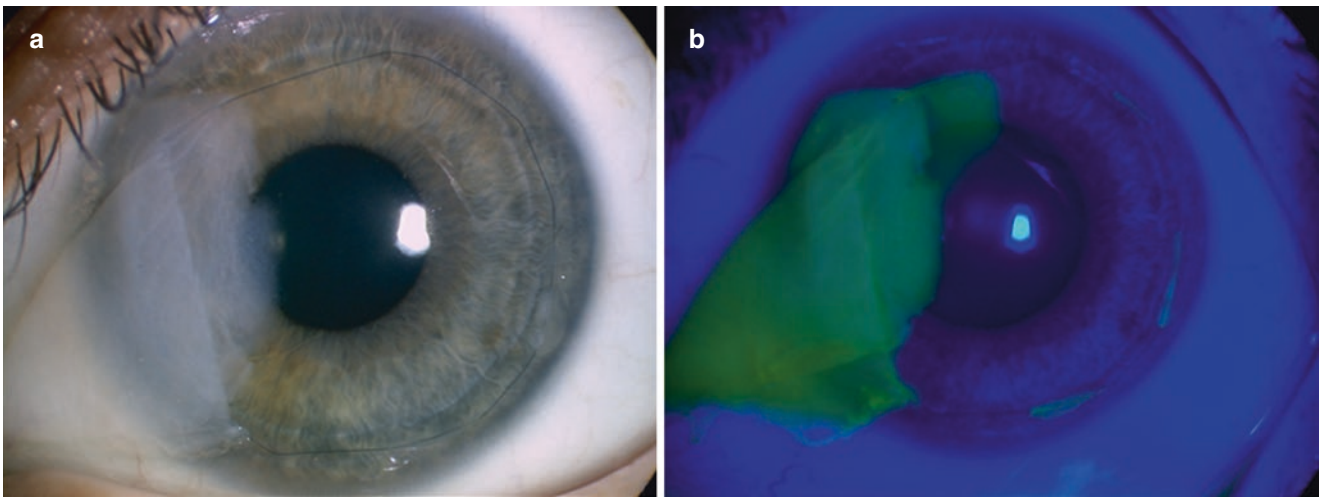

Fig. 12.4 (**a**–**b**) An amniotic membrane patch may be a good alternative to therapeutic contact lens in some cases with extensive epithelial defects. Clinical photograph (**a**) without and (**b**) with fluorescein staining 4 weeks after epithelial ingrowth removal and amniotic membrane transplantation. Some remnants of amniotic membrane may remain for a few weeks after surgery, and are removed at the slit lamp

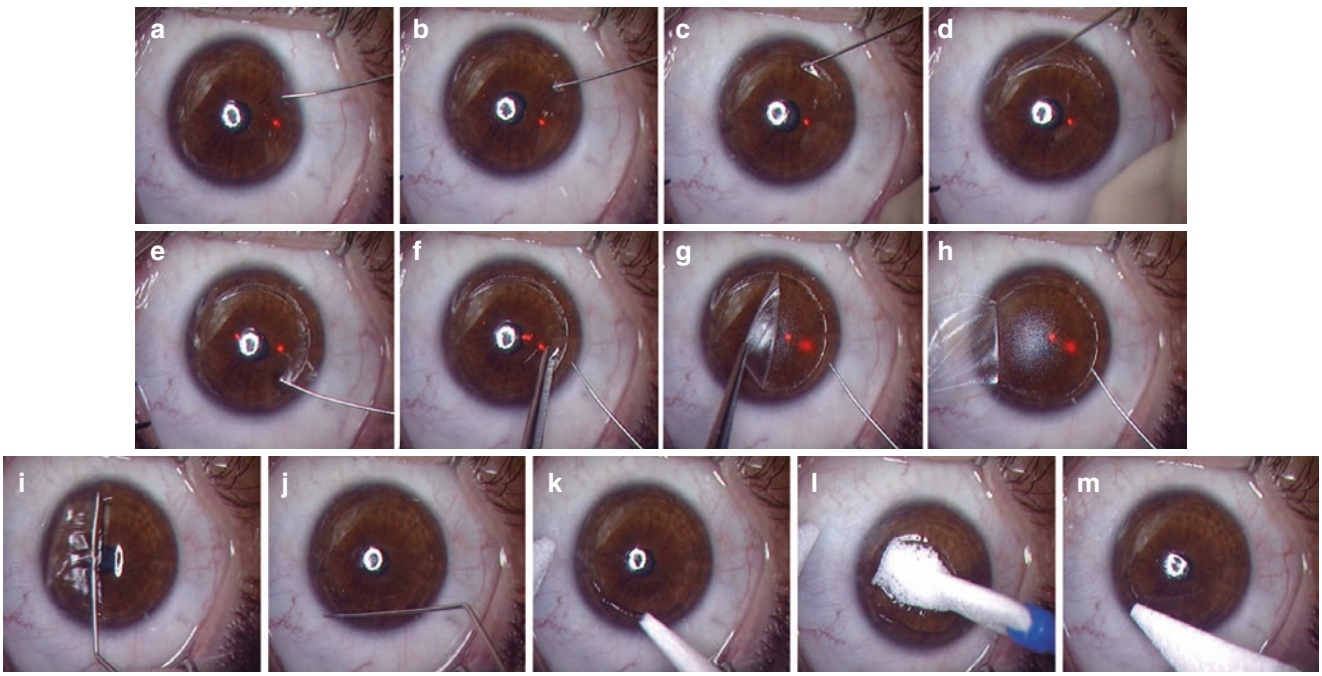

Fig. 12.5 (**a**–**m**) Circular flap rhexis to relift the LASIK flap. Trauma to the flap edges is minimized

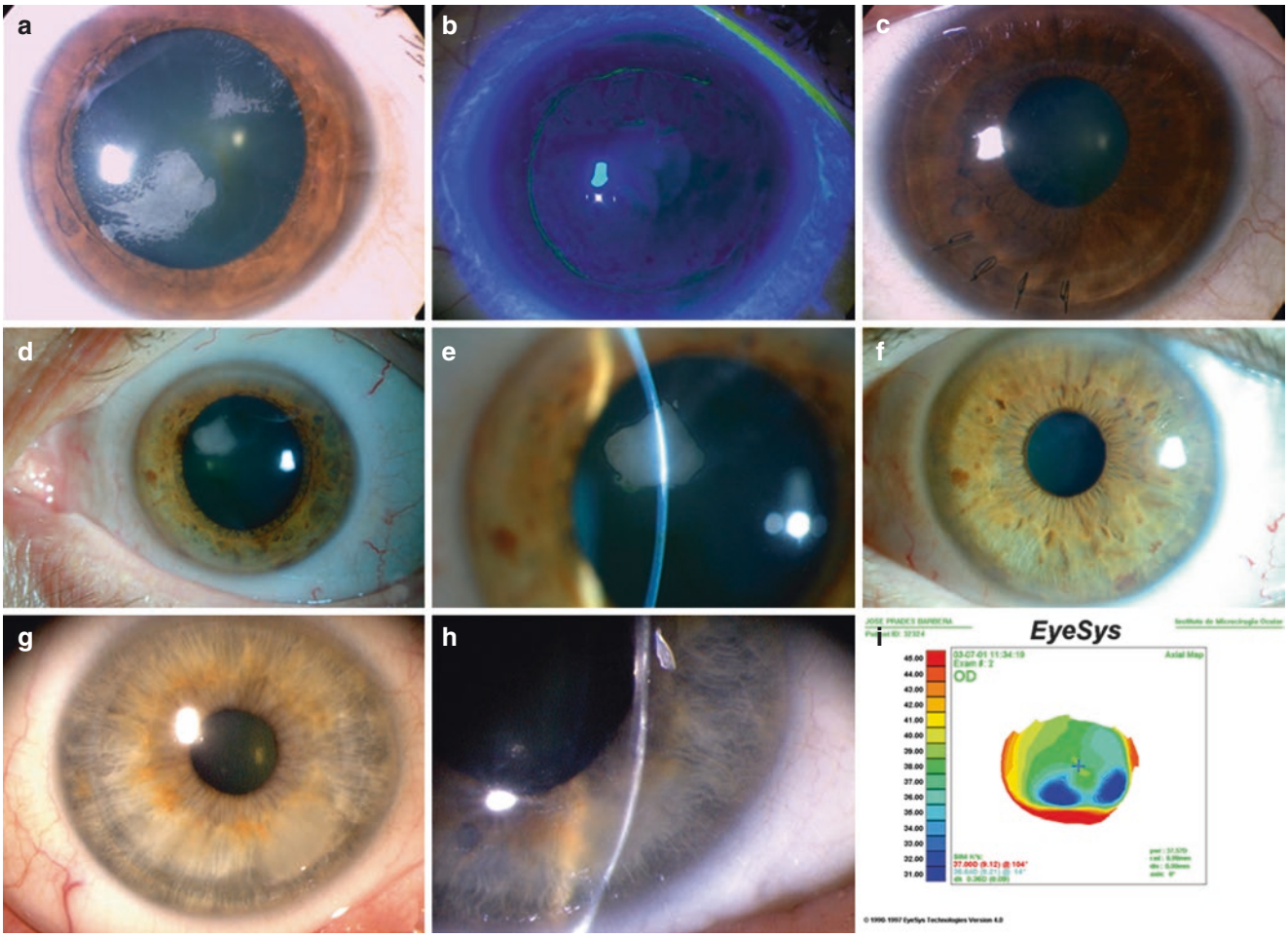

Fig. 12.6 Clinical photographs of epithelial ingrowth after LASIK. (**a**–**c**) In some cases, the flap is sutured after epithelial ingrowth cleaning. Suturing is specially indicated when flap edges are irregular. (**d**–**f**) Clinically significant epithelial ingrowth requires cleaning of the interface. No flap suturing was required in this case. (**g**–**i**) Stromal melting secondary to aggressive epithelial ingrowth. (**i**) Stromal melting may cause irregular astigmatism and severe irregularities in the corneal topography

other sequelae. Surgical treatment would only be required if epithelial ingrowth shows rapid progression, affects directly or indirectly the visual function, or causes severe flap melting [47].

Surgical treatment of epithelial ingrowth consists of relifting the flap and scraping the epithelium cysts and sheet that are present both at the stromal bed and at the stromal side of the flap. The rate of recurrence of epithelial ingrowth after flap lift and scraping ranges from 5 to 68% using various techniques [6, 39, 40, 48]. In our experience, suturing the flap after cleaning of the interface may be effective in reducing the recurrences (Fig. 12.6) [49]. Although some authors have suggested that alcohol or antimetabolite drugs (mitomycin C) may be used to treat recurrent epithelial ingrowth [50], in our opinion they may increase the risk of secondary melting and are contraindicated.

Epithelial ingrowth may masquerade as stromal edema associated with persistent epithelial defects. Delayed diagnosis may result in irreversible visual loss due to stromal melting and/or infectious keratitis [51]. If untreated, advanced flap melting associated with epithelial ingrowth might require flap amputation [6, 14, 15, 52]. DLK grades III and IV require aggressive treatment to minimize visual and anatomical sequelae. The treatment of advanced DLK includes an intensive regimen of oral and topical steroids and flap relift to clean the interface in some cases (Fig. 12.7) [42].

In summary, severe corneal melting after excimer laser procedures is a very rare phenomenon of potentially severe consequences. Prompt diagnosis and treatment is crucial.

Take-Home Pearls

- Corneal melting is the final common response of the stroma to a variety of insults.
- Multiple factors contribute to corneal melting after LASIK, including dry eye or autoimmune diseases. The use of topical NSAIDs might potentiate these factors.
- Melting is commonly associated with inflammatory disorders of the interface, such as DLK.

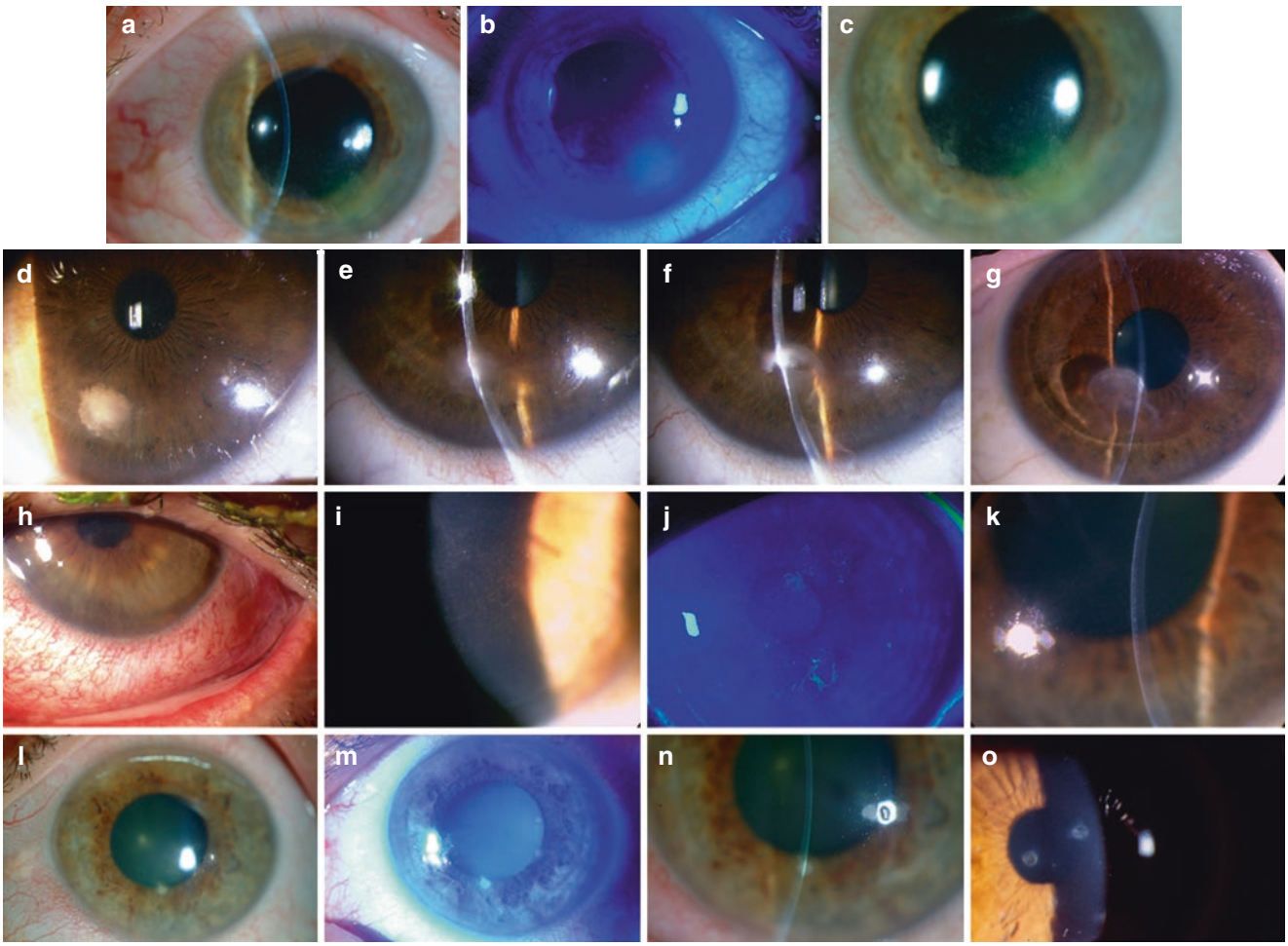

Fig. 12.7 Infectious keratitis after LASIK, either located at the epithelium or at the interface, may induce DLK and secondary focal or diffuse stromal lysis. Prompt treatment is essential to avoid sequelae. (**a**–**c**) Herpetic epithelial infection. (**d**–**g**) Mycobacterial interface infectious keratitis. Significant necrosis of the flap is observed. (**h**–**k**) Adenoviral infection. (**l**–**o**) Pneumococcal infection at the interface. Focal melting and corneal thinning is observed

- Epithelial ingrowth and flap edge melting are more common after LASIK reoperations. An accurate surgical technique is crucial to avoid these complications.
- Stromal melting is usually a self-limited phenomenon.
- Aggressive treatment is required in those very rare, severe cases of advanced epithelial ingrowth or DLK.

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Dry Eye

13

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Core Messages

- Dry eye is the most common early and late postoperative complication after LASIK surgery.
- LASIK-induced dry eye is caused by a combination of decreased corneal innervation and chronic ocular inflammation.
- LASIK-induced dry eye is manifested clinically by the presence of fluctuation of visual acuity and punctate epithelial erosions but minimally decreased average tear production.
- LINE is the preferred term to describe this condition when it occurs after LASIK or LASIK enhancements in an eye with no symptoms or signs of dry eye prior to surgery. Some eyes likely have both LINE and underlying inflammatory dry eye disease.
- Optimization of the ocular surface is an important step to improving patient satisfaction after LASIK surgery.

13.1 Introduction

For the past two decades, LASIK has become the most popular corneal refractive surgery in the United States and most of the world. Although a high satisfaction rate is reported, dry eye is the most early and late adverse effect of LASIK [1]. The purpose of this chapter is to review epidemiology, risk factors, clinical manifestations, diagnostic techniques, and management of dry eye in patients undergoing LASIK surgery.

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13.2 Epidemiology of Dry Eye in LASIK Patients

Estimating the incidence and prevalence of dry eye that occurs after LASIK is difficult since a significant proportion of patients who have this procedure develop a subtle, difficult-to-diagnose form of the disease. There is also a lack of standardized criteria to define this condition. Also, the signs and symptoms of dry eye after LASIK are more prevalent in the early phases of the disease, with a natural tendency for the disorder to resolve over time [2]. However, patients still may report dry eye over long-term follow-up with an occurrence of chronic dry eye disease ranging from 20% to 40% at least 6 months after surgery [3].

13.2.1 Primary Procedures

13.2.1.1 LASIK for Myopia

The incidence of dry eye after LASIK has been estimated to range between 5% [4] and 52% [1] among Caucasian patients, with a higher reported incidence among Asians [4]. This transitory condition, which typically resolves within 6–9 months after surgery [5], is thought to result from a combination of mechanisms.

The pathophysiologic definition of dry eye was changed to a dysfunction of the integrated ocular surface-secretory glandular functional unit [6, 7]. Communication between the ocular surface and lacrimal glands occurs through a sensory autonomic neural reflex loop. The sensory nerves innervating the ocular surface connect with efferent autonomic nerves in the brainstem that stimulate secretion of tear fluid and proteins by the accessory and main lacrimal glands. Ocular surface sensitivity has been found to decrease as aqueous tear

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production and clearance of tears from the ocular surface decrease. This decrease in surface sensation exacerbates dry eye because sensory-stimulated reflex tearing is decreased, resulting in decreased ability of the lacrimal glands to respond to ocular surface insults [6]. Adequate aqueous tear production and clearance with normal mucous gland function are finely controlled by balancing the innervation of the ocular surface and the tear-secreting glands to prevent surface dryness and protect the ocular surface. Inflammation plays an important role as well in the pathogenesis of dry eye, and it has been elucidated over the past decade [8]. Decreased tear production and tear clearance lead to chronic inflammation of the ocular surface. This inflammatory response consists of cellular infiltration of the ocular surface by activated T lymphocytes, with increased expression of adhesion molecules and inflammatory cytokines, increased concentrations of inflammatory cytokines in the tear fluid, and increased activity of matrix-degrading enzymes such as matrix metalloproteinase MMP-9 in the tear fluid [9].

Corneal sensitivity decreases after LASIK because of surgical amputation during flap creation and laser ablation of the nerve fibers innervating the central cornea [2, 10–13]. This, at least partially, interrupts the cornea-lacrimal gland reflex arc that influences both basal and stimulated tear production, tear clearance, and blink rate.

Importantly, impairment of corneal sensitivity also is associated with diminished secretion of trophic modulators that regulate corneal cell metabolism and viability [10, 14, 15]. This deficiency is associated with inadequate healing, even after minor injury, which is a characteristic of neurotrophic ulcers [14]. Thus, we believe that dry eye in postoperative LASIK patients actually represents an overlap syndrome of inflammatory dry eye and LASIK-induced neurotrophic epitheliopathy (LINE). The term LINE was coined by Wilson [10, 11] to describe dry eye occurring after LASIK and LASIK enhancements that lasts 6–9 months after surgery.

Thus, dry eye after LASIK likely represents a multifactorial spectrum of the condition that includes in all cases neurotrophic epitheliopathy component and, in many cases, underlying inflammatory dry eye, in addition to several other potential disorders affecting the ocular surface (Fig. 13.1).

13.2.1.2 LASIK for Hyperopia

The development of punctate epithelial keratopathy after LASIK is more prevalent after high hyperopic corrections compared with similar myopic corrections [16, 17]. In addition to decreased corneal staining, hyperopic corrections can also result in a reduction in tear film stability and reduced tear volume [18]. Hyperopic ablations require larger flaps and more peripheral ablations, which affect the magnitude and duration of corneal sensitivity loss to a greater extent [18]. Furthermore, the central corneal steepening induced by hyperopic ablations can also lead to alterations in blink dynamics and ocular surface tear spreading.

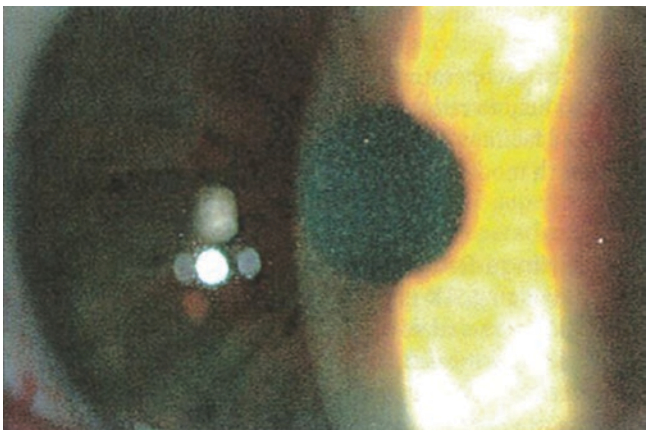

Fig. 13.1 Slit-lamp photo of punctate epithelial erosions in a cornea at 1 week after LASIK. The patient had no symptoms or signs of dry eye prior to surgery, suggesting that this represents a relatively pure case of LASIK-induced neurotrophic epitheliopathy [original figure 5.1.1]

13.2.2 LASIK Enhancements

LASIK enhancements are traditionally performed between 3 and 9 months after surgery when patients are thought to have achieved refractive stability. Despite technological advances in excimer laser with custom ablation profiles and femtosecond laser flap creation, refractive regression still occurs after LASIK, primarily due to wound healing-related factors such as epithelial hyperplasia and stromal remodeling [19, 20]. Patients experiencing refractive regression can be retreated by lifting the flap and reapplying the excimer laser to further reshape the stromal bed or by surface ablation procedures such as photorefractive keratectomy.

The incidence of regression after myopic LASIK can be as high as 27% and, in some studies, has been found to be associated with the presence of chronic dry eye [21]. In this patient population, female sex, higher attempted correction, and higher ablation depth have also been correlated with myopic regression. Preoperative increased ocular surface staining, lower tear volume, tear instability, decreased corneal sensation, and dry eye symptoms have also been correlated with myopic regression in myopic patients [21].

Regression rates for patients undergoing hyperopic LASIK have been calculated to be close to 32%, with similar correlations between dry eye symptoms, greater preoperative ocular surface staining scores, and lower tear volume [18].

Dry eye symptoms have not been shown to increase after myopic LASIK enhancements despite documented higher ocular surface rose bengal or lissamine green staining scores. Interestingly, in this patient population, both Schirmer's tests and tear breakup time (TBUT) have been reported to be

within normal limits, despite a documented reduction in corneal sensitivity for up to 6 months after surgery compared with pre-enhancement levels [22]. This further supports the theory that LASIK-induced dry eye may be partially caused by a neurotrophic epitheliopathy of the cornea [10, 11]. Interestingly, the presence of clinically controlled underlying rheumatic diseases, which predisposes to dry eye, does not seem to increase the rate of refractive regression or enhancements after LASIK surgery [23].

13.3 Risk Factors

Several preoperative (female, gender race, preexisting dry eye syndrome) as well as intraoperative (hinge diameter, higher attempted corrections, ablation depth, microkeratome LASIK) risk factors have been correlated with the development of dry eye after LASIK. Understanding these risk factors can aid the refractive surgeon in the selection of effective strategies to optimize the ocular surface prior to surgery, which in turn can result in improved refractive outcomes.

13.3.1 Patient Population

13.3.1.1 Gender and Age

The incidence of dry eye in female patients has been shown to be significantly higher than for male in large population-based epidemiologic studies [24]. Female gender has been found to correlate with higher rates of myopic [21] and hyperopic [18] regression after LASIK. In addition, increasing age is also associated with dry eye after LASIK, with more reports of post-LASIK ocular dryness in older (over 40 years) individuals [25, 26].

Hormonal differences, more specifically a reduction in androgen levels in peri- or postmenopausal females, may also account for the increase overall prevalence of dry eye symptoms after LASIK surgery [18, 27].

13.3.1.2 Race

Asian patients have been found to have higher prevalence of dry eye symptoms after LASIK compared with Caucasians [4]. Clinically, Asian eyes may experience a longer recovery time for their preoperative dry eye parameters (TBUT, PRT, Schirmer's test, staining score, and corneal sensation) to return to baseline values after LASIK [4, 12, 28] and, thus, experience a more prolonged and severe form of the disease. This notion holds true even when patients are matched for laser surgical ablation depth with Caucasian eyes [4].

It has been speculated that larger changes in tear film parameters seen in Asian populations after LASIK result from differences in the degree of refractive correction, contact lens wear, and orbit and eyelid anatomy [4].

13.3.2 Preexisting Dry Eye Syndrome

Diagnosing the presence of preexisting dry eye syndrome (DES) is one of the most important components for preoperative evaluation of patients considering LASIK surgery [29]. As was previously emphasized, the presence of DES can affect corneal wound healing leading to refractive regression [19] and increased need for enhancements [21].

Preexisting dry eye of different degrees of severity has been documented in 38–75% of patients seeking myopic LASIK surgery [30]. Even though visual outcomes in patients with preexisting dry eye and those with probable or no dry eye have not been shown to be significantly different in terms of best-corrected visual acuity and uncorrected visual acuity up to 12 months after surgery, these patients tend to have more dry eye symptoms, higher ocular surface staining scores, and lower Schirmer's test results [31]. In addition, patients without preoperative dry eye have been shown to undergone earlier recovery of corneal sensitivity (3 vs 6 months) compared with patients' preexisting dry eye [31].

Finally, preoperative optimization of ocular surface can also help to reduce the risk of intraoperative complications and facilitate the performance of LASIK surgery in patients with moderate forms of preoperative dry eye [31, 32].

13.3.3 Hinge-Related Factors

The subject of corneal innervation has gained importance in recent years because of the observation that corneal nerves are routinely injured following modern refractive surgery procedures. Creation of LASIK flap transects the epithelial/subepithelial and superficial stromal nerve plexus located at the edge of the flap and along flap interface, resulting in decreased corneal sensitivity [33]. This damage can lead to transient or chronic neurotrophic deficits [10, 11]. Some studies suggest the corneal nerves predominantly enter the cornea at the 9 and 3 o'clock positions, and, therefore, a vertical flap (superior) would interrupt more corneal innervation compared to a horizontal flap (nasal hinge) [34]. Thus, these studies suggest that nasally hinged flap may cause less loss of sensitivity than a superior-hinged flap. However, recent histopathological studies by Muller et al. [35] performed in human corneas showed conclusively that no larger nerve trunks were present at 3 and 9 o'clock in human cornea but that nerve trunks are equally distributed around the corneal circumference. Other studies [36–38] confirmed these findings.

In terms of dry eye parameters and corneal sensitivity, the results from previous studies with mechanical microkeratome that attempted to spare horizontally oriented corneal stromal nerves during flap preparation via making a nasal-hinged flap versus making a superior-hinged flap were

inconsistent [39]. Some authors reported less corneal sensitivity and low incidence of dry eye syndrome in nasal-hinged flap eyes [12, 34]. In addition, greater tear BUT and Schirmer's test values in nasal-hinged eyes than in superior-hinged eyes were also reported [40]. Most likely, the studies of nasal versus superior flap sensation differences were confounded by differences in flap diameters and thickness between the patients with nasal and superior flap [39].

More recent studies have compared the effect of varying hinge position on dry eye parameters after LASIK with femtosecond laser. The results show no difference between the two hinge positions with regard to corneal sensation, dry eye symptoms, and signs [41, 42]. The femtosecond laser allows creation of horizontally or vertically oriented flaps with the same diameter and thickness. Two studies reported that when performing LASIK with femtosecond laser, hinge position had no effect on corneal sensation or dry eye disease parameters [41, 42]. Femtosecond lasers have the advantage of generating more consistent and predictable flap diameters and thicknesses compared to microkeratomes [43]. There may also be fewer flap-related complications, including reduced epithelial injury and faster recovery of corneal sensation with use of femtosecond laser [44]. One study found that eyes with femtosecond laser flaps had a lower incidence of LASIK-associated dry eye and required less treatment for the disorder [45]. A deeper lamellar dissection is expected to create a larger volume of tissue through which nerves must regenerate, thus delaying the return of corneal sensation [46]. Thus, the lower incidence of dry eye signs and symptoms with femtosecond lasers may be attributed to the creation of thinner flaps, resulting in decreased interruption of corneal innervation and less damage to the ocular surface in general [42, 45].

Finally, factors such as hinge width and flap diameter may also play important roles in LASIK-associated dry eye. One study [34] showed that the loss of corneal sensation and the presence of dry eye syndrome were greater in eyes with a narrow hinge (0.6 mm) flap than in eyes with wider hinge (1.2 mm) flap.

13.3.4 Femtosecond Laser

The femtosecond laser precisely creates variable thickness and diameter corneal flaps with virtually unlimited variation for LASIK. The femtosecond laser has many advantages over mechanical microkeratomes including improved predictability, better flap uniformity, better variation of hinge position and size, astigmatic neutrality, and reduced incidence of epithelial defects, buttonholes, and cap perforations [47]. One study has reported dry eye after LASIK in 66 eyes (33 patients) with the femtosecond laser (assessed by the Ocular Surface Disease Index), with values of 22.9% after the first week postoperatively and 21.9% after the first month. Overall, symptoms were mild and resolved over the first month. The lower incidence of dry eye signs and symptoms with the femtosecond laser has been attributed to lower suction on the eye and creation of thinner flaps, resulting in a greater residual stromal bed and less corneal denervation [7].

Interestingly, another study [45] found less dry eye symptoms in the femtosecond laser group compared to the microkeratome group even when the groups were matched for flap thickness. This finding suggests that factors other than flap thickness are important in the pathophysiology of LASIK-induced dry eye.

Small incision lenticule extraction (SMILE) is a recent procedure using the femtosecond laser to create an intrastromal lenticule that is removed through a small corneal incision [48]. Contrary to LASIK, this all-in-one femtosecond refractive surgery does not require an excimer laser photoablation, at least for the primary surgery, or a full flap cut. As a result, SMILE could constitute a corneal refractive surgery associated with less post-surgery dry eye because of the small tunnel to the surface [49]. However, there are few studies directly comparing SMILE and LASIK with regard to dry eye in a masked study, and, therefore, further study is needed for definite conclusions.

13.3.5 High Attempted Corrections and Ablation Depth

High refractive errors by themselves do not correlate with increased risk of dry eye, although prolonged use of contact lenses to correct these errors can lead to alterations in tear secretion and clearance and prolonged recovery of corneal sensitivity up to 16 months after LASIK [12, 50].

Higher refractive errors necessitate deeper ablations and larger treatment zones to minimize postoperative optical aberrations. The deeper the laser ablation, the greater the distance required for the regenerating nerve trunks to travel in order to reinnervate the corneal epithelium following surgery [1]. Deeper ablation may also lead to more pronounced and prolonged reduction in corneal sensitivity [50].

Regression analysis has estimated that for every diopter of treated spherical equivalent of myopia, there is a 20% greater chance of developing dry eye (based on fluorescein staining alone) in low myopic correction [1]. In addition, laser-calculated ablation depth and flap thickness have also been correlated with dry eye [1]. High attempted myopic correction has also been shown to increase the incidence of myopic regression and further need LASIK enhancements [21]. The same can be said for patients with high hyperopic corrections in whom punctate epithelial keratopathy after LASIK is more prevalent compared with similar magnitudes of myopic correction [51].

13.4 Diagnostic Approach to Patients with Dry Eye After LASIK

13.4.1 Clinical Manifestation

Clinical manifestation of dry eye after LASIK are better characterized by exploring the patients' symptoms, performing a comprehensive clinical examination, and understanding the mechanisms leading to dry eye after LASIK surgery.

In general, dry eye has been defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear and inflammation of the ocular surface [9]. Dry eye can be further classified into tear deficiency (production), increased evaporative loss (lipid dysfunction such as in ocular rosacea), or poor blink distribution (mechanical) over the ocular surface. Recently, however, it has become clear that tear composition is also an important factor in the pathophysiology of dry eye disease [52]. Following LASIK surgery, the additional influence of the neurotrophic contribution of transient loss of innervation to the flap is also an important factor [10–12].

13.4.2 Pathophysiology

The creation of the LASIK flap along with the photoablation of the corneal nerve plexuses by the excimer laser during LASIK surgery can lead to the development of a neurotrophic state of the ocular surface [10]. Decreased corneal sensitivity can lead to both quantitative and qualitative tear film abnormalities [3, 53]. Chronic sensory denervation of the cornea also leads to increased cytokine and growth factor expression and release [54], increased tear film osmolarity [55, 56], mucin deficiency [30], as well as alterations in the blink frequency [2]—all contributing to abnormalities of the ocular surface. These changes can also contribute to the development of chronic inflammation of the ocular surface, which can be demonstrated histologically by the presence of activated lymphocytes and loss of conjunctival goblet cells in LASIK patients [57, 58]. Therefore, conceptually, the pathogenesis of dry eye after LASIK should be considered multifactorial.

13.4.3 Dry Eye Symptoms After LASIK

A high proportion of patients undergoing LASIK surgery develop dry eye symptoms during early postoperative course. Patients' dry eye symptoms have been shown, however, to correlate poorly with the results of clinical tests for dry eye [53]. Since the cornea becomes neurotrophic after LASIK [11], patient complaints can be different from classic dry eye patients. Visual fluctuation, which is exacerbated during certain times of the day (e.g., glare at night or night vision problems), is probably the most common presenting problem of dry eye after LASIK [21]. In addition, patients may also complain of dryness, foreign-body sensation, and tearing. In severe cases where there is trauma to the epithelium or occult basement membrane dystrophy, patients can also develop symptoms related to recurrent erosion syndrome after LASIK, which, although rare, is a source of significant patient morbidity when it occurs [13]. Moreover, the presence of chronic dry eye has been correlated with the development of refractive regression in both myopic [21] and hyperopic [18] patients—which may also be a source of visual fluctuation in these patients. Importantly, the punctate epithelial erosions on the flap after LASIK are highly variable in their location over time and their effects on light scattering and, therefore, trigger variable visual quality.

13.4.4 Clinical Signs

Clinical signs of dry eye after LASIK can be divided into three groups: tear film-related abnormalities, ocular surface staining, and corneal sensation abnormalities. In practice, patients with LASIK-induced dry eye usually present with a combination of the above-described signs of dry eye.

13.4.4.1 Tear Film-Related Abnormalities

Evaluation of the tear film can be divided into four basic components: tear secretion, tear volume, tear osmolarity, and tear stability.

Tear Secretion

The Schirmer I test without anesthetic is classically considered a test of reflex tear secretion in response to conjunctival stimulation. It is a useful test for the evaluation of dry eye, although the diagnosis or exclusion of dry eye cannot be made on the basis of this test alone. It is by far the simplest test for assessing aqueous tear production. Less than 6 mm of wetting after 5 min is often cited as indicative of LASIK surgery relevant tear deficiency [59], although the reliability of the test may be affected by environmental conditions such as temperature or humidity. The Schirmer I test can be performed after instillation of a topical anesthetic, and it has been assumed to measure the basal tear secretion rate in the absence of a reflex component. It is likely, however, that sensory and psychological stimuli other than conjunctival stimuli alone are involved in reflex tear secretion [59]. For example, nasal anesthesia reduces the Schirmer value obtained from the test. The Schirmer II test assesses reflex secretion of tears in response to nasal stimulation in addition to the conjunctival stimulation.

This test is very uncomfortable for the patient, as it involves vigorous stimulation of the nasal mucosa [60].

Tear secretion measured by either basic tear secretion or Schirmer's test I has been shown to decrease, albeit by relatively small amounts, after LASIK surgery compared with preoperative levels [2, 12, 61, 62]. This decrease in tear secretion has been consistently observed in several studies at 1 month after LASIK surgery [2, 12, 61] with some studies returning to baseline levels by 3 or 6 months [2, 12]. The cutoff established by an investigator (measured filter paper wetting) can significantly alter both the sensitivity and specificity of these tests and, therefore, the results of the trials. However, in some patients with sign and symptoms of dry eye after LASIK, no statistically significant differences in tear secretion (Schirmer's test I) have been found compared with asymptomatic eyes from 1 to 6 months after surgery despite of the presence of ocular surface staining with fluorescein and rose bengal [10]. In our opinion, the Schirmer's test is most useful preoperatively if it is consistently low (less than 5 mm wetting in 5 min) and is used as an indication that a particular patient is not a good candidate for LASIK unless the test is significantly improved over time by treatment of the underlying dry eye disease. Importantly, even patients with completely normal Schirmer's tests can develop severe LASIK dry eye—presumably due to the neurotrophic component of the condition.

Tear Film Volume

The phenol red thread test (PRT) is said to provide an index of tear volume, which is related to tear secretory rate and thus detects aqueous-deficient dry eye disease. The test uses a cotton thread that has been treated with phenol red, a pH sensitive substance that changes from yellow to red on contact with the near neutral pH of the tears [59]. The end of the cotton thread is gently placed over the lower eyelid (as in the Schirmer's test), and the wetted length of the thread is measured after 15 s. Using a cutoff value of 6 mm for the diagnosis of dry eye, this test shows less variation between individual patients and is reportedly better at detecting dry eye than the Schirmer's test [59]. However, there is not universal agreement about its value compared to the Schirmer's test. As the test only takes a short time, the effects of environmental conditions, such as humidity, are minimized. The Japanese diagnostic criteria for dry eye use a cutoff value of 10 mm for the phenol red thread test [60].

PRT has not been shown to decrease in the eyes after myopic LASIK surgery compared with control eyes [63]. Tear volume, as measured with this technique, has not been shown to correlate with either age or decrease in corneal sensitivity in age-matched control patients with myopia [63]. In contrast, when preoperative PRT values are compared with postoperative PRT values in the same patients with myopia undergoing LASIK, PRT has been shown to decrease compared to baseline at 1 and 2 weeks, 1 month, and 3 months after surgery [21]. Similar results have been found in hyperopic patients with chronic dry eye who have undergone LASIK [18]. In addition, hyperopic regression has also been correlated with lower PRT results at 2 weeks and 1 month in patients with preexisting reduced PRT values prior to surgery [18].

Tear Film Osmolarity

Elevated osmolarity of the tear film has been reported to be a hallmark and defining feature of dry eye disease, but previous methods of measurement have been laborious and time consuming. Recent availability of an in-office instrument for determination of tear film osmolarity has allowed more clinical application of such technology [55]. A new tear osmometer (TearLab Corp, San Diego, CA) has been approved by the FDA for marketing in the United States [56]. This same technology is available in Europe and Canada and is in clinical trials in Japan. The device uses a disposable tip (lab on a chip), which collects a 50 nL sample upon contact with the inferior lateral marginal tear strip. The tears are collected in a microchannel, and tear osmolarity is measured using electrical impedance within 3 s. The collecting pen and chip are inserted into a desktop unit, and the osmolarity value is displayed within 10 s. Results obtained with this technology have been shown to be equivalent to those obtained with laboratory instruments requiring much larger samples, transfer of samples, and more than 15 min to perform [53].

In a multi-site clinical study of 299 subjects, tear osmolarity alone, compared to the most commonly performed objective tests for the diagnosis of dry eye disease, showed a linear relationship to increasing severity of disease measured using a composite index of severity across the entire range of severity [56]. In addition, tear osmolarity had a positive predictive value in the diagnosis of dry eye disease of 86%, the highest of all the objective measures tested [55, 56]. Measurement of both eyes is recommended due to the transient effects of compensatory mechanisms that lower tear osmolarity in the early stages of dry eye disease. These effects are seen asymmetrically, and the higher value is reflective of disease effects [53]. In our experience, however, the results of the test are also often highly variable in normal patients without any signs or symptoms of dry eye. Frequently values vary significantly in the same eye in the same environment performed only minutes apart. Thus, the utility of the method is questioned by many surgeons and scientists.

The tear film has been shown to significantly decrease after LASIK for myopia compared to preoperative levels at 3 and 6 months after surgery [64]. The increase in tear osmolarity seen after LASIK surgery can be explained by two different mechanisms. These include decreased tear production or increased tear evaporation.

Tear Film

The tear breakup test (TBUT) is the standard clinical test for estimating tear film stability [59]. It is a provocative test in the sense that the instillation of fluorescein shortens the normal breakup time. Breakup is best observed with use of a blue exciter and yellow barrier filter, while the patient refrains from blinking. The yellow filter, however, is not essential. The breakup time is the time that elapses from the last blink to the first appearance of a random dark spot in the fluorescein-stained film. Breakup can be seen to evolve in a characteristic way with time. The normal tear film breakup time varies between individuals and in the same person at different times of the day. In general, a breakup time of less than 10 s suggests an unstable tear film. Tear breakup time is reduced in all forms of dry eye [60].

A noninvasive test of tear stability is available that does not involve the instillation of fluorescein dye. In this test, the noninvasive breakup time (NIBUT) test, tear breakup time is measured as the time between the last blink and the breakup of a reflected image of a target on the tear film [59].

TBUT values have been consistently shown to decrease after LASIK surgery [8, 18, 21, 62]. Decreased TBUT can be measured as early as 1–7 days after LASIK surgery with variable recovery time to baseline levels. Decreased TBUT has also been correlated with subjective scores of dryness during the first 3 months after LASIK surgery [2]. In addition, lower TBUT values have been associated with regression after LASIK at both 6 and 12 months after surgery [2]. TBUT can be reduced after LASIK due to a decrease in corneal sensitivity, which in turn can lead to decreased tear secretion and increased evaporative tear loss [2]. Moreover, surgical injury (intraoperative trauma to the corneal epithelium and postoperative toxicity from eye drops) can also lead to an irregular ocular surface and affect TBUT values [62]. An irregular tear film interface after surgery can lead to patient dissatisfaction with LASIK surgery by inducing higher order aberrations such as coma and trefoil [65].

13.4.4.2 Ocular Surface Staining

Ocular surface staining after the installation of dye is considered as an important element in the evaluation of patients with dry eye. Staining patterns of the cornea and conjunctiva can be graded using different methods such as the Oxford grading scheme [66]. The Oxford grading scheme, or a modified version of this test, has been used in several clinical trials to assess the presence of dry eye before and after LASIK surgery [4, 12, 32, 41, 63]. Fluorescein sodium, rose bengal, and lissamine green have been all used as staining agents to evaluate the severity and distribution of ocular surface abnormalities related to dry eye in LASIK patients. The order in which these tests are performed is important, since both rose bengal and lissamine green can affect the results of the Schirmer's test and tear breakup time test due to the induction of reflex tearing.

Surface Dyes

Fluorescein Sodium

Fluorescein sodium is a xanthine-derived dye (yellow colored), which is routinely used to assess the pre-cornea tear meniscus and ocular surface. Fluorescein has the advantage of being well tolerated and relatively nontoxic to corneal epithelial cells. Fluorescein is applied as a solution or after moistening the tip of a fluorescein-impregnated paper strip, which is applied to the inferior conjunctival fornix. The patient is then asked to blink several times, and the presence and pattern of staining is assessed with the use of a cobalt blue exciter filter. Importantly, fluorescein stains where the basement membrane or underlying stroma is exposed by epithelial injury. A disadvantage of this technique is the rapid penetration of fluorescein into the corneal stroma in the presence of epithelial defects, which can blur the margins of the staining defect [59]. Also, many patients with moderate to severe dry eye, including LINE, have no staining with fluorescein when there is heavy staining of the cornea and/or conjunctiva with lissamine green or rose bengal.

Rose Bengal

Rose bengal is a fluorinated dye (pink in color), which causes dose-dependent staining of the cornea and conjunctiva where there is disruption of the mucinous layer of the conjunctiva or cornea [50]. Installation of a drop of rose bengal should be performed, while the patient is looking down and after topical anesthetic administration in order to minimize patient discomfort. Rose bengal staining of the ocular surface can be enhanced using a red-free (green) light source. Since rose bengal does not diffuse beyond the conjunctival epithelium and the staining pattern can be visualized for a longer period of time compared to fluorescein. A major disadvantage of rose bengal use is related to its intrinsic toxicity to corneal epithelial cells and pain in eyes with severe dry eye. Importantly, rose bengal is NOT a vital dye—in culture it stains both dead and live cells equally well unless the cells are coated with a protecting layer such as mucins [67].

Lissamine Green

Lissamine green is a synthetic dye that causes dose-dependent staining of the ocular surface but induces less toxicity to the ocular surface compared with rose bengal. Lissamine green, viewed in white light, produces a staining pattern similar to rose bengal, in that staining is best seen over the white of the sclera and least on the cornea, over a dark iris. Like fluorescein, it is well tolerated. Although lissamine green has not been systematically studied, it likely also stains areas on the conjunctiva and cornea where there is

disruption of the mucinous protective layer covering these cells [59]. As with rose bengal [67], lissamine green is not a vital stain and stains live and dead cells equally well in the absence of a protective coating such as mucins.

Oxford Grading Scheme

The Oxford grading scheme was developed to quantify the amount of cornea and conjunctival epithelial surface damage in patients with dry eye [68]. This grading scheme uses a standardized chart with a series of panels depicting the distribution of ocular surface staining in increasing order of severity. The examiner compares the overall pattern of the staining seen during the clinical examination with the appearance of each panel and grades the severity of ocular staining accordingly.

Significance of Ocular Surface Staining in LASIK Patients

Ocular surface staining related to pure LINE after LASIK surgery is usually confined to the area of the flap, often sparing the flap edges. Punctate epithelial erosions can develop as early as 1 week [12] and usually peak by 1–3 months after LASIK surgery [12, 18, 44]. Ocular staining scores have a tendency to return to preoperative baseline levels by 6–12 months after surgery [12, 21, 49].

13.4.4.3 Ocular Sensation Abnormalities

The integrity of the ocular surface-trigeminal nerve-brainstem-facial nerve-lacrimal gland axis is essential for the maintenance of the basic refractive properties of the cornea. This complex neuronal network regulates, among other functions, tear production (basal and stimulated) and the blink rate, which are essential for optimal refraction of light at the air-tear interface.

Corneal sensitivity measured by esthesiometric techniques may be greatly reduced before and after LASIK surgery [1, 2, 4, 21, 22]. This reduction in corneal sensation has been associated with contact lenses wear, decreased tear production, higher staining scores, tear instability, and reduced blink rate in some patients after LASIK.

Esthesiometry Methods

Cochet-Bonnet Esthesiometer

The Cochet-Bonnet esthesiometer is considered the gold standard for the assessment of corneal sensitivity for touch sensation. Briefly, this technique uses a 60-mm-long and 0.12-mm-wide adjustable nylon monofilament. The monofilament is soft when fully extended and becomes rigid as the length is shortened with a hand piece in 5-mm decrements. The monofilament is then applied to the surface of the cornea in a perpendicular plane while the patients look straight ahead. The length of the monofilament is shortened until the patient feel it for the first time, and then the monofilament length is subsequently recorded. In principle, the higher the number recorded (longer filament length), the more sensitive the cornea. It is important to use this test at the beginning of the exam and prior to anesthetic drop use.

Central corneal sensitivity decreases by about 50% of the Cochet-Bonnet filament length after LASIK and recovers gradually to nearly preoperative levels between 6 months and a year [28, 34, 41, 69]. However, since preoperative and postoperative central corneal sensitivity measurements are truncated due to the limitation of the Cochet-Bonnet esthesiometer [70], postoperative corneal sensitivity may not return to "real" preoperative levels. The change in sensitivity after LASIK varies between different regions in the flap, with higher levels of sensitivity and faster recovery rate at the hinge side compared with slower recovery rate in the central cornea [46, 71, 72]. Peripheral sensitivity within the flap and the central cornea sensitivity returns to preoperative levels within a year after LASIK [33, 46]. Conversely, some authors have reported that central sensitivity, measured using the Cochet-Bonnet esthesiometer, does not return to preoperative values by study end at 3 weeks, 6 months [50, 72], or 16 months [12] postoperatively. The differences in corneal sensitivity between studies may be due to the relatively short time period of the study designs and other factors such as the reliability of the esthesiometer, the truncated measurement range of this instrument [70], a diurnal variability of ocular sensitivity [73], or differences between the surgical procedures (i.e., different flap hinge positions, degree of refractive correction or flap diameter) [3].

13.4.5 Conjunctival Goblet Cell Density

Goblet cell density, a histopathological feature of dry eye [3], and its alteration after LASIK are thought to contribute to dry eye by affecting the production of mucins [58], which have an important role in the stabilization of the tear film [74]. Goblet cell density decreases significantly and returns to preoperative levels between 6 and 9 months after LASIK [58, 75]. Several mechanisms have been proposed to explain the reduction in goblet cell density after LASIK, including factors associated with the surgical procedure and corneal nerve damage [58, 76]. It could also be related to changes in the overall milieu of the tear film with a decrease in growth factors that are essential to goblet cell viability in the period after LASIK surgery. It has been suggested that a greater reduction of goblet cell density occurs after a femtosecond laser procedure because the duration of vacuum suction is longer than with mechanical microkeratome [58]. However, one study found that the duration of suction time was independent of the alteration in goblet cell density after LASIK [76]. Further, it has been speculated that the femtosecond laser applies less force and, hence, results in less damage to

the conjunctiva [45]. Therefore, the argument that longer treatment time impacts goblet cell density has not been validated. A compelling argument is that goblet cell density reduction after LASIK may be a secondary effect of corneal nerve damage and subsequent inflammation [75, 77] and secondary changes in tear film growth factors.

13.4.6 Subjective Evaluation of the Ocular Surface Disease

The Ocular Surface Disease Index (OSDI) was developed by the Outcomes Research Group at Allergan (Irvine, CA). This index has been validated in prospective clinical trials and has been shown to effectively discriminate and grade the severity of dry eye symptoms [78].

Briefly, the OSDI consists of 12 questions that have been designed to gather information regarding the severity of dry eye symptoms. The completed questionnaire is graded using a severity scale from 0 to 4. Items 1–5 consist of symptom-related questions, items 6–9 assess how much dry eye symptoms interfere with daily tasks, and item 10–12 assess environmental conditions that can potentially exacerbate dry eye symptoms. The frequency of symptoms is recorded using the severity scale previously mentioned. A score of 0 indicates that symptoms are not present in time, a score of 1 some of the time, a score of 2 half of the time, a score of 3 most of the time, and a score of 4 all of the time. The OSDI is then scored using the following formula: OSDI = sum of severity score for all questions answered/total number of questions answered × 4 [59, 78].

In our experience, the OSDI provides a valuable tool for detecting patients with occult dry eye during the screening process for refractive surgery.

13.5 Management

Optimization of the ocular surface is an important step to improving patient satisfaction and outcomes after LASIK surgery. The management of dry eye begins during the preoperative screening examination, when patient's signs and symptoms are assessed, and an individualized treatment regimen devised to prepare ascertain whether the patient is a candidate for LASIK and, if so, the ocular surface optimized prior to surgery.

Assessment begins with the diagnosis and treatment of rosacea-blepharitis. Either of these conditions may exacerbate the dry eye condition and increase the overall inflammatory state of the ocular surface. Treatment of these conditions include lid hygiene regimens such as regular mechanical expression of the glands ("warm compression") and in some cases the use of oral doxycycline and topical antibiotics [79].

In patients who present symptoms alone, symptoms and signs, or signs alone of the dry eye disease, including onset of contact lens intolerance, and conjunctival and/or corneal staining with rose bengal or lissamine green, it is imperative to treat the underlying condition because these patients are predisposed to the development of severe LASIK-induced neurotropic epitheliopathy (LINE) after LASIK [10, 11]. In addition, any punctate epithelial erosions of the corneal surface may induce artifact in wavefront measurements used to drive custom corneal ablations with the excimer laser. Although artificial tears and several other treatment modalities may be helpful, topical cyclosporine A 0.05% (Restasis, Allergan, Irvine, CA) has become the mainstay of treatment for many refractive surgeons, since pretreatment prior LASIK surgery and continued treatment in the months after surgery has been found to markedly reduce LASIK-induced dry eye and improve outcomes of LASIK surgery [32, 80]. Importantly, the only evidence of underlying dry eye and a predisposition to severe LINE may be a history of contact lens intolerance with otherwise normal examinations. We commonly treat patients with these symptoms for 2–3 months prior to LASIK and for 6–8 months after LASIK as prophylaxis against LINE and LASIK-induced dry eye [32].

13.5.1 Topical Preparations

13.5.1.1 Artificial Tears

Lubrication of the ocular surface is a mainstay of treatment of LASIK-induced dry eye prior to and after surgery. Tear supplements have varied formulations [53]. Some tear substitutes add electrolytes, which are present in normal tears, to help prevent ocular surface damage. Potassium and bicarbonate ions are important for surface ocular health and are included in Bion Tears (Alcon, Inc., Fort Worth, TX) and TheraTears (Advanced Vision Research/Akorn, Lake Forest, IL). Because bicarbonate is not stable (breaking down into water and carbon dioxide), these formulations are packaged in foil. Dry eye patients have elevated tear osmolarity. This causes both corneal and conjunctival surface changes, because the hyperosmotic tear film is pro-inflammatory [81]. HypoTears (Novartis, Duluth, GA) and TheraTears are hypotonic artificial tears based on this principle. Optive (Allergan, Inc., Irvine, CA) is a tear supplement formulated with compatible solutes (e.g., glycerin, erythritol, and levocarnitine) that distribute between the tear film and intracellular fluid in a way that protects against the effects of hyperosmolarity of the tear film. The main component of most supplemental tear preparations is the viscous agent. These are macromolecular complexes that increase the residence time of the supplement in the tear film. Depending on the viscosity of the lubricant, the supplement may cause blurred vision. The common base polymers in tear supplements are carboxymethylcellulose

and hydroxymethylcellulose. Systane (Alcon, Inc., Fort Worth, TX) contains hydroxypropyl-guar (HP-guar), a gelling agent that has been combined with glycol 400 and propylene glycol to prevent corneal desiccation. In addition to viscous agents, certain tear supplements attempt to mimic the lipid component of tears. Refresh Optive Advanced (Allergan) contains castor oil and is labeled "lipid enhanced to retard evaporation." Mineral oil is a major component of Soothe XP (Bausch and Lomb, Rochester, NY). Systane Balance (Alcon) has a lipid emulsion in addition to the HP-guar to stabilize the lipid layer of the tear film. A combination of mineral oils is used in Retaine MGD (Ocusoft, Richmond, TX). Hyaluronic acid is a highly hygroscopic viscous agent that has surface coating properties and is a component of many tear products outside the United States [53].

Among the wide variety of tear supplements, none is clearly superior. Head-to-head studies may show some comparative improvement in symptoms and objective signs [53]. Preservatives in the tear supplements commonly have an impact on the ocular surface, especially preservatives that tend to be used in inexpensive formulations prepared and sold by large pharmacy chains. Thus, benzalkonium chloride and EDTA are toxic to the ocular surface and commonly cause rose bengal and lissamine green staining of the ocular surface as well as heightened patient symptoms of "dry eye." The toxicity of preservatives increases with more frequent use and in patients with dry eye, because of decreased tear volumes and more susceptibility to preservative toxicity. Therefore, when supplemental tears are used more than three to four times a day, preservative-free unit dose vials are recommended [53].

Ophthalmic ointments are the thickest of lubricants used to protect the ocular surface. Ointments adhere to the surface longer than either artificial tear or gel supplements. They are typically used before bedtime to provide relief of dry eye symptoms, enabling sleep [53].

13.5.1.2 Lid Scrubs and Mechanical Compression of the Meibomian Glands

Management of rosacea-blepharitis and meibomian gland dysfunction also represents a very important step for the optimization of the ocular surface. As a first step, blepharitis should be managed with the use of commercially available lid scrubs and warm compresses, along with lid hygiene with neutral detergents such as baby shampoo. Ocular rosacea and meibomian gland dysfunction are best treated with mechanical compression of the eyelids after warm compress or in the shower, while warm water is impacting the closed eye so that the meibum is more fluid and easier to express. As a second step, oral tetracyclines (doxycycline) 40–100 mg once or twice a day can also be a useful adjuvant due to the changes it makes to meibum and the matrix metalloproteinase inhibition properties of these medications. Matrix metalloproteinase activity has been shown to be increased in patients with rosacea-associated corneal diseases [79].

13.5.1.3 Topical Cyclosporine A

Cyclosporine A 0.05% ophthalmic solution (Restasis) has been extensively used for the management of dry eye and has found increasing acceptance among refractive surgeons for optimizing the ocular surface prior to surgery and treatment of LASIK-induced dry eye with or without LINE [32, 80]. Presumably cyclosporine A is effective in the treatment of what is thought to be pure LINE due to actual underlying inflammatory dry eye that is commonly symptom and sign free prior to LASIK surgery. Our approach is to institute treatment with topical cyclosporine A in any patient who has preoperative signs and/or symptoms of dry eye, especially if there is conjunctival or corneal staining with rose bengal or lissamine green. These patients are reevaluated at 1-month intervals for resolution of their dry eye symptoms and signs prior to completion of the preoperative evaluation. (e.g., obtaining wavefront measurements). In our experience, over 50% of the patients with preoperative symptoms and signs will complete the resolution within 1 month of the instituting treatment (likely because they tend to be less severe dry eye patients) and can complete their preoperative evaluation and proceed to LASIK surgery with continued administration of cyclosporine A for 6–8 months after surgery [32]. Some patients take several months of treatment with cyclosporine A before there is a complete resolution of symptoms and signs and surgery can be performed. Approximately 10–15% of patients will continue to have symptoms and/or signs of dry eye despite topical cyclosporine A treatment for 6 or more months. In our opinion, these latter individuals are no good candidates for refractive surgery [32].

Topical cyclosporine A treatment has proven to be very safe [82]. Some patients (approximately 10–15%) have stinging upon initial installation of cyclosporine A. This typically occurs in more severe patients with moderate to severe conjunctival and/or cornea staining [83]. Stinging can be minimized by concurrent temporary application of a topical corticosteroid such as prednisolone acetate 1% or loteprednol etabonate 0.5%, typically for 10–14 days [13]. The corticosteroid drop is then discontinued, and the topical cyclosporine A continued beyond surgery—stopping only on the day of the surgery out of concern, the vehicle could somehow diffuse beneath the flap.

Patients who are treated preoperatively and postoperatively with topical cyclosporine A rarely develop clinically significant LASIK-induced neurotrophic epitheliopathy (LINE). If LINE develops despite cyclosporine A treatment, then cyclosporine A should be continued and may be increased to four times per day and may be augmented with

other modalities including non-preserved artificial tears and ointments, oral omega fatty acids, and punctal plugs.

Some patients with no symptoms or signs of dry eye disease prior to LASIK will develop LINE after LASIK surgery [32]. Many of these eyes have underlying occult inflammatory dry eye disease, and transecting the corneal nerves adds another stressor that tips the eye over the threshold to clinical disease. Once treatment is instituted, the cyclosporine A is typically continued 6–8 months and, in our experience, is highly effective in treating the disorder. Some patients have recurrence of dry eye signs and symptoms when the cyclosporine A is discontinued and elected to continue the cyclosporine A indefinitely. It is important to remember that dry eye often progresses in eyes that never had LASIK surgery and such apparent dry eye "caused or worsened by LASIK" might have occurred even if surgery had not been performed. Subsequent LASIK enhancements should include cyclosporine A pretreatment because LINE recurs in virtually 100% of cases without treatment. Consideration can also be given to sequential LASIK enhancement so that symptoms are minimized.

13.5.2 Punctal Plugs

Our use of punctal plug has declined markedly since topical cyclosporine A treatment became available. Punctal plug occlusion is not recommended in patients with underlying inflammatory etiology responsible for the development of their dry eye until the inflammation has been controlled with anti-inflammatory treatment. Tears containing inflammatory cytokines can become stagnant in the conjunctival sac through the action of punctal plugs and can further exacerbate damage to the ocular surface.

In LASIK patients who continued to demonstrate signs of dry eye such as punctate epithelial erosions, punctal plugs are a reasonable adjuvant. If despite cyclosporine A treatment a patient continues to have LINE, then punctal plug may be a helpful addition to augment treatment [84, 85].

13.5.3 Oral Dietary Supplements

Nutrition supplementation with omega-3 essential fatty acids has been associated with reduction in chronic dry eye symptoms [86]. Omega-3 fatty acids are considered anti-inflammatory agents [87]. Although the role of nutritional supplementation has not yet been evaluated in the context of LASIK surgery, dietary supplementation represents a logical addition to support ocular surface and corneal health, especially in moderate to severe dry eye patients who do not respond adequately to topical cyclosporine A or if topical cyclosporine A is not available.

13.5.4 Autologous Serum

The use of autologous serum should be exceedingly rare after LASIK because most patients who might need this form of treatment have been effectively screened in the preoperative evaluation and are too severe to be good candidates for refractive surgery. Thus, if a patient fails cyclosporine A treatment or this treatment is not available and they continue to have punctate ocular surface staining with rose bengal despite intensive non-preserved artificial tears and punctal plug, then they should not undergo LASIK surgery. Occasionally, however, patients who have symptoms and signs develop after LASIK that are unresponsive to other treatments, and treatment with autologous serum becomes a good option. Despite lack of regulatory approval, autologous serum (20–50% topical solution) is now documented in numerous reports to have benefit in a variety of patients suffering ocular surface disease, including Sjögren's disease [88], graft-versus-host disease, Stevens-Johnson syndrome, cicatricial pemphigoid, and other conditions where refractive surgery is typically not a good option [89]. Autologous serum contains fibronectin, vitamin A, cytokines, and growth factors, as well as anti-inflammatory substances, such as interleukin-1 receptor antagonist and inhibitors of matrix metalloproteinases. It is not clear which of those constituents is most helpful, but significant improvement in symptoms, fluorescein TBUT, and rose bengal staining scores have been reported compared with artificial tears in many patients [90]. The disadvantages of using autologous serum include the nuisance of preparation, the need to refrigerate the drops, the potential risk of infection if contamination of the solution occurs, and the expense [91]. The stability of frozen autologous serum has been verified, however, for up to 3 months [90]. Typically, the serum is applied topically four to eight times daily, and this can be done in conjunction with other therapies, including cyclosporine A [53].

Topical autologous plasma has been reported to improve corneal epithelial healing and improve corneal nerve morphology and function in patients with neurotrophic keratopathy [92].

Conclusion

Dry eye is the most common complication associated with LASIK surgery. LASIK-induced dry eye represents a multifactorial condition that is manifested clinically by the presence of fluctuation in visual acuity, punctate epithelial erosions, and decreased tear production. Patients with LINE can develop punctate epithelial erosions and lissamine green/rose bengal staining of the ocular surface in the presence of normal Schirmer's tests. Damage to corneal nerves, induced by the creation of the LASIK flap and excimer laser tissue ablation, induces a transient dry eye state via denervation, leading to decreased tear pro-

duction, altered cytokines expression (which modulate wound healing), loss of conjunctival goblet cells (which reduces mucin production), and decreased blink rate (causing mechanical problems with tear distribution over the ocular surface).

Management of dry eye after LASIK begins during the screening visit, with optimization of the ocular surface using artificial tears, warm compresses, and lid hygiene and treating the underlying ocular surface inflammation with immunomodulatory agents such as cyclosporine A.

Take-Home Pearls

- The ocular surface should be optimized prior to LASIK surgery.
- Recognition and treatment of rosacea-blepharitis should include lid hygiene and lid compression regimens and in some cases oral doxycycline and topical antibiotics.
- Lubrication of the ocular surface with non-preserved artificial tears is a mainstay of treatment of LASIK-induced dry eye prior and after surgery.
- Topical cyclosporine A 0.05% is especially helpful in the prophylaxis and treatment of LASIK-induced neurotrophic epitheliopathy (LINE). Patients who are pretreated with topical cyclosporine A rarely develop LINE.
- Although sometimes helpful, punctal plug occlusion is not recommended as a first-line treatment in patients with an underlying inflammatory-based dry eye since inflammatory cytokines may be maintained at high levels within the tears.

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Post-LASIK Corneal Dysesthesia

14

Jorge L. Alio, Miguel A. Teus, Jorge L. Alio del Barrio, and Andreas Katsanos

Core Messages

- Post-LASIK corneal dysesthesia is a new entity that may explain unresolved dry eye symptoms that persist months postoperatively.
- This chapter discusses the fundamentals of post-LASIK corneal dysesthesia.

Corneal dysesthesia after LASIK is the symptomatic presence of persistent dry eye disease post-operatively, with the absence of clinical signs. Patients complain of symptoms such as foreign body sensation, burning, and pain with no or minimal clinical evidence of dry eye signs and without any other ocular surface inflammatory conditions.

This entity has been found in clinical practice for some time. Patients with a disproportionate level of ocular symptoms following LASIK can take months or years to solve. Meanwhile, these patients suffer a long-standing process of ocular discomfort which is not alleviated with any lubricating or anti-inflammatory topical medication. Many attempts have been made by many surgeons, empirically, in the past to solve this problem but without success.

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Typically, corneal dysesthesia syndrome following LASIK is characterized in young to middle-aged patients who have received medical treatment for dry eye post-LASIK and symptoms were not achieved. Ocular signs may improve if present, however symptoms remain unresolved. These patients typically complain of foreign body sensation and pain, which is variable and frequently affected by environmental conditions. The lack of symptom relief despite topical treatment creates a stressful condition for both the patient and doctor.

We have identified a series of cases where this type of ocular dysesthesia following LASIK was treated successfully by flap lifting and repositioning, in some cases associated with an ablation of the residual refractive error.

14.1 Fundamentals of Post-LASIK Corneal Dysesthesia

It is well known that LASIK flap dissection induces an important reduction in corneal sensitivity, mainly due to the fact that corneal nerves are cut by the microkeratome or the femtosecond laser. Experimental evidence has shown that soon after the corneal injury, the damaged nerves begin to regenerate forming nerve-end neuromas [1]. In addition, the intact axons in the neighboring areas of the cornea begin to sprout and to invade the denerved area with newly formed branches [1, 2]. It has been proven that during this regeneration process, these nerves exhibit an abnormal excitability that causes the generation of impulses in the absence of a nociceptive stimuli, leading to the reduction of the pain threshold (hyperalgesia) as well as an exaggerated pain responses to normal stimuli (allodynia) (Fig. 14.1) [3, 4]. This increased electrical activity in the injured corneal nerves may explain the disparity between the clinically observed dryness signs and the reported symptoms [4]. In fact, it has been shown that neither tear osmolarity nor the

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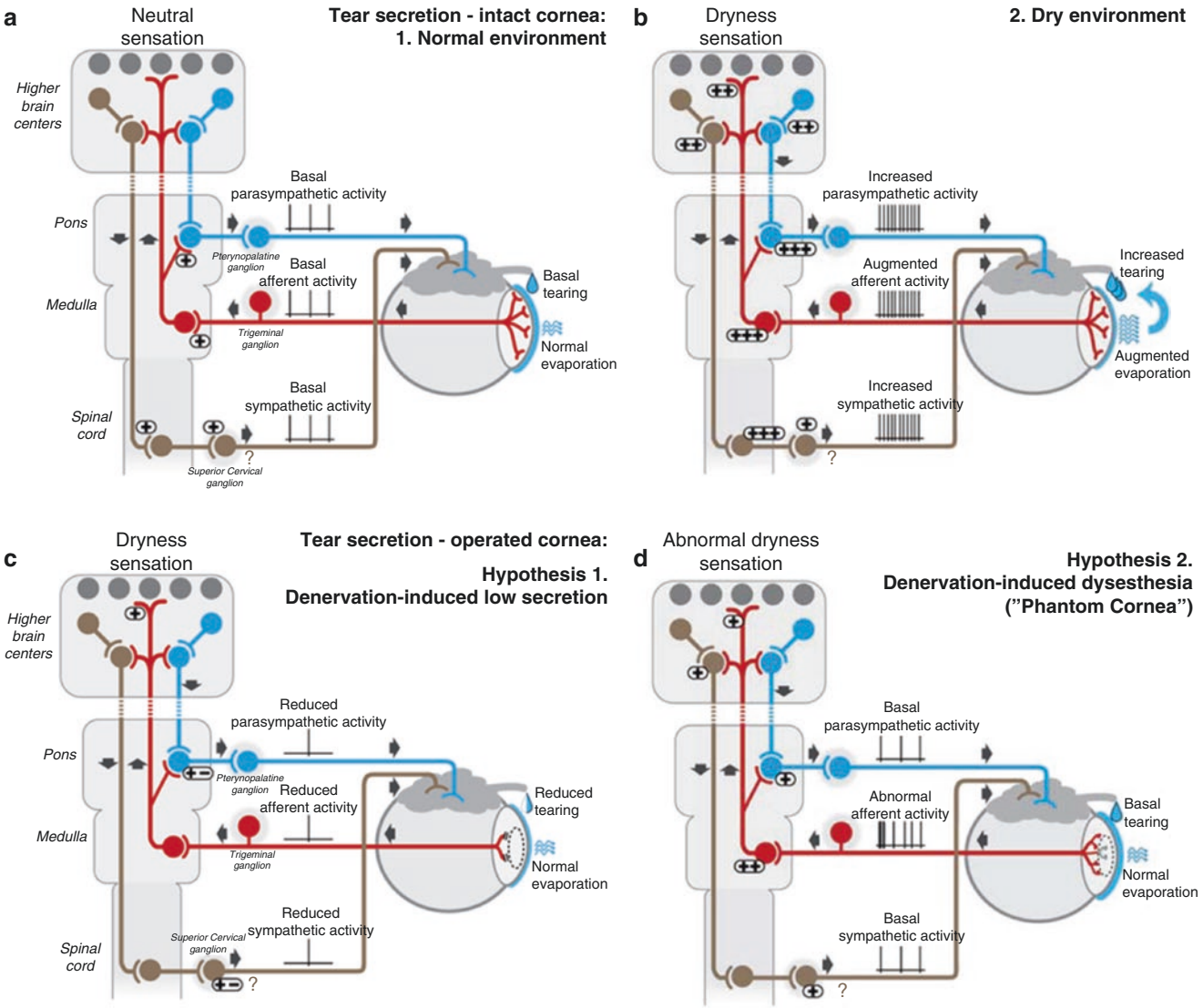

Fig. 14.1 Schematic representation of the "lacrimal functional unit" (Belmonte C.). (**a**) Basal tear secretion is maintained by low-frequency impulse activity in corneal sensory nerves, which travel to the central nervous system and activate reflex tear fluid (parasympathetic) and perhaps also protein secretion (sympathetic). The basal afferent sensory inflow does not elicit conscious sensations. (**b**) When the ocular surface dries or is irritated, sensory afferent impulse activity increases and evokes an augmented tear secretion. Tearing can also be evoked by activation of cerebral areas involved in the emotional response (not represented). (**c**) Hypothetical effect of photorefractive surgery on tear secretion. Injury to corneal sensory nerves reduces the afferent impulse activity that maintains basal tear secretion. This causes a decrease in tear production and ocular surface dryness, which in turn stimulates intact corneal sensory nerves, evoking eye dryness sensations. (**d**) Second hypothetical effect of photorefractive surgery on tear secretion. Injured corneal sensory nerves produce aberrant impulse discharges, evoking eye dryness sensations despite the limited alterations of lacrimal secretion (Reprinted from Belmonte C. Eye dryness sensations after refractive surgery: impaired tear secretion or "phantom" cornea? J Refract Surg. 2007;23:598–602)

Schirmer test is significantly affected by LASIK procedures, although patients usually complain about dry eye [5]. Probably, long-persisting abnormal nerve branches could exhibit an exaggerated electrical reactivity in some eyes (Fig. 14.1), a possibility that may explain those rare but frustrating cases of long-standing neuropathic pain after LASIK. There is a common belief that, as the corneal sensitivity to mechanical stimuli (as measured with the Cochet-Bonnet esthesiometer) is recovered months after surgery, the patient's dryness sensation should improve as well, but this fact may not be true. Actually, it has been reported that the main corneal sensory receptors involved in the "dry eye" sensation are the cold thermoreceptors, which show an extreme sensibility to detect minimal changes in the ocular surface temperature, thus being able to detect the evaporation of the tear film layer [6]. Thus, it might well be that a cornea may show a normal response to a mechanical stimulus but still have an impaired function of the cold thermoreceptor nerve endings which may show an abnormal "dysfunctional" electrical hyperactivity (Fig. 14.1).

Table 14.1 Corneal dysesthesia following LASIK

Patient's age	Time elapsed since LASIK at the moment of the flap lift (unilateral)	OSDI[a] in the affected eye	Punctate keratopathy[b] (Oxford)		BUT sec		Meniscus height		OSDI in treated eye 1 month	OSDI 3 months	OSDI 6 months	OSDI 1 year
			RE	LE	RE	LE	RE	LE				
29	18 months	25	1	1	12	12	1	1	12	10	0	0
33	26 months	23	0	0	11	10	1	1	10	0	0	0
45	12 months	20	0	0	10	12	0.7	1	20	20	10	0
47	12 months	20	1	1	12	12	1	1	20	19	5	5
32	17 months	15	0	0	14	14	1	1	12	0	0	0
40	24 months	19	1	0	16	17	1	1	20	20	10	0

Data concerning the affected and the contralateral eye following flap lifting

[a]Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640–50

[b]Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118:615–21

Furthermore, the electrical activity of the cold thermoreceptor neurons is the only one that shows an increased activity when the tear osmolarity is slightly elevated [7], which may explain the higher frequency of dry eye symptoms after LASIK in patients with preoperative dry eye.

For these reasons we believe that, in addition to the usual dry eye treatment, new therapeutic options will be necessary in order to ameliorate LASIK-induced dry eye symptoms. A potentially fruitful approach could be the use of medications designed to decrease the excessive electrical activity of the damaged corneal nerves. In this respect, membrane-stabilizing drugs such as tricyclic antidepressants, anticonvulsants, anesthetics, and a range of calcium channel blockers could prove useful [8]. Maneuvers such as LASIK flap lifting may offer an alternative treatment option by cutting the aberrant regenerating nerves, leading to a new and less dysfunctional nerve plexus development.

14.2 Post-LASIK Corneal Dysesthesia Case Series

A total of six cases suffering from corneal dysesthesia syndrome following LASIK have been treated by us. All the cases were at least 16 months following the LASIK procedure and had a mean age of 30.5 years (from 26–53). At the time of treatment, the patients had a normal breakup time, tear film meniscus of 0.75–1 mm, and negative evidence of ocular surface inflammation. Four cases showed mostly unilateral symptoms, while two were bilateral with more relevant symptoms in one eye. All cases were treated by flap lifting only in the most symptomatic eye, and three cases were retreated with the residual refractive error that was present at the moment of the surgery. All cases were treated by the same surgeon (JLA) with the same excimer laser (Amaris Schwind 500). Prior to the surgery, all patients were extensively treated with topical lubricants, continuing postoperatively. The description of the clinical cases is shown in Table 14.1.

Patients were evaluated postoperatively at day 1, 1 month, and 6 months. All cases had their ocular surface symptoms solved at the third month, while in three cases they were solved by the first month. No cases were symptomatic 6 months after the reoperation.

Conclusion

Post-LASIK corneal dysesthesia is a new clinical entity that may explain those uncommon but bothersome cases in which untreatable symptoms of DES persist months postoperatively, despite improving clinical signs. This challenging clinical entity can be improved by flap lifting which, from our experience, has proven to be effective in all cases identified by our group. Nevertheless, scientific studies and larger series are still required in order to definitely demonstrate the efficacy of this therapy.

Corneal dysesthesia following LASIK should be considered in the differential diagnosis and treatment of apparently long-standing DED, in which clinical evidence of dry eye is lacking or borderline and where conventional topical DES therapy has failed. This new entity is distinctively different from the previous descriptions of similar entities such as LASIK-induced neurothrophic epitheliopathy [9]. The main difference being that punctate epitheliopathy and clinical evidence of dry eye are consistent features, where in corneal dysesthesia symptoms are prominent without clinical signs of DED.

Take-Home Pearls

- Corneal dysesthesia should be considered in the differential diagnosis and treatment of DED.
- This challenging clinical entity can be improved by flap lifting.

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Epithelial Ingrowth

15

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Core Messages

- Epithelial ingrowth is diagnosed from careful observation of the cornea and the flap at the slit lamp after LASIK surgery. In some cases, confocal microscopy examination can help to confirm the diagnosis.
- Epithelial ingrowth has a variable incidence between 1% and 42%. However, clinically significant ingrowth does not occur very often and in the majority of cases does not need any type of treatment [24].
- Treatment of epithelial ingrowth is observational in the majority of cases. If the disease does not progress over time, surgical intervention is not warranted. If progression is observed and documented, surgical treatment has to be undertaken.
- Several different techniques have been proposed to treat this annoying complication. All of them agree that the epithelium has to be cleaned from the stroma, from the undersurface of the flap, and from the edges of the wound.

15.1 Introduction

There are several reasons to consider epithelial ingrowth as the most important complication of LASIK surgery:

(a) It is the most frequent complication of LASIK surgery. Reports in literature varied from 1% to 42%. (1) However, the great majority of cases are not clinically significant. They do not interfere with the result of the surgery nor do they cause damage to the visual acuity [1, 13].
(b) On the other hand, clinically significant epithelial ingrowth, although with a variable incidence between 1% and 3.5%, is a sight-threatening complication if left untreated. The cells may progress toward the visual axis, leady to a decrease visual acuity, melting of the flap, and, pothdally permanent corneal damage [12, 21].
(c) Surgical treatment when needed is very difficult.
(d) New advances in the technique are directly responsible for decreasing the presence of epithelial ingrowth.

15.2 Etiology of Epithelial Ingrowth

There are several theories regadly the for Epithelial ingrowth etiology. Probably the most accepted theory is the active proliferation of epithelium at the flap edge and under the flap into the interface, filling virtual cavities left during the surgical procedure. This process starts immediately after surgery. Another theory considers the introduction of the epithelial cells under the flap during surgery by the microkeratome blade, with a syringe during the irrigation phase, with the sponge when cleaning or drying, or even with forceps, if used [11].

Regardless of the mechanism of implantation of epithelial cells under the flap, those cells are active stratified squamous epithelial cells with a basement membrane derived either from the corneal epithelium or from the conjunctival epithelium [23]. Undoubtedly, the most important factor in the production of epithelial ingrowth is bad surgical technique or the use of inadequate instruments [15]. This complication has even been mentioned and documented in the new SMILE procedure and has been equated with bad surgical techniques as well [19].

15.3 Risk Factors

Even with no unique theory about the origin of epithelial cells growing in the interface between the flap and the stroma, there are several well-known risk factors:

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1. Enhancement surgery. Re-lifting of the flap has been very well documented as a trigger factor for placement of epithelial cells under the flap. This is particularly true when the flap is old and the lifting is traumatic or difficult [4].
2. Any type of complication with the creation of the flap can cause growth of the epithelial cells, such as buttonhole, irregular cuts, irregular stroma under the flap, irregular gutter, or even decentered flaps. The use of defective microkeratomes with uneven or irregular advancement, or non-smooth or sharp borders, can cause irregular flaps, irregular stromal beds, or irregular borders, with bad junction between the two epitheliums, leaving a virtual space that is almost always filled with the epithelial cells [12].
3. Dislocation of the flap after surgery due to trauma or poor adhesion.
4. Presence of striae or folds.
5. Bad surgical technique with excessive manipulation of the flap, excessive irrigation, or careless flap replacement that produces poor adhesion of the flap to the residual stroma, leaving a virtual space easily infiltrated by epithelial cells [21].
6. Retreatments, past-syland procedures, or presence of radial keratotomy cuts, or a corneal transplant [11].
7. Laser ablation of the corneal epithelium at the border of the flap when the ablation zone is larger than the flap creating a gap, which opens a window for the cells to go into.

15.4 Clinical Manifestations and Diagnosis of Epithelial Ingrowth

One of the problems of epithelial ingrowth is the lack of symptoms in the initial phases. Patients may start complaining of photophobia, foreign body sensation, or red eye. In advanced stages of the disease, however, patients may complain of diminished visual acuity or visual symptoms such as, glare, haloes, or night visual disturbances. This may be attributed to a large growth at the periphery, producing some type of irregular astigmatism, or growth of epithelial cells toward the center of the pupil, or the initiation of melting of the flap due to necrosis and inflammation caused by keratolysis of the surrounding tissue [22].

Epithelial ingrowth diagnosis is almost exclusively done by careful slit lamp examination of the cornea after LASIK surgery. Only in very rare occasions, the growth goes undiagnosed with microscopic view, and some form of special illumination technique may be needed, such as tangential light or retroillumination with a dilated pupil. Careful examination of the gap at the borders of the flap in the first 24 h after surgery is mandatory, especially inferior examination in superior hinge or temporally in the nasal hinge. In advanced cases, corneal topography could help show the irregular astigmatism. The use of confocal microscopy has been suggested for the diagnosis of epithelial cells in the interface of lamellar corneal transplants.

Epithelial ingrowth has two clear forms of presentation:

(a) White or grayish small spots or lines at the periphery within 2.0 mm of the peripheral edge of the flap. These may be diffused or localized in a cluster. It is usually a benign form of presentation, which remains stationary without further progression. These forms of growth may even dissolve and disappear over time without any harm or only leave a small and discrete haze at the interface [3].
(b) Pearl-like islands of different sizes, elevated white or grayish colonies, sheets, cysts, or elevated strands with delineated borders, or without them, adopting a more diffused form. This is the more aggressive presentation of epithelial ingrowth, usually progressive toward the center of the pupil, and/or laterally, and sometimes merging with the neighboring cells. These cells eventually involve the affected area of the flap and cause melting and retraction at the periphery of the flap. If left untreated complete keratolysis, disappearance of the flap, scarring, cells spreading over the entire cornea, and complete damage of the tissue may occur [2].

15.5 Classification of Epithelial Ingrowth

Several classifications of epithelial ingrowth have been made. Dr. Aron Gulani presented a very [25] useful one in the tenth European Society Meeting of Cataract and Refractive Surgery in Nice, France:

Grade 1: Epithelium under the flap as localized island at the periphery. It does not block the red reflex.
Grade 2: Epithelium grows diffusely at the periphery of the flap, with a faint line in front of it. It distorts the red reflex.
Grade 3: Diffuse epithelium under the flap with total blockage of the red reflex.

This clinical classification is helpful and used in our clinic as a decision factor. When the red reflex is affected (grades 2 and 3), surgical intervention is necessary.

Another classification from Dr. Jeffrey Machat is useful in defining severity and treatment. It is the most used one for this complication [26]:

Grade 1: Faintly visible ingrowth 2 mm from the flap edge, with a demarcation line and no involvement of the flap. It is nonprogressive and requires observation only.
Grade 2: Epithelial nests of cells within the 2 mm at the periphery of the flap, with no clear demarcation line and some involvement of the flap, which is thickened and gray. It may require treatment in case it progresses.

Grade 3: The epithelial cells grow more than 2 mm from the edge in whitish nests that approach the visual axis. Flap is involved, thickened and melted, or eroded. This requires urgent treatment.

For practical purposes in our clinic, we use a personal classification based on the clinical manifestations of the disease:

Grade 1: The epithelial ingrowth does not cause any symptoms or does not interfere with the visual acuity. Observation only.

Grade 2: The decrease in VA or distortion referred by patient may be attributed to the ingrowth. Mild symptom presents as a foreign body sensation. Surgical removal of the epithelial cells or YAG laser is warranted.

Grade 3: Progression toward the visual axis of the cells. Surgical intervention is needed.

Grade 4: Damage of the flap, melting observed, as well as spreading of the cells. Removal plus additional treatment is preferred (chemical debridement added to removal, stitches, etc.).

15.6 Management of Epithelial Ingrowth

The mainstay of the treatment of epithelial ingrowth is observation, since surgical treatment is complicated and has a high incidence of recurrence (up to 10%). At the same time, however, early treatment is easier and successful most of the time [27, 29]. Therefore, early diagnosis of the progressive or dangerous epithelial ingrowth is essential in the management of this complication. Surgical option must be undertaken at the right time and in the exact moment since lifting the flap brings the danger of spreading the cells in the interface or activating the ones that are inactive [14].

Careful follow-up is necessary. Slit lamp examination, photos, and fluorescein staining are crucial to elucidate if the epithelial cells are growing and jeopardizing visual acuity [28]. Since the treatment is divided into observation and intervention, clinical judgment is essential. There are several reasons to perform surgical treatment. The presence of any of these situations makes the difficult decision inevitable:

(a) When epithelial cells progress toward the visual axis and BCVA is in danger
(b) When epithelial ingrowth is not progressing but the peripheral cysts create elevations that cause irregular and untreatable astigmatism
(c) When the flap starts to melt

15.7 Surgical Treatment of Epithelial Ingrowth

Once it has been decided to surgically treat this complication, there are steps to follow. In general, if the cysts are peripheral, well limited, and they are not close to the visual axis, YAG laser can be performed to explode the cysts as described by Alio et al. [20]. The advantage is in the fact that no lifting of the flap is necessary and the risks associated with it are avoided. YAG laser is used in intensity of 0.2–0.6 mj, with direct application to the cysts, trying to leave a space among every shot. This type of treatment has been reported to be effective in 80% of the cases, including retreatments.

If cleaning of the nests is determined, it must be done by carefully lifting the flap. Before the epithelium is broken, the border should be determined by microscopic inspection. If the edge is not easily seen, gentle pressure on the limbus will help. The epithelium is then broken only at the junction, and a thin spatula should be used to enter the interface under the flap, which should be lifted completely, or partially if preferred, but giving enough space for the cleaning. If they detach easily, epithelial sheets must be removed using forceps, or by gentle scraping, by spatula or by sponge. Special care must be taken not to reseed the epithelial cells. Only one cell is enough for the epithelium to reproduce under the flap. It is of particular importance to clean not only the stromal bed but also the stromal face of the flap.

There is some controversy about suturing the flap or a bandage contact lens after it has been replaced [5]. After the cleaning has been completed, I strongly advice suturing the flap in very severe cases or in any case that the second time flap is cleaned (recurrence) [17]. The stitches stay in place for a few days until the epithelium covers the wound [7] and no recurrence is seen. The majority of studies advocate for the use of a bandage contact lens after the cleaning has finished. Fewer studies showed more incidence of recurrence with a contact lens than without. However, we encourage the use of a bandage contact lens for a few days after the removal of the cells, even in mild to moderate cases. The lens acts as a base for the cells to grow over instead of entering under the flap.

In case of reappearance of the epithelial cells, or in very severe forms of this complication, many different methods have been proposed to help remove all the epithelial cells that may remain under the flap**.** *Of course all these methods are only additive therapy; under no circumstance do they replace a meticulous and proper cleaning of the cells from the stroma, the undersurface of the flap, and the wound edges***.** Those methods have the intention to kill the cells that are not visible under the microscope, and therefore they must be applied after the manual cleaning of the epithelial ingrowth has been performed.

Two very popular additive chemicals used to kill epithelial cells are ethanol [16] (reports from 20% to 50%) and mitomycin C (MMC) [10] 0.02% applied with a Merocel sponge after the cleaning and left in place for a couple of minutes before being carefully removed by washing with balanced salt solution. In our experience we acknowledge that MMC does not prevent the recurrences of epithelial ingrowth, while the toxicity of alcohol may prevent severe forms of recurrence but at the risk of causing stromal scarring.

Another widely used method to clean the "invisible" epithelial cells is the application of excimer laser in the form of PTK in the internal surface of the flap, as well as in the stromal bed [9]. Since deeper treatments may have undesirable refractive results, some authors have advocated 10 μm deep as the standard PTK application [18]. Cryotherapy on both surfaces is another proposed method with few applications after the cleaning.

Regardless of the method of treatment, the surgeon needs to be sure the flap apposition is perfect and there is no space left under it. Contact lens is advisable, and in some instances, suture of the flap and even glue [6] on the edge can help to maintain the epithelial cells away from the interface [8].

15.8 Prevention of Epithelial Ingrowth

Because surgical treatment of this condition is difficult and complicated and the disease can turn into a sight-threatening problem with loss of best-corrected visual acuity, prevention is the best treatment. The use of the best available technology is essential. It has been demonstrated that femtosecond flaps produce less tendency for epithelial ingrowth, due to the less angulation of the entrance, the sharp borders, and the regular stromal bed. The use of better microkeratomes with new sharp and clean blades is also advised. Few rules apply to help prevent this complication:

1. Always use the best and most advanced technology for LASIK, with well-maintained microkeratomes and new blades. Femtosecond flaps are highly recommended.
2. Avoid excessive manipulation of the flap and excessive irrigation. When the flap is replaced, make sure the gap at the junction is minimal and there is complete contact between the undersurface of the flap and the stromal bed. Take all the time necessary to have a perfect surgery.
3. In case of epithelial defect, place a bandage contact lens to use it as a frame to guide the epithelial cells over the flap.
4. Avoid re-lifting of the flap whenever possible, and, if needed, careful manipulation and proper surgical technique should follow. Placement of a bandage contact lens is advised, and the lens must remain in place until the gap epithelializes.
5. Use special care in cases of previous radial keratotomy when a flap is produced. Align the radial cuts from the flap with the ones in the recipient. Consider surface ablation instead of LASIK in those cases with irregular or too many cuts. Bandage lens must be considered.
6. Avoid too large ablation zones or too small flaps in order to protect the remaining cornea from the excimer laser. If it is an inevitable situation, then place a bandage contact lens until the gap closes.
7. The presence of wrinkles, folds, or displaced flaps must be corrected immediately as soon as they are seen to give less time for the cells to grow.

Conclusions

Epithelial ingrowth is probably the most frequent complication of LASIK surgery. It has been reported from 1% to 42%. It is difficult to manage; therefore, prevention is key. Once it is diagnosed, it is recommended to: (1) observe if the cells do not grow or jeopardize visual acuity and (2) surgical intervention if the cells progress toward the visual axis or they interfere with the visual acuity.

Surgical management of this complication is based on careful manual removal of all the cells under the flap, cleaning the stromal bed and the inner surface of the flap. Additional therapies have been advocated and should be used with careful judgment from the surgeon.

Take-Home Pearls

- Prevention is key for this complication. Careful techniques with the latest technology are clearly the best option.
- Observation is always better if the epithelial cells do not cause damage of the visual acuity or if they remain inactive under the flap without further growth.
- Surgical treatment is decided only in these three situations: (a) when cells progress toward the visual axis and the BCVA is in danger, (b) when the peripheral cysts are elevated causing irregular astigmatism or symptoms, and (c) when there is documented involvement of the flap.
- The foundation of the surgical treatment is manual, careful, and thoughtful cleaning of the sheets of cells, making sure there are no remnants that could proliferate again. Additional chemicals or YAG laser ablation, or PTK, can be used.
- Always consider bandage contact lens in complicated cases. Stitches to suture the flap, or glue, can also be considered.

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Corneal Ectasia

16

Julie M. Schallhorn, J. Bradley Randleman, and R. Doyle Stulting

Core Messages

- Proven risk factors for ectasia after laser in situ keratomileusis (LASIK):
  - Ectatic corneal disease
  - Forme fruste keratoconus and other suspicious topographic and tomographic patterns identified preoperatively
  - Low residual stromal bed (RSB) thickness
  - Low preoperative corneal thickness
  - High percent tissue altered at the time of surgery
  - Young patient age
- Potential risk factors for ectasia after LASIK:
  - Chronic trauma (eye rubbing)
  - Family history of ectatic corneal disease
  - Unstable refractions with preoperative best spectacle-corrected visual acuity worse than 20/20
- Treatments other than LASIK are more suitable for at-risk candidates:
  - Phakic IOLs for high myopia
  - Surface ablation in select circumstances
- Effective management strategies for ectasia after LASIK include:
  - Rigid gas permeable (RGP) contact lenses
  - Scleral contact lenses
  - Intracorneal ring segments
  - Corneal cross-linking (CXL)
  - CXL plus refractive therapies
  - Corneal transplantation
- New techniques for measuring corneal biomechanics should facilitate identification of patients at risk for corneal ectasia.

16.1 Introduction

Postoperative corneal ectasia is the progressive steepening and thinning of the cornea after laser vision correction surgery that causes a reduction in uncorrected and often best spectacle-corrected visual acuity [1]. It remains one of the most insidious and feared complications after photorefractive keratectomy (PRK) or laser in situ keratomileusis (LASIK). Since the first reports by Seiler and colleagues in 1998 [2, 3], postoperative ectasia has been the source of extensive discussion [4–7] as it has both medical and medicolegal ramifications for patient screening and postoperative management [8]. Recently, the first cases of corneal ectasia after small incision lenticule extraction (SMILE) were reported, indicating that this procedure is not without the risk of ectasia [9–11].

Hundreds of cases of postoperative ectasia have been reported in the literature, but there are very few large studies [1, 12–18]. From these reports, a variety of risk factors have been proposed, including young patient age, high myopia, low residual stromal bed thickness, low preoperative corneal thickness, high percent tissue altered (PTA), and forme fruste keratoconus. Patients have also developed ectasia without any of these proposed risk factors [12–14, 19–21].

The aim of this chapter is to discuss proven and probable risk factors for postoperative ectasia, strategies for avoiding this complication, and management options for visual rehabilitation when postoperative ectasia occurs.

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16.2 Postoperative Ectasia: What Do We Currently Know?

The estimated incidence of ectasia after LASIK ranges from 0.04% [1] to 0.9% [22], with most estimates between 0.2% and 0.6% [15, 16, 18]. More than 50% of ophthalmologists who responded to the International Society of Refractive Surgery of the American Academy of Ophthalmology (ISRS/AAO) practice patterns survey in 2004 had at least one case of ectasia in their practice [23]; thus, the true incidence may be higher than currently reported [24]. More than 50% of cases present within the first 12 months [17]; however, its onset can be considerably later [19, 20]. In some instances, ectasia has become manifest 10 or more years after PRK [25–27].

Corneal refractive surgery by definition alters the shape, thickness, curvature, and tensile strength of the normal cornea. Keratocyte density is greatest in the anterior 10% of the stroma and lowest in the posterior 40% of the stroma [28, 29]; it decreases more significantly in the anterior stroma after PRK and in the posterior corneal stroma after LASIK [30]. Studies indicate that tensile strength is greatest in the anterior one-third and weakest in the posterior two-thirds of the corneal stroma [31, 32]. Further, the corneal flap does not contribute to the tensile strength of the cornea after LASIK [2, 33, 34]. Dawson and colleagues [31] have estimated that routine surgery on normal corneas decreases tensile strength by 13% after PRK and 27% after LASIK. Andreassen and colleagues found the elastic modulus of the keratoconic cornea to be 1.6–2.5 (average 2.1) times less than that of a normal cornea [35]. Biomechanical modeling approaches utilizing corneal plasticity and viscoelasticity [36] and factoring corneal parameters such as Young's modulus, Poisson's ratio, and curvature radius [37] may provide further insight into the ectatic process. It is possible that patients predisposed to the development of ectasia may have measurable alterations in corneal biomechanical properties prior to the clinical manifestation of any ectatic disease, and thus the development of screening criteria based on corneal biomechanics may be a useful screening methodology [38]. Unfortunately, further investigation in this area is hampered by lack of an effective means of measuring corneal biomechanical properties in vivo. This may be achievable in the near future with minimally invasive, nondestructive measurements such as Ocular Coherence Tomography (OCT) elastography [39] and Brillouin microscopy [32].

Rather than representing a specific disease entity, postoperative ectasia, like keratoconus, most likely represents an end-stage manifestation of corneal instability that arises from a variety of causes, including reduced preoperative corneal biomechanical stability, residual stromal bed too low to maintain structural integrity, chronic trauma, and patients otherwise destined to develop keratoconus. Specific risk factors for the development of postoperative ectasia have been recognized, and screening schemes have been developed to reduce the incidence of postoperative ectasia.

16.3 Risk Factors for Postoperative Ectasia

Recognized risk factors for ectasia include corneal ectatic disorders, forme fruste keratoconus as defined by Placido-based corneal topographic pattern analysis, low residual stromal bed thickness, young age, high percent tissue altered (PTA), and low preoperative corneal thickness (Table 16.1). However, aside from a preoperative diagnosis of an ectatic condition, there is no one risk factor that will definitively predict the occurrence of postoperative ectasia.

The aforementioned factors are surrogates for how much a refractive procedure alters the biomechanical stability of the cornea, and how much alteration the cornea can withstand. Patients with an innately reduced biomechanical strength of the cornea are more susceptible to the development of ectasia with or without undergoing refractive surgery, which is why screening to identify keratoconus suspect or forme fruste keratoconus is so important, and why younger patients who have not had time to manifest an ectatic condition are at higher risk of postoperative ectasia. In patients who would not have developed ectasia without surgery, it is likely that a subtle innate reduction in biomechanical integrity combined with a degree of tissue alteration higher than the cornea can withstand results in ectasia after corneal refractive surgery.

16.3.1 High Myopia

Eyes that developed ectasia have been significantly more myopic than controls in previous studies [1, 17], and there are many reports of ectasia developing after treatment for extreme myopia (>−12 D) [15, 16, 40–42]. However, ectasia has also been reported in many patients with low myopia and hyperopia; thus, the level of myopia may in itself be a poor predictor for ectasia, as long as surgeons avoid treating extreme myopia. Probably a better marker than the degree of myopia is percent tissue altered (PTA) [43]. A very thick cornea

Table 16.1 Defined risk factors for postoperative ectasia

• Keratoconus
• Pellucid marginal corneal degeneration
• Abnormal preoperative topography (forme fruste keratoconus)
• Low residual stromal bed thickness
• Young age
• Low preoperative corneal thickness
• High percentage of tissue altered

can sustain a higher treatment of myopia with relatively smaller alteration in total tissue than a thin cornea with a lower myopic treatment.

16.3.2 Preoperative Corneal Thickness

In comparative studies [1, 17], ectasia cases had significantly thinner corneas preoperatively than did controls. Keratoconic corneas are generally thinner than normal corneas [44, 45]; therefore, low preoperative corneal thickness could be indicative of an abnormal cornea that is destined to develop keratoconus. Alternatively, thinner corneas could be at higher risk for ectasia because there is a higher probability that a thicker than expected corneal flap will result in an extremely low RSB that does not provide sufficient structural integrity to prevent ectasia.

16.3.3 Low Residual Stromal Bed Thickness and Percent Tissue Altered

Ectasia cases have had a significantly lower calculated RSB than controls in comparative studies [1, 17], and low RSB has always been suspected to be one of the most significant risk factors for postoperative ectasia. Factors contributing to low RSB include treatment of high refractive errors, excessive flap thickness, and deeper than expected stromal ablations. There can be significant variability in the measurement of corneal thickness, flap thickness, and ablation depth [46–53]. While most of the microkeratome plate markings overestimate average actual flap thickness, flap thickness can vary widely, and excessively thick flaps still occur. Additionally, previous studies have found that actual ablation depth is often greater than estimated ablation depth [47, 48].

A residual stromal bed thickness of 250 μm has been accepted as the minimum for the safe performance of LASIK; however, ectasia has occurred after LASIK in eyes with a wide range of RSB thicknesses, including those greater than 300 μm, confirmed by intraoperative pachymetry, and after PRK in eyes with RSB greater than 350 μm [25, 26, 54]. Conversely, many eyes that underwent successful LASIK without ectasia had RSB less than 225 μm [1]. Thus, decreasing RSB likely represents a continuum of risk for postoperative ectasia without a definitive safety cutoff.

In the vast majority of published ectasia cases, RSB has been calculated rather than measured. Only 31% of respondents to the ISRS/AAO survey routinely measure flap or residual stromal bed thickness intraoperatively [23]. Using a probability model that accounts for imprecision in corneal thickness, flap thickness, and laser ablation depth measurements, Reinstein and colleagues [55] determined that, depending on the microkeratome used, up to 33% of eyes with attempted RSB thickness of 250 μm could have actual RSB less than 200 μm. Given the known variability in flap thickness that can occur with both mechanical and femtosecond lasers [56, 57], we recommend intraoperative pachymetry for all patients that may be at risk for low RSB.

Recently, percent tissue altered (PTA) has been proposed as a more discriminative measure than RSB as it more accurately reflects the amount of alteration of the corneal stroma than the RSB [58]. The PTA is calculated by summing the flap thickness (FT) and ablation depth (AD) and dividing by the central corneal thickness (CCT) as in the following formula: PTA = (FT + AD)/CCT * 100. In one retrospective study, a cutoff value of 40% offered a sensitivity of 97% and specificity of 89% in discriminating between patients who developed postoperative ectasia and those who did not [43].

16.3.4 Patient Age

Ectasia cases were significantly younger than controls in recent comparative studies [14, 17], and most reported cases of ectasia without other risk factors have been in very young patients. Younger corneas may be more elastic due to decreased natural collagen cross-linking that occurs with age, making them more susceptible to structural deformation. Additionally, some younger patients may be destined to develop keratoconus in their fourth to sixth decade of life [59, 60] and therefore may not yet have exhibited abnormal topographic patterns prior to surgery.

16.3.5 Ectatic Corneal Disorders and Abnormal Topographic Patterns

Ectatic disorders, including keratoconus, pellucid marginal corneal degeneration, and defined abnormal topographic patterns (forme fruste keratoconus) [61] are the most significant risk factors for postoperative ectasia, so great diligence should be applied to preoperative topography evaluation. In addition to forme fruste keratoconus, the members of the AAO/ISRS/ASCRS joint committee recommend avoiding LASIK in patients with asymmetric inferior corneal steepening or asymmetric bow tie patterns with skewed steep radial axes above and below the horizontal meridian [8]. Other factors, such as contact lens warpage and keratoconjunctivitis sicca, can create topographic changes that resemble those of forme fruste keratoconus [62]. These factors may make it more challenging to differentiate normal from abnormal topographies. We therefore recommend repeating topographic examination at a later time in questionable cases and, if available, utilizing multiple technologies, since a variety of imaging systems can provide unique information [63] (Fig. 16.1).

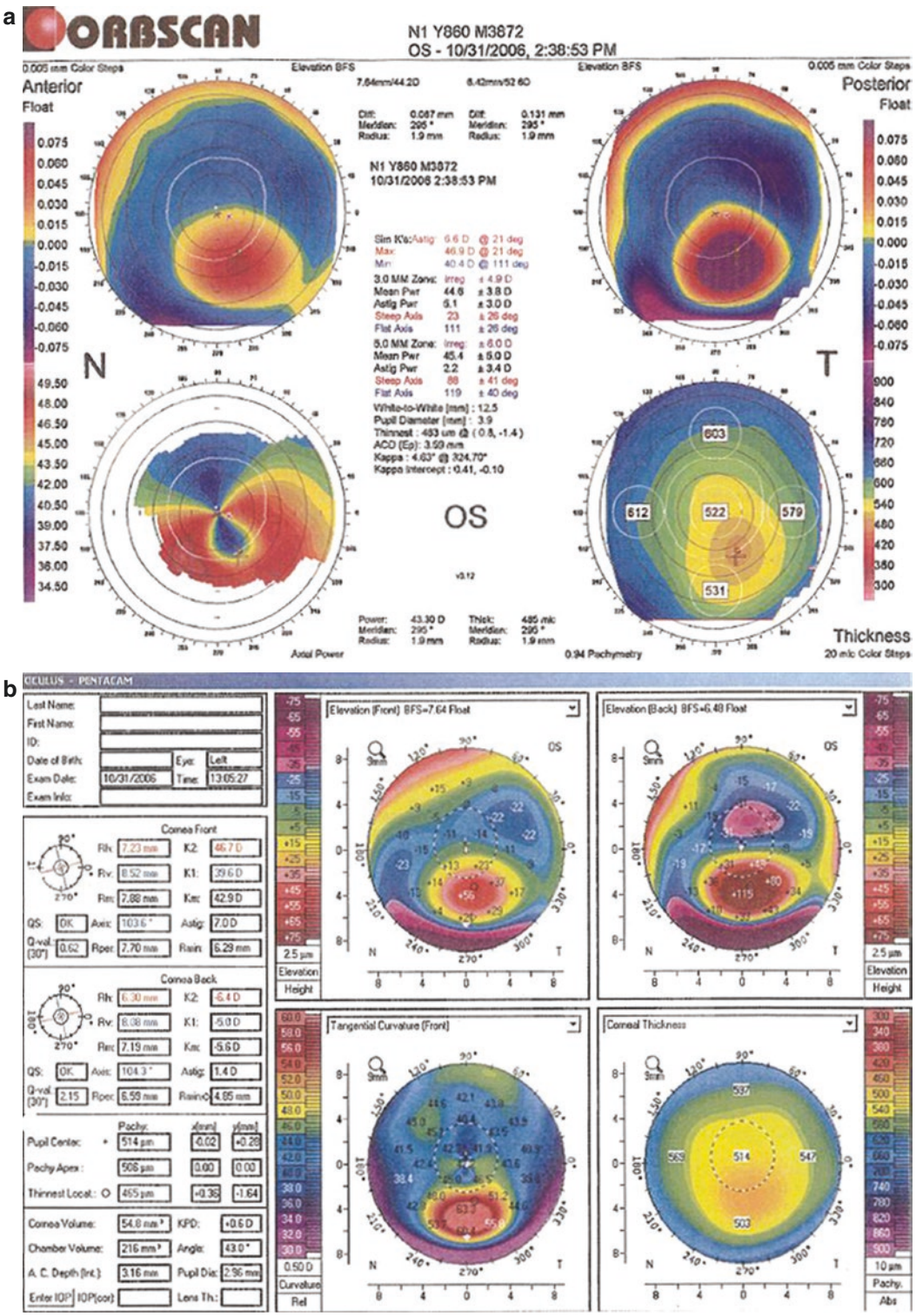

Fig. 16.1 Preoperative topographies of a patient with early ectatic corneal disease. (**a**) Orbscan II image (Bausch & Lomb Surgical, Inc. San Dimas, CA) of the left eye. The anterior and posterior float values (*upper right* and *left* images, respectively) both demonstrate significant elevations inferiorly. The thickness map (*bottom right*) displays a central thickness of 522 μm and demonstrates an inferior area of thinning corresponding to the areas of elevation on the anterior and posterior float images. The Placido-based keratometric image (*bottom left*) displays a crab-claw pattern, with superior flattening and asymmetric inferior steepening. (**b**) Pentacam image (Oculus, Inc., Lynwood, CA) of the same eye. Note the similar appearance in the front and back elevation maps (*upper right* and *left* images, respectively) as compared to the Orbscan II anterior and posterior float maps. The corneal thickness maps are also similar. However, the tangential curvature map displays significant inferior steepening suggestive of keratoconus rather than the Placido-based "crab-claw" image suggestive of pellucid marginal corneal degeneration. This patient is at high risk for postoperative ectasia and therefore a poor candidate for corneal refractive surgery (original Figure 5.3.1a and b)

There is evidence to suggest that in forme fruste keratoconus, changes are detectable in the posterior cornea [64] prior to any detectable changes in the anterior cornea. Slit beam scanning or Scheimpflug imaging can be very helpful in detecting posterior corneal abnormalities suspicious for forme fruste keratoconus. The addition of these techniques to the preoperative screening regimen may help to better differentiate pre-ectatic conditions from those patients with normal corneas. However, there is not yet definitive evidence that information about the posterior corneal curvature provides any additional predictive power to that of currently reported systems.

Although it is known that keratoconic corneas are thinner than normal corneas [44, 45], the development of corneal pachymetry mapping using tomographic imaging has given us new insight into how corneal thickness can be used to differentiate normal corneas from ectatic ones. Corneal pachymetry mapping using OCT has demonstrated that keratoconic corneas are more focally abnormal and more asymmetric than normal corneas [65]. Pachymetry mapping using Scheimpflug imaging has demonstrated that it is not simply the thinness of a cornea that is a risk for keratoconus but rather the spatial profile of the change in thickness [66, 67]. This observation has formed the basis for an ectasia detection tool available on the Oculus Pentacam (Wetzlar, Germany), the Belin-Ambrosio Enhanced Ectasia Display [68]. Screening with this tool may become a useful adjunct to identify potential ectasia-susceptible cases [69]; however its utility has not been evaluated in a refractive population.

Imaging of the corneal epithelium using spectral or Fourier domain OCT or very high frequency ultrasound can also provide helpful information to differentiate normal corneas from those with early ectasia. The corneal epithelium is not static, but rather remodels itself in response to the curvature of the underlying cornea [70]. Corneal epithelial mapping demonstrates focal epithelial thinning over areas of increased corneal curvature [71, 72] and may be the earliest observable abnormality in forme fruste keratoconus [73].

16.3.6 Other Potential Risk Factors

In addition to the aforementioned risk factors, other factors should be considered, including more subtle topographic abnormalities and high-order aberrations, multiple enhancements, chronic trauma (eye rubbing), family history of keratoconus, and refractive instability with preoperative best spectacle-corrected visual acuity worse than 20/20 (Table 16.2).

Some patients have very asymmetric topographic patterns in only one eye or subtle changes in both eyes with significant topographic asymmetry between eyes; if patients have suspicious topographic patterns in either eye, they should be excluded from excimer laser corneal refractive surgery bilaterally. Increased high-order aberrations, especially increased coma, may be an early indicator of keratoconus [74]. Eye rubbing can cause or exacerbate keratoconus [75–77]. Refractive instability with decreased BSCVA may be a sign of progressive changes in the shape of the cornea. The significance of these findings remains undetermined; however, all of these factors should be taken into consideration, especially in borderline cases.

Table 16.2 Potential risk factors for postoperative ectasia

- Suspicious topography
  - Asymmetric bow tie pattern
  - Inferior steepening
  - Topographic asymmetry between eyes
- Chronic trauma (eye rubbing)
- Refractive instability
- Family history of keratoconus
- Preoperative best spectacle-corrected visual acuity worse than 20/20

16.3.7 Ectasia Risk Factor Screening: Summary

In order to improve upon our current screening approaches, we propose utilizing screening techniques that take into account preoperative topography and tomography, residual stromal bed thickness, patient age, preoperative corneal thickness and the PTA, and the aforementioned potential risk factors in borderline cases.

16.4 Prevention of Postoperative Ectasia

16.4.1 Utilizing Alternative Treatment Strategies for At-Risk Patients

The best treatment for postoperative ectasia is to avoid its occurrence. Some patients at risk for ectasia after LASIK may be suitable candidates for surface ablation—especially those with normal topographies but thinner corneas, low predicted RSB, or younger age. However, we currently do not advocate performing surface ablation in keratoconus suspects without detailed, patient-specific informed consent. It may be possible to perform LASIK or surface ablation combined with CXL in young or highly myopic patients [78, 79]. Although promising, there are currently no long-term studies evaluating the ability of this approach to prevent ectasia. Phakic intraocular lens implantation may also prove beneficial for candidates at risk for ectasia, as lens implantation does not alter the structural integrity of the cornea. These lenses have recently shown promising results

in eyes with keratoconus [80, 81] and in patients that have developed postoperative ectasia.

Refractive surgery using small incision lenticule extraction (SMILE) may be appropriate for thinner corneas or higher ablations, as it leaves the anterior stroma untouched. Finite element modeling has demonstrated considerably less strain in the anterior cornea after SMILE as compared to LASIK [82], and tensile strength modeling has shown greater preservation of anterior tensile strength relative to PRK or LASIK [83]. However, SMILE should probably be avoided in patients with abnormal or highly suspicious topographies, as cases of ectasia after SMILE have been reported in these patients [9–11].

16.4.2 Utilizing New Technology to Identify Abnormal Corneas

A number of new techniques have been developed to measure corneal biomechanical integrity. Corneal interferometry [84] and dynamic corneal imaging [85] may allow identification of at-risk patients with normal topographies but reduced biomechanical integrity preoperatively. Corneal hysteresis and corneal resistance factor measurements using the Ocular Response Analyzer (Reichert, Depew, NY) have not shown utility in discriminating between normal and keratoconic corneas [86–88], but other derivative properties of the applanation waveform do show some promise [89]. Brillouin microscopy may be of use in differentiating between keratoconic and normal corneas, although more studies remain to be done [32]. Optical coherence elastography, although very new, may be able to analyze corneal viscoelasticity and provide a much needed method of measuring corneal biomechanical properties in vivo [39, 90].

16.4.3 Avoiding LASIK Retreatment in Corneas with Low Residual Stromal Bed Thickness

As corneal thickness measurements taken months after initial LASIK usually overestimate RSB thickness [91, 92], accurate assessment of actual RSB prior to retreatment is critical to avoid excessive ablation of the posterior stroma. This can be avoided by utilizing intraoperative pachymetry measurements prior to laser ablation at the time of retreatment, or by utilizing confocal microscopy [93] or high-speed OCT [94, 95] prior to retreatment, as these instruments can accurately measure residual stromal bed thickness even before the flap is lifted. In patients with a low RSB, a surface ablation retreatment procedure over the flap is an alternative solution that prevents any further loss of the structural integrity of the cornea, as the flap does not contribute to this [96].

16.5 Management of Postoperative Ectasia

Corneal cross-linking has become the preferred treatment for postoperative ectasia, as it appears to be able to effectively halt further progression of ectatic changes [97, 98]. Using riboflavin as a photosensitizer, followed by ultraviolet-A exposure, Wollensak and colleagues [99] found that collagen cross-linking halted the progression of keratoconus and in many cases reversed the ectatic process, as evidenced by a reduction in corneal steepening and refractive error. Further studies have confirmed initial results and evaluated endothelial toxicity [100–102]. Multiple studies have confirmed its utility in this condition [103].

Mild or nonprogressive cases of ectasia may be managed with conservative measures, including soft contact lenses [14] for mild cases and progressing to rigid gas permeable contact lenses, intracorneal ring segments, and corneal transplantation for more severe cases (Fig. 16.2). There are also reports of reversing early ectasia with intraocular pressure-lowering medications [104]; however, the long-term efficacy of this treatment remains to be determined.

Rigid gas permeable contact lenses may be necessary for visual rehabilitation [1, 105]. In general, fitting strategies for postoperative ectasia are similar to those for keratoconus [105–107]. Various specific lens styles can be used, including standard aspheric, multicurve, or reverse geometry lenses. The further development of large diameter scleral contact lenses has made fitting very ectatic or abnormally shaped corneas significantly more successful [108]. The specific fitting parameters should be customized to each case, as postoperative ectatic corneas may present quite dissimilarly.

Intracorneal ring segments (Intacs, Addition Technology, Inc., Sunnyvale, CA) have shown some promising results that have been reported when used off-label to treat postoperative ectasia [40, 109–112]. Techniques reported have varied with regard to wound location and the size, symmetry, and number of Intacs placed; thus, the specific technique that will best stabilize the ectatic cornea remains to be determined.

Obviously, corneal transplantation should be the final option; however, when patients undergo penetrating keratoplasty for ectasia, their long-term outcomes should be excellent and comparable to those in patients with keratoconus [113, 114]. Deep anterior lamellar keratoplasty is another viable surgical option for postoperative ectasia with comparable visual outcomes and significantly reduced rejection risk [115–117].

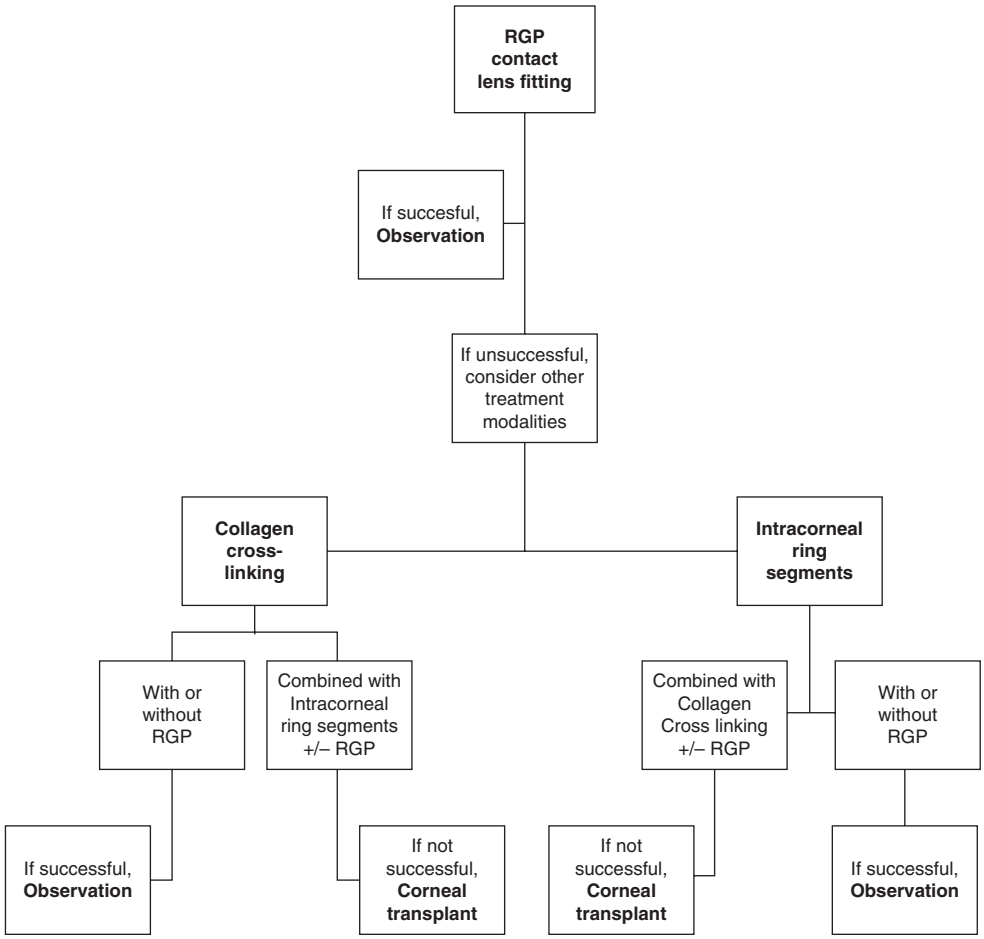

Fig. 16.2 Treatment algorithm for advanced postoperative ectasia. RGP contact lenses are generally the first treatment attempted and are usually sufficient for visual rehabilitation. When RGP fitting fails, intracorneal ring segments, collagen cross-linking, and RGP lenses can be utilized in a variety of a combinations before resorting to corneal transplantation (Original Figure 5.3.2)

Conclusions

Proven risk factors for ectasia after corneal refractive surgery include ectatic corneal disease, forme fruste keratoconus, low residual stromal bed, high percentage of tissue altered, low preoperative corneal thickness, and young age. Percent tissue altered may prove to be a useful addition. Other factors, such as suspicious corneal topographies, unstable refractions, a family history of ectatic corneal disease, a history of eye rubbing, or an underlying increase in corneal elasticity may also be predictive of corneal ectasia after refractive surgery. There is no single characteristic that identifies all at-risk patients, and we believe that a screening strategy that selectively weighs all of these factors will be more effective than considering any of the factors in isolation. Nevertheless, some patients may still develop postoperative ectasia without any of the aforementioned risk factors.

Alternative surgical options, including surface ablation, phakic intraocular lenses, and possibly combined collagen cross-linking, should be considered for patients at risk for postoperative ectasia. When postoperative ectasia occurs, corneal cross-linking should be performed if available to prevent further ectatic changes. Rigid gas permeable contact lenses and intracorneal ring segments can be useful adjuvants to restore functional visual acuity.

Take-Home Pearls

- Diligently analyze preoperative topographic patterns.
- Measure intraoperative pachymetry in all patients at risk for low RSB.
- Heightened scrutiny is warranted for younger patients.
- No single risk factor identifies all at-risk patients.
- Utilizing risk factors in a combined fashion will improve preoperative screening.
- Utilize options other than LASIK for at-risk patients.
- Collagen cross-linking should be considered in patients with postoperative ectasia. RGP lenses and intracorneal ring segments, in isolation or in combination, can effectively rehabilitate most eyes with ectasia.

- When necessary, corneal transplantation should have a high success rate comparable to grafts performed for keratoconus.

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Ptosis

17

Pete Setabutr and Bryan Sires

Core Messages

- Ptosis after refractive surgery can be either transient or persistent.
- Patients with persistent ptosis may be candidates for repair.
- This chapter covers the Anatomy, etiology, examination, and treatment of ptosis.

17.1 Introduction

Postsurgical ptosis is a well-known complication of anterior segment surgery [1]. It is more commonly discussed with regard to cataract surgery but it is a risk of refractive surgery as well. A basic understanding of this complication and its management is important for any refractive surgeon. It will allow the surgeon to explain this complication to the patient, reassure them when appropriate, and develop practices to minimize its occurrence.

Ptosis after refractive surgery can be either transient or persistent. The exact incidence of either is not currently known. Transient ptosis, which usually resolves in 6 months, is typically classified as mechanical ptosis secondary to swelling or inflammation. Typically, persistent ptosis (unresolved at 6 months), after refractive surgery, is classified as acquired aponeurotic ptosis. This type of ptosis is the result of stretching or dehiscence or disinsertion of the levator aponeurosis from its normal position on the anterior face of the tarsus [1]. Examination of aponeurotic ptosis reveals a decreased margin reflex distance (MRD), good levator function (LF), and an elevated eyelid crease.

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Patients with persistent ptosis may be candidates for repair. Either external or internal approaches are viable options in these patients.

17.2 Anatomy and Factors Predisposing to Ptosis After Refractive Surgery

A solid grasp of the upper eyelid anatomy will help in the understanding of potential causes and management of ptosis after refractive surgery. The upper eyelid is a structure of great importance with regard to the protection and maintenance of clear vision [2]. The upper eyelid functions to protect the ocular surface from debris and maintain moisture on the anterior surface of the eye. Each blink cycle evenly spreads tears over the ocular surface and directs the tears toward the lacrimal drain. There are several anatomic layers to the upper eyelid (Fig. 17.1). The skin is thin, with minimal subcutaneous fat compared with other regions of the body. This is helpful in creating well-concealed, fine scars after surgery. Most incisions are made in the lid crease. The eyelid crease is formed by elastic fibers that come from the levator aponeurosis and insert into the dermis of the skin, causing it to indent. Below the skin is the primary protractor of the eyelid called the orbicularis oculi muscle. This muscle is innervated by the facial nerve. The pretarsal and preseptal components of the orbicularis oculi muscle provide the involuntary blink for ocular surface maintenance, while the orbital component is for the voluntary blink. Beneath the orbicularis oculi muscle is a thin, multilayered sheet of connective tissue called the septum. The septum separates the anterior structure of the eyelid from the orbit. Behind the septum, the orbital fat and the lacrimal gland are found anterior to the levator muscle and aponeurosis. The nasal fat is white, the preaponeurotic fat is yellow, and the lacrimal gland is gray (Fig. 17.2). The preaponeurotic fat usually drapes over the lacrimal gland laterally in the eyelid. These colors are helpful in identifying your location during surgery [3]. Posterior to the preaponeurotic fat lie the two

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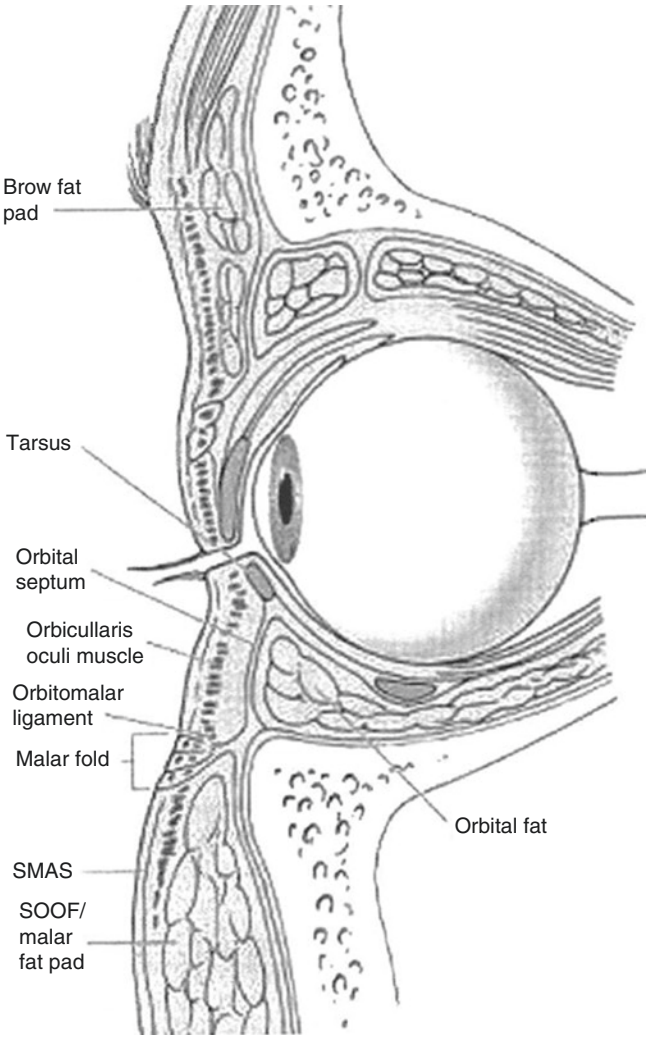

Fig. 17.1 Illustration of the anatomy of the upper eyelid showing various layers. The anterior surgical lamella is made up of the skin and orbicularis oculi muscle layer. The middle layer is the orbital septum. The posterior lamella is composed of the retractors (Müller's muscle and levator aponeurosis/muscle), tarsus, and palpebral conjunctiva [original Fig. 4.6.1]

retractors of the eyelid, the levator muscle (and its aponeurosis) and Müller's muscle. The levator is innervated by the superior division of the oculomotor nerve, while Müller's muscle is sympathetically innervated. The levator muscle and its aponeurosis, which sit anterior to the Müller's muscle, attach to the anterior surface of the tarsus. It is at this point where disinsertion may occur. Müller's muscle attaches to the superior border of the tarsus. The most posterior structure of the upper eyelid is the palpebral conjunctiva. The conjunctiva is densely adherent to the tarsus and loosely attached elsewhere.

The surgical anatomy is divided into the anterior, middle, and posterior eyelid lamellae. The anterior lamella is made up of the skin and orbicularis oculi muscle. The middle lamella is the orbital septum. The posterior lamella is the

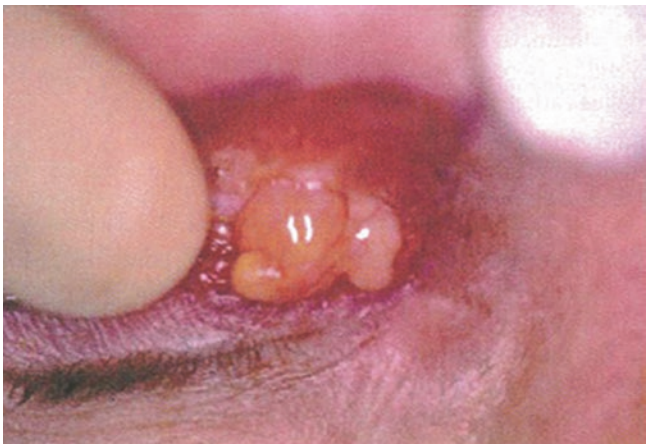

Fig. 17.2 External photograph demonstrating the color difference between the nasal fat (*white*) and the preaponeurotic fat (*yellow*). A higher carotenoid content is the cause of the yellow fat [original Fig. 4.6.2]

superior levator muscle, Müller's muscle, tarsus, and the conjunctiva. When discussing surgical anatomy of the eyelid, it is conceptually easier to think of these three lamellae rather than the several layers independently.

17.3 Etiology

Many factors can influence the etiology of ptosis associated with refractive surgery. These factors can be present before, during, and after refractive surgery.

A common pre-refractive surgery etiology is related to a history of contact lens wear, commonly seen in patients undergoing refractive surgery. Studies have shown a significant association between contact lens wear and ptosis [4]. Originally, the link was believed to be just with hard contact lenses; however, recent reports suggest an association with soft contact lenses as well [5, 13]. Most agree that the underlying etiology is aponeurotic disinsertion or dehiscence. It has been theorized that this is due to the antagonistic action of the orbicularis oculi and levator muscle during lens removal, stretching of the upper eyelid during attempts at lens removal, repeated forceful rubbing of the lens during blinking, and irritation causing frequent blinking and blepharospasm [6].

Some patients may be susceptible to aponeurotic ptosis. Studies have demonstrated that ptosis patients have decreased carotenoid content in the preaponeurotic fat [14]. These carotenoids are believed to play an antioxidative, protective role for the highly metabolic levator muscle that sits just under the fat. Patients who develop ptosis, as the result of contact lens use or refractive surgery, may have been more susceptible to ptosis later in life if neither of these interventions had occurred due to a possible inherent decreased amount of antioxidants in their orbital fat [7].

During refractive surgery itself, the lid speculum may be the primary culprit for causing ptosis. Tension of the eyelids against the speculum causing stretching, dehiscence, or disinsertion of the levator muscle or aponeurosis has been suggested as a likely etiology of ptosis in this setting [1]. Another alternative is the stretching of the eyelids with the adhesive drape removal after completion of the procedure. This risk could be minimized if care is taken during removal of the drape.

Another recognized cause of transient ptosis in a patient who's undergone refractive surgery is mechanical ptosis secondary to eyelid edema. Patience and reassurance are recommended as this typically resolves spontaneously.

17.4 Examination

The exam of a ptosis patient includes a complete eye exam with special attention to the eyelids, tear lake, and ocular surface. Measurements of the eyelids are critical to assessing ptosis. The margin reflex distance 1 (MRD1), the distance from the upper eyelid margin to a fine light reflection on the central cornea, can give an indication of the degree of ptosis. A normal MRD1 measurement is 3–5 mm. There are ethnic differences, with the Asian eyelid MRD1, being lower on average [8]. The upper eyelid crease in Caucasian eyelids is positioned above the eyelid margin at about 8 mm in men and 10 mm in women. The Asian eyelid has a lower crease at about 5 mm or none at all in about half of the Asian population. In aponeurotic ptosis seen after refractive surgery, the eyelid crease height may be higher than it was previously. This is suggestive of attenuation and stretching of the levator aponeurosis. The complete excursion of the upper eyelid from down to up is an indicator of levator function (LF). A normal measurement is greater than 10 mm. LF is typically not altered in aponeurotic ptosis. There is usually complete eyelid closure or no lagophthalmos seen in aponeurotic ptosis.

Dry eye assessment is important when assessing any ptosis patient. This is even more important in the refractive surgery patient as the procedure itself may lead to decreased tear productio-n. It is important to remember that repair of ptosis could bring about a small amount of lagophthalmos and increase exposure and dryness. Up to 2 mm of lagophthalmos may be tolerated in individuals with normal protective mechanisms such as Bell's phenomenon, intact corneal sensation, and tear lake height. If a dry eye state is recognized, a more conservative surgery (less elevation of the eyelid) should be performed to avoid these complications. Slit-lamp biomicroscopy with the use of fluorescein dye and the Schirmer paper strip are useful techniques to assess dry eye.

Visual field testing is an important component in the preoperative evaluation. These tests determine the degree to which the superior field is obstructed. Insurance companies have specific criteria such as MRD1 height, visual field percentage obstruction, and photographs to determine coverage. If these are not met, then the ptosis condition is considered cosmetic in nature and not covered by insurance. The percentage of visual field obstructed by the ptotic eyelid is determined by performing a visual field test in a relaxed state followed by a repeated visual field test with the lids lifted to their normal anatomical position.

Photographs are also a vital part of the preoperative evaluation. Specific views are needed to properly record a patient's eyelid position. The first view is a "raccoon view," which is a straight on shot of both eyes and the periocular area. This helps confirm the MRD1. Secondly, views from both sides will help demonstrate the obstruction of the visual field from the eyelid position.

Unilateral ptosis is a special condition requiring further preoperative testing [3]. Hering's law states that equal and simultaneous innervation flows to the synergistic muscles concerned with the desired direction of movement. If not considered, there is a possibility that the ptosis pattern can be reversed if only correcting the initially observed ptotic eyelid. Thus, it is necessary to see the effect of lifting the more ptotic eyelid. The test can be done manually or pharmacologically (2.5% phenylephrine). If Hering's phenomenon is present, then both eyelids should be repaired at the same time. If not present during testing, then the patient should be informed that there is a possibility that the opposite eyelid could droop following correction of the unilateral ptotic eyelid.

17.5 Treatment

Several surgical techniques exist to repair aponeurotic ptosis. These include open and small-incision levator aponeurosis tucks/advancements and conjunctiva-Müller's muscle excisions. The surgical treatment of ptosis has evolved considerably with the advent of small-incision levator aponeurotic surgery. This section is devoted only to the small-incision approach.

The classic open levator surgery involved an incision across the entire eyelid crease, with opening of the entire septum to expose the horizontal extent of the levator aponeurosis and muscle. Many factors, such as the amount of local anesthesia, the use of epinephrine, overhead lights, patient consciousness, inadvertent injection of the levator muscle, Hering's phenomenon, etc., can influence the outcome of the eyelid height. The small-incision technique uses an incision about a third the size of the classic technique [9]. This means less anesthesia and epinephrine are required, and there is a

reduced chance of infiltrating the levator muscle. Also, less of the orbicularis oculi muscle is anesthetized, maintaining a more normal balance between retractors and protractors. The classic open technique and small-incision technique have been compared side by side on an efficiency basis. The small-incision technique is completed in half the time, with similar results achieved concerning the height of the eyelid. However, the small-incision technique outperformed the classic technique in achieving desirable contour of the upper eyelid [10].

The small-incision technique involves an eyelid crease incision over the central third of the eyelid crease [9]. Premarking the suture placement can expedite the procedure and improve results [11]. Dissection is carried through the orbicularis oculi muscle down to the external surface of the central tarsus. An appropriate amount of tarsus is removed so that a partial-thickness suture can be passed through it (Fig. 17.3). Next, the conjoined tendon (blending of the levator aponeurosis and the septum) is grasped and placed on inferiorly directed traction. The central orbital septum is opened, exposing the preaponeurotic fat. The undersurface of the fat is cleaned exposing the musculoaponeurotic junction. At this point, one or two sutures are passed from the tarsus up to the junction. The horizontal position of the sutures is important. The goal is to achieve lift at a point just nasal to the pupil and at the lateral limbus. The tension of the sutures is adjusted with the patient awake and cooperative to determine the set points so the height and contour are symmetric. Once completed, the ends of the suture are tied and cut. A single eyelid crease reformation suture is then placed from the new inferior edge of the levator aponeurosis to the inferior edge of the orbicularis oculi muscle. The skin is then closed (Fig. 17.4).

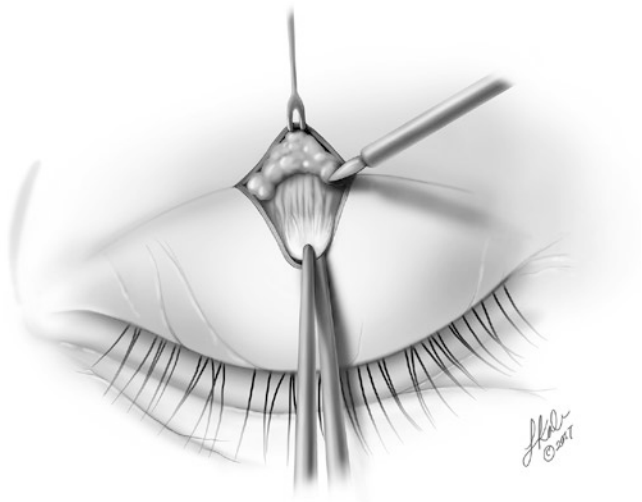

Fig. 17.3 Illustration of the small-incision surgical approach. The incision is only 8–10 mm in length or a third of the eyelid and allows exposure of the tarsus and levator aponeurosis after dissection through the orbital septum. The corresponding tarsus is cleaned below for passage of the suture for anchoring [original Fig. 4.6.3]

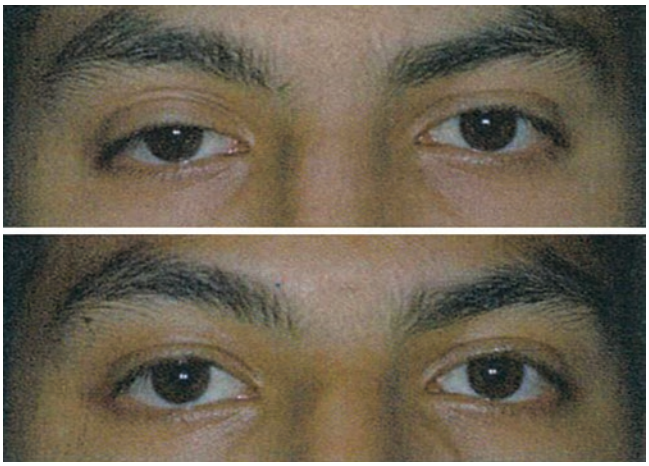

Fig. 17.4 Before and after external photographs of a patient who underwent the small-incision approach of the right upper eyelid and achieved a symmetric result [original Fig. 4.6.4]

Recently, the small-incision ptosis repair technique has been described as a resection utilizing a formulaic ratio to achieve the desired height [12]. All of these techniques are easily combined with other upper eyelid procedures such as blepharoplasty and entropion/eyelash ptosis repair.

Take-Home Pearls

- Ptosis caused by refractive surgery is influenced by many factors including contact lens use, lid speculum and drape use, and patient predisposition.
- Examination is useful to help determine the ptosis type; aponeurotic ptosis includes a low margin reflex distance, with good levator function and an elevated eyelid crease.
- Aponeurotic surgical repair is the usual type of ptosis surgery.
- Repair is best achieved with the small-incision, external levator tuck technique.

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Part IV

Refractive Miscalculation

Refractive Miscalculation with Refractive Surprise: Sphere

18

Arturo S. Chayet, Luis F. Torres, and Javier Lopez

Core Messages

- Although a spherical refractive error is Quite uncommon using excimer technology, its clinical impact may be devastating for the patient and the surgeon.
- There are several sources of mistakes that may cause a refractive surprise: a human source, laser-related condition, laser suite conditions, and the patient's response to surgery.
- Most of the causes that end in a refractive surprise are preventable and must be recognized, understood, and avoided by each refractive surgeon.
- A well-organized facility and an enthusiastic refractive team must be involved in the prevention of the occurrence of these mistakes, supporting the work of the refractive surgeon.
- Corneal wound-healing response is of particular relevance for refractive surgical procedures because it is a major determinant of their efficacy and safety. Unfortunately, these conditions cannot be screened preoperatively and therefore cannot be predicted.

18.1 Sphere

Sphere corrections are being done in more than 95% of the cases of excimer laser surgery. Therefore, it is of major paramount to do an accurate correction in order to achieve the expected result. A careful and methodical assessment of laser refractive procedure will prevent miscalculations and/or a refractive surprise.

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18.2 Introduction

Although results from laser refractive procedures have been reported to achieve 20/20 uncorrected visual acuity in as high as 90% or more of the cases, it's accuracy is not absolute, with some cases ending in an under- or overcorrection. These minor defects can be detected as early as on the first postoperative visit [1–3]. However, a significant refractive surprise due to an error in the sphere is fortunately quite uncommon, and it may happen in about 1:1000 cases or less [4, 5]. When this happens, the surgeon must always recognize all the possible causes of the mistake and base the decision of retreatment on a correct evaluation of what went wrong [6, 7].

The most common causes of sphere mistakes after excimer surgery are:

– Human
– Laser
– Laser suite conditions
– Patient

In this chapter the authors briefly review each of these sources, which may have an effect on the residual spherical error after excimer surgery. Some authors have extensively reviewed complications after excimer surgery [8–11].

18.3 Refractive Surprise of Human Source

Human mistakes are one of the most common sources of sphere error after surgery. A careful protocol, which includes proper refraction, data entry, laser maintenance, and calibration, is key to avoid a refractive surprise in excimer surgery.

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18.4 Data Entry Errors

- Typing the wrong number on the keyboard.
  This could happen because the person entering the data types too quickly or can happen due to a bad visualization of the number. Relying on handwritten data can be a problem.
- Using the information form, a chart of another patient can lead to the wrong data entry.
- The chances of incorrect preoperative data entry into the laser computer database may be lowered when using automated refraction data linked to laser computer software, minimizing the chances of human error and obtaining results that are more consistent [12, 13].

18.5 Inaccurate Refraction

- Bad refraction technique
  The most accurate data to be used in excimer surgery is the one from the patient manifest refraction. Using cycloplegic refraction can lead to an undercorrection in a young myopic patient and to an overcorrection on a young hyperopic patient. Surgeons may use their own experience to decide when to use manifest or cycloplegic refractive data and may want to keep an ongoing continuous analysis of results to get their own refractive nomogram.
- Lens-induced myopic shift
  We have found three most common causes for a lens-related myopic shift: (1) nuclear sclerosis, (2) hyperglycemia, and (3) near-work activity-induced myopia. The surgeon should carefully review the course of the patient refraction, and any recent or sudden change in the sphere should prompt the surgeon to search for the source. Every patient before excimer surgery should be screened for any signs of cataracts, should be asked for any history of diabetes, and should be consulted on their current near-work activity habits. We recommend all of our excimer surgery patients to use the 20/20/20 rule, which means that for every 20 min of near-work activity, they should take a 20-s break looking 20 feet or further to relax the accommodation from the prolonged near-work activity.
  A lack of recognition of the above conditions will have a negative effect on the refractive results after excimer treatments [1, 12, 14–16].

18.6 Laser Source

Many lasers are now available worldwide [17]. The surgeon must check preoperatively are the components of the excimer that is going to be used. Each laser is subject to a number of steps that must be followed in order to obtain an appropriate calibration. A typical laser checklist includes:

- Evaluation of the optical system for correct functioning
- Fluence testing
- Homogeneity of the beam
- Alignment beams and reticules and concentric with the test ablation
- Eye tracking

18.7 Bad Calibration

The test for fluence and homogeneity is similar for every type of laser. Each laser has a target (PMMA) to ablate, which acts as the parameter to evaluate fluence and uniformity. For checking fluence, the surgeon must evaluate whether the number of laser pulses for ablating the target falls within the laser manufacturer's approved range. If inadequate, then modifications in voltage and gas must be performed to adjust fluence until optimal conditions.

18.8 Ablation Issues

In order to evaluate how evenly the energy is distributed in the ablated tissue (beam homogeneity), the surgeon must check the appearance of the ablation on the target used for the fluence test. The surgeon must check the regularity in the pattern of ablation, which will be neither symmetrical nor asymmetrical. For example, the central ablation is less than peripheral ablation. All of these variations will result in too much or too little power and hence will influence the visual outcome of every patient. More ablation in the center of the periphery will also lead to refractive changes such as a hyperopic shift and a myopic shift, respectively [18–21].

18.9 Laser Suite Conditions

Surgical and environmental factors may alter tissue hydration and, consequently, laser effectiveness. After cutting and lifting the flap, it is necessary to maintain the corneal stroma with a consistent and reproducible hydration level.

18.9.1 Dry Conditions

Drying excessively the stromal surface after flap lifting with microsponges, waiting too long before ablation, and allowing the stromal tissue under high illumination for a long time period are all predisposing factors for stromal dehydration, which will translate clinically in a greater photoablative effect of the laser, leading to overcorrection.

18.9.2 Humid Condition

Excessive stromal hydration for an inadequate surgical technique or a surgical environment in which the humidity is higher than usual may lead to undercorrection because the ablative effect of laser pulses becomes less effective, being absorbed by humidity.

18.9.3 Room Air Quality

The cleaner the air, the more tendencies for overcorrection. In general, any particles or gases in the air will decrease the laser beam efficiency.

It is important to calibrate from time to time the laser to compensate for any changes in the condition of the laser suite to avoid any potential for under- or overcorrections [6, 14, 15, 22, 23].

18.10 Patient Source

Corneal wound-healing response is of particular relevance for refractive surgical procedures because it is a major determinant of their efficacy and safety [24–26]. As this response is usually more intense following PRK than LASIK for the same attempted correction, its modulations are more critical and clinically more important after surface ablation procedures [24]. Preservation of the central corneal epithelium, with subsequent less epithelial-stromal cell interaction and lower rates of keratocyte apoptosis and necrosis, may explain the less intense response after LASIK compared to PRK in which disruption of the basement membrane overlaying the central cornea exposes anterior stromal keratocytes to the effect of cytokines and growth factors released by the injured epithelial cells and to factors present in the tear film [16, 27–29]. Epithelial hyperplasia and stromal remodeling are two wound-healing-related processes that make major contributions to refractive accuracy and stability after PRK. In the case of epithelial hyperplasia, the variable number of activated keratocytes and myofibroblasts producing cytokines that modulate cellular proliferation and differentiation is likely an important determinant of the refractive outcome of surgery in a particular eye [24]. Mitomycin C (MMC) has been widely used to prevent haze and regression after PRK. Its mechanism of action appears to be by the blocked replication of keratocytes or other progenitor cells of myofibroblasts. When MMC is being used, the surgeon should take in consideration the decrease in wound remodeling of the cornea and therefore the potential for less regression of the refractive effect; some surgeon will adjust the laser ablation nomogram by 10–20% of less ablation if MMC is being used [25, 30, 31].

After LASIK, wound-healing responses may also be responsible for refractive variations. Epithelial hyperplasia has been shown to have a role in the regression of refractive effect after LASIK [6, 26].

Unfortunately, there is not a way to predict the response of each individual laser vision correction, and therefore a small variation from patient to patient may be observed.

Take-Home Pearls

- A refractive surprise due to an error in the sphere is quiet uncommon after surface ablation procedures or LASIK.
- The magnitude of the error may depend on the source of the event.
- Human mistakes during data entry into the laser software may cause serious complications after the surgery and must be avoided using automated data systems and a well-organized team. The surgeon must always double-check all refractive data before each surgery is performed.
- A complete ophthalmic examination performed by experienced individuals will lower the chances of possible mistakes due to inaccurate refraction.
- The surgeon must check preoperatively all the components of the excimer, with careful attention to an adequate fluence and homogeneity of the system, ensuring that the number of laser pulses for ablating the targets falls within the laser manufacturer's approved range.
- Laser suite conditions must be optimal before, during, and after each surgery. The surgeon must ensure a consistent and reproducible hydration level of the corneal stroma, taking into account all the surgical and environmental factors that may alter laser effectiveness. Corneal wound-healing response is a major determinant of refractive efficacy and safety after surgery. This response is

usually more intense after PRK than LASIK. Epithelial hyperplasia and stromal remodeling are two wound-healing-related processes that make major contributions to refractive accuracy and stability after PRK. After LASIK, the wound-healing process involves some degree of new tissue deposition. Those eyes with excessive or reduced wound healing will have an atypical effect from the photoablation, with a consequent suboptimal refractive outcome. Unfortunately, these conditions cannot be screened preoperatively and therefore cannot be predicted.

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Astigmatism Surprise After Refractive Surgery

19

Noel Alpins and George Stamatelatos

Core Messages

- Misalignment of the surgical treatment is the major source of refractive surprise in relation to astigmatism.
- Sources of misalignment include cyclotorsion from the seated to supine position, a physical turning of the patients head or intentionally placing a cataract incision on a meridian other than the steepest corneal meridian due to ergonomic factors or to more accurately neutralise the corneal astigmatism using a toric IOL.
- Corneal incisions, no matter how small, should be analysed vectorially to determine what effect, if any, they have had on the preoperative corneal astigmatism.
- Refractive cataract surgeons employing a technique to correct astigmatism at the time of surgery (toric IOLs, LRIs, etc.) need to consider the effect of the phaco incision on the remaining astigmatism; otherwise, the IOL or LRI will be misaligned and/or undercorrected.
- The forces acting to change the corneal structure in a misaligned treatment are flattening (or steepening) and torque. These result in a reduction (or increase) of astigmatism at the intended meridian and also a change (rotation) in the meridian of the astigmatism. (Furthermore, placing the toric IOL at an axis that is not the steepest corneal meridian or the toric IOL rotating over time.)
- Vector analysis is a useful tool to calculate the effects of a misaligned treatment on the remaining astigmatism.

The ultimate goal of modern refractive surgery is to meet, or even exceed, the expectations of the patient. In regard to the spherical component of the correction, this involves obtaining the intended target, which is not necessarily emmetropia. However, concerning the astigmatic component, the universal primary goal is to achieve the maximum reduction of astigmatism. The secondary goal is to ensure any remaining cylinder, unable to be eliminated from the optical system due to corneo-refractive differences, is optimised towards a more favourable with-the-rule orientation.

Addressing the correction of astigmatism is crucial for the refractive surgeon as a large majority of patients have significant preoperative cylinder. Ninety percent of the population has detectable astigmatism, with 25% having more than 1.0D [1]. An uncorrected astigmatic error of 1.0D will, on average, decrease visual acuity to the level of 20/30 or 20/40 depending on its orientation [2]. Aside from blurring of vision, uncorrected astigmatism can also cause distortion, glare, asthenopia, headaches and monocular diplopia.

Surgical treatments that incorporate astigmatic correction include excimer laser surgery such as photoastigmatic refractive keratectomy (PARK), laser in situ keratomileusis (LASIK) and laser-assisted subepithelial keratomileusis (LASEK) including epi-LASEK. These procedures have been shown to be effective at correcting low to moderate levels of astigmatism [1, 3, 4]. However, 15–20% of cataract patients also have >1.5D of astigmatism [5], and with advances in technology, the modern cataract surgeon must also consider the treatment of astigmatism as part of the surgical goal. This is particularly true as refractive clear lens exchange surgery is widely becoming more popular, and these patients tend to be young and demanding of excellent visual results. Options for correcting astigmatism at the time of cataract surgery include placing the phaco incision along the steepest corneal meridian [6–8], paired opposite clear corneal incisions along the steepest meridian [9], phakic [10] and pseudophakic [11, 12] toric IOLs, limbal relaxing incisions (LRIs) [13], peripheral corneal relaxing incisions (PCRIs) [5], and astigmatic keratotomy (AK) [14].

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19.1 Misaligned Treatments

In many cases an astigmatic postoperative surprise is due to the treatment being misaligned with the steepest corneal meridian, otherwise known as 'off-axis'. An unplanned misaligned treatment not only changes the magnitude of the astigmatism in a manner different than intended but will also impact on the orientation of the astigmatism. A wavefront-guided laser surgery designed to correct higher-order aberrations may in fact induce significant aberrations if misaligned, even if the astigmatic component is minimal. This is noticeable for treatments misaligned by only 2 degrees [15], and the room for error is tightened even further in patients with large pupils of 7 mm or more [16]. With such tight criteria, it is important to understand the causes of misalignment, the forces that act to change the cornea in a misaligned treatment and how to analyse outcomes of misaligned treatments to improve future results.

19.2 Sources of Misalignment

The underlying cause for off-axis treatments may be something as simple as a slight misalignment of the patient's head. There are, however, other factors that need to be considered.

19.2.1 Cyclotorsion

As the position of the eye changes, it undergoes natural rotational movements around the central axes known as cyclotorsion. The amount of cyclotorsion depends on the individual and the fixation stimulus but is usually within 15° of the resting position [15]. In relation to refractive surgery, it is the amount of torsion when the patient moves from the seated position to supine that is important, which is typically between 2° and 7° [15]. Therefore, the meridian of the astigmatism measured by the keratometer or topographer where the patient is seated upright may significantly change as the patient lies down for surgery, resulting in a treatment that may be misaligned by up to 7°. This is well outside the recommended 2° limit for a wavefront-guided ablation.

With such a high level of precision required, many laser machines now incorporate tracking systems to account for cyclotorsion by identifying iris landmarks and rotating the treatment accordingly from the wavefront machine to the laser machine. While off-axis effects are a little more forgiving in cataract surgery, alignment errors can be minimised by marking the corneal meridian for toric IOLs or LRIs with the patient seated in an upright position or using computer-assisted guiding systems such as the Alcon Verion™ and Zeiss Callisto eye®.

19.2.2 The Elusive 'Astigmatically Neutral' Incision

The size of the clear corneal incision used to access the anterior chamber for cataract surgery has reduced in recent times. The routine 3 mm incision has moved to sub-2 mm with the gaining popularity of microincisional cataract surgery (MICS), whether bimanual or coaxial. Many surgeons would claim the incision to be 'astigmatically neutral' and therefore do not include it in their surgical calculations. However, while the astigmatism induced by the surgery is certainly reduced with smaller incisions, an astigmatic analysis of the surgically induced astigmatism vector (SIA) to quantify the amount is still required. Any incision, no matter how small, may still have an impact on the corneal structure and will alter the astigmatic magnitude and/or direction.

Therefore, a toric IOL or LRI may be placed exactly where the surgeon intended, yet if the effects of the incision (change in magnitude and orientation) are not taken into account, the results will still be compromised. The final visual outcome may still be acceptable to the patient depending on how much alignment error occurs [17]. However, if there is a thorough understanding of the forces at play during surgery, a merely acceptable outcome can be optimised to an even better one.

19.3 Understanding and Analysing Misaligned Treatments

19.3.1 Forces that Act to Change the Cornea

There are several forces that act to influence the cornea throughout the course of incisional and ablative surgery. *Flattening* and *steepening* of the cornea are the forces most commonly considered as these are the basic underlying principles of refractive surgery. In a perfect surgery, the cornea is flattened at the steepest meridian (or steepened at the flattest meridian or a combination of both) to reduce the magnitude of the astigmatism. However, if the treatment is not perfectly aligned and applied off-axis, another component becomes evident. This component is known as *torque*, which has two effects on the remaining astigmatism: it acts to increase the magnitude and also to rotate the meridian in a clockwise or counterclockwise direction [18]. It is the torque component that is commonly disregarded, yet this is the major source of postoperative surprises in relation to astigmatism. In order for any refractive surgeon (excimer laser or IOL) to achieve maximum results, a thorough understanding of these forces is required.

19.3.2 Vector Analysis of Outcomes

As astigmatism has both magnitude and direction, it may be represented by vectors, and therefore vector analysis is a simple and effective tool for analysing the astigmatic outcomes from surgery [2, 18–20]. The *target induced astigmatism vector (TIA)* is the astigmatic change the surgery was intended to induce, and the *surgically induced astigmatism vector (SIA)* is the astigmatic change actually induced by the surgery. The various relationships between the SIA and TIA can determine whether too much or too little treatment was applied and whether the treatment was aligned effectively or not.

The amount of misalignment is the *angle of error* (AE) and is described by the angle subtended between the SIA and TIA. The AE is positive if the SIA lies in a counterclockwise (CCW) direction to the axis of the TIA, and similarly the AE is negative if the SIA lies in a clockwise (CW) direction relative to the TIA. In a misaligned treatment, the SIA acts to change the cornea in two ways: a proportion of the induced change will act to rotate the astigmatic meridian (through the effect of torque) and the remaining proportion will act to flatten the cornea at the intended meridian. This latter change is known as the *flattening effect* (FE) measured in dioptres and is dependent on the AE:

FE = SIA cosine 2AE.

It can be seen from the above formula that the FE is equal to the SIA when the AE is zero and the treatment is perfectly aligned. The effective proportion of flattening achieved is the *flattening index* (FI) and is equal to the FE divided by the TIA. The relationship between the amount of misalignment and the amount of flattening is seen in Fig. 19.1. This model assumes a full correction of astigmatism is achieved (i.e. the SIA = TIA). It is seen that the FI is reduced as the AE increases. When the treatment is misaligned by 30°, the effective proportion of flattening at the intended axis is reduced by half, with the other half being the torque effect. When the misalignment is 45°, there is no flattening effect at all, and the only force acting to change the cornea is torque. If the misalignment is greater than 45°, there is a negative flattening effect (i.e. the cornea is steepened).

It is a common misconception to regard a misaligned treatment as causing an undercorrection in the magnitude of the astigmatism. However, this is not strictly correct. An over- or undercorrection is determined by the *correction index* (CI), which is the ratio of SIA to TIA. The CI is equal to 1.0 if a full correction of astigmatism occurs. If the CI is greater than 1.0, an overcorrection has occurred, and similarly a CI of less than 1.0 indicates an undercorrection. In a misaligned treatment, the magnitude of the SIA is in fact unaffected as it is independent from the AE, and therefore the CI is also unaffected. Instead a misaligned treatment results in a shift of the orientation of the existing astigmatism (through the effect of torque). The effect of the misaligned treatment on the remaining astigmatism magnitude and axis can be seen in Figs. 19.2 and 19.3.

19.3.3 Example

Let us look at an example to demonstrate. This form of analysis applies for both laser and incisional surgery, so we use a general example that can be used for all refractive surgery. A patient scheduled for refractive surgery has 2.0D corneal astigmatism at a 25° meridian. The surgeon performs uncomplicated surgery

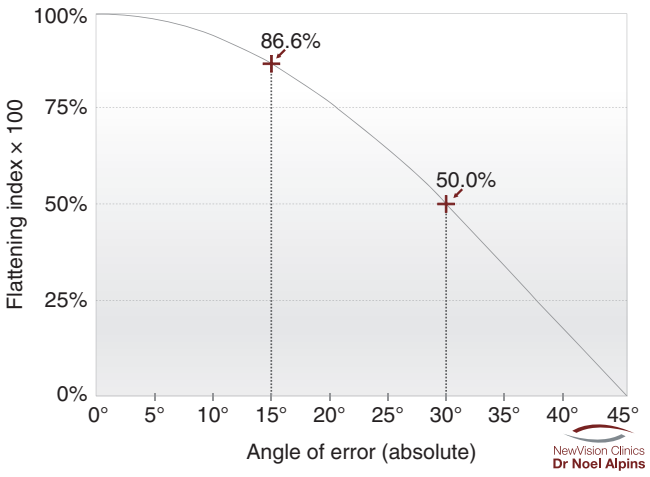

Fig. 19.1 (Alpins) Effect of misaligned astigmatism treatment on flattening index when SIA = TIA

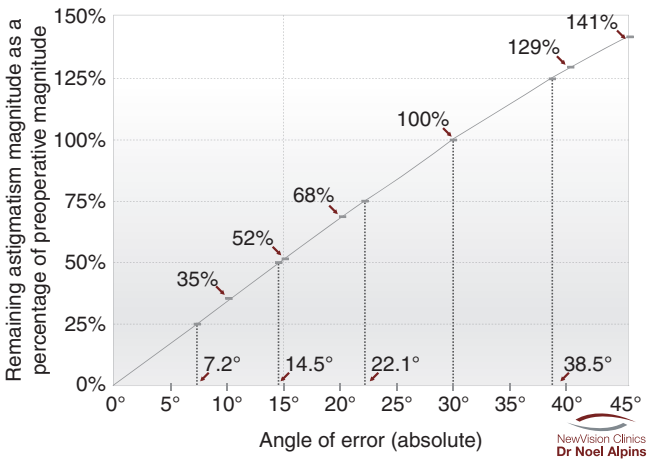

Fig. 19.2 (Alpins) Effect of misaligned astigmatism treatment on remaining astigmatism magnitude

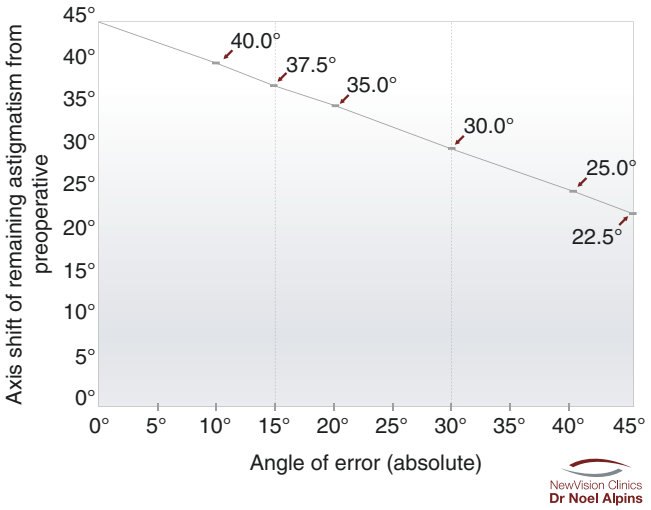

Fig. 19.3 (Alpins) Effect of misaligned astigmatism treatment on remaining astigmatism axis

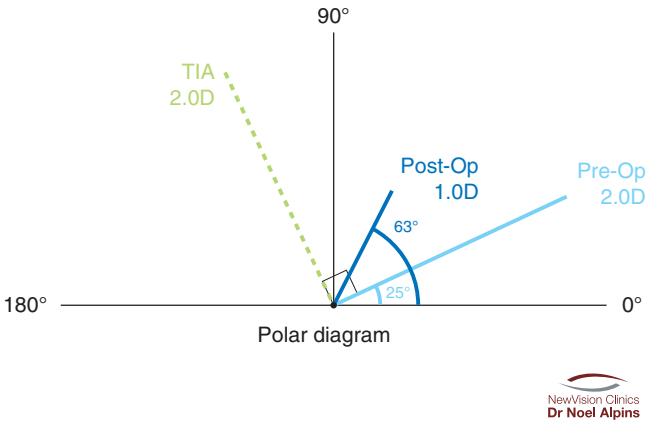

Fig. 19.4 Polar diagram displaying the pre- and postoperative status as it appears on the eye. The TIA is the intended astigmatic treatment and is perpendicular to the preoperative value

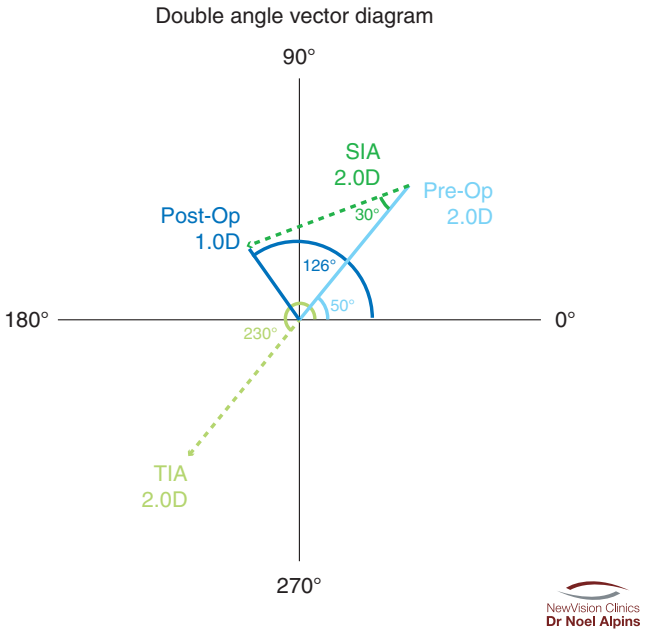

Fig. 19.5 Double-angle vector diagram to allow analysis of the outcome. All the angles have been doubled without altering the magnitudes. This allows calculation of the SIA vector

that was thought to be aligned correctly, but postoperatively the corneal astigmatism is measured again and found to be 1.0D at 63°. Why did this happen?

A polar diagram is a simple way to represent astigmatism as it appears on the eye. This is seen in Fig. 19.4, where the preoperative value of 2.0D at 25° is represented by the light blue line, and similarly the dark blue line represents the postoperative value of 1.0D at 63°. The TIA represents the amount of astigmatic change the surgeon wants to induce. A reduction of astigmatism may be achieved either by flattening the cornea at 25° or by steepening the cornea at the perpendicular meridian of 115°. However, as the TIA always represents a steepening force, it is displayed on the polar diagram at the perpendicular meridian of 115° as seen in Fig. 19.4. In this example the magnitude of the TIA is equal to that of the preoperative value as the surgery was intended to achieve a full correction of astigmatism.

To allow analysis of the results, the polar diagram (which represents the situation as it appears on the eye) must be converted to a mathematical construct. This is easily done by doubling all the angles to create a double-angle vector diagram (DAVD) as seen in Fig. 19.5. The magnitudes remain unchanged, and the angles are simply doubled.

The SIA is the vector joining from the pre- to the postoperative values. This vector may be moved to the origin without changing the magnitude or the angle as seen in Fig. 19.6. The SIA and TIA in this example are equal in length, indicating a full correction of astigmatism and a correction index of 1.0. Therefore, even though the amount of flattening and thus the reduction in astigmatism magnitude at the intended meridian were less than expected, there has not been an undercorrection of astigmatism magnitude. The angle between the SIA and TIA may then be easily measured at 30°. A line is drawn perpendicularly between these two vectors to give the FE, which in this case is 86.6% the length of the TIA. This represents almost a 15% loss of flattening effect at the intended meridian.

In order to represent this in 'real' terms on the eye, the DAVD is converted back to a polar diagram by simply halving the angles, again leaving the magnitudes unchanged, as shown in Fig. 19.7. The angle between the SIA and TIA (i.e. the AE) is now 15°. It is therefore easily seen that the treatment was actually applied 15° off-axis in a CW direction.

Therefore by vector analysis, the loss of flattening effect at the intended placement of the astigmatism treatment (whether incision or ablation) is around 15% when the treatment is 15° 'off-axis' from the intended meridian. This relationship

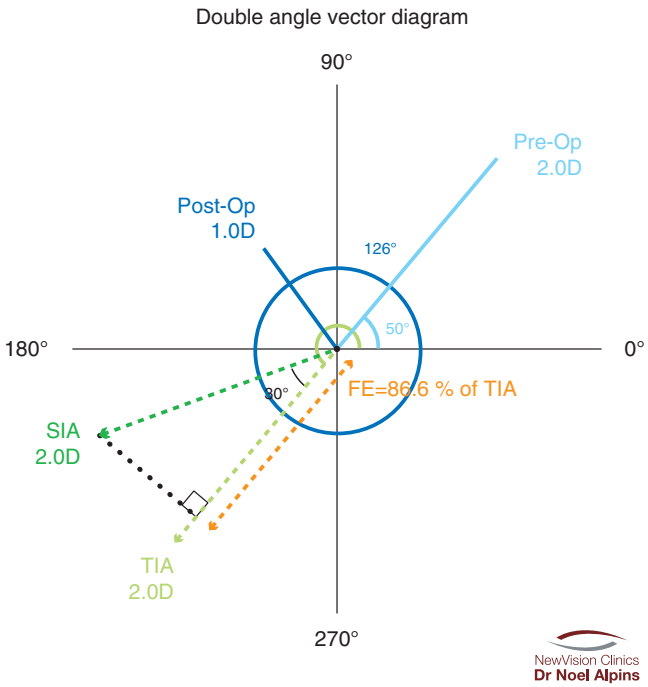

Fig. 19.6 Double-angle vector diagram where the SIA has been moved to the origin without altering the angle subtended or the magnitude. This allows calculation of the flattening effect

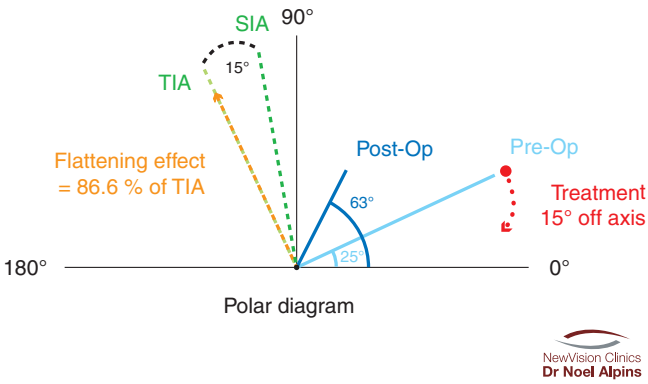

Fig. 19.7 Polar diagram representing the analysis as it would appear on the eye. The angles have been halved without altering the magnitudes. The AE subtended by the SIA and TIA is 15°, so it is easy to see the treatment was misaligned by this amount

between the AE and FI correlates with Fig. 19.1. The remaining 13.4% of the SIA acted as torque to rotate the remaining astigmatism. Figures 19.2 and 19.3 display the effect of misalignment on the remaining astigmatism magnitude and axis. It can be seen from these graphs that a misalignment of 15° in this example reduces the magnitude of the astigmatism by approximately 50% and shifts the meridian by 37.5°. This correlates with our example where the astigmatism was reduced by half and rotated from 25° to 63°. It is important to note in this example that this reduction is just a scalar comparison of pre- and postoperative astigmatism magnitudes.

19.3.4 Practical Use in the Clinical Setting

Imagine the surgery in the above example was cataract surgery and the surgeon was to perform LRIs at the time of cataract surgery to correct the astigmatism. If the incision wasn't taken into account, the LRI would be centred around 25°, based on the assumption that the preoperative value of 2.0D at 25° hadn't changed. In fact, the effect of the cataract incision has changed the astigmatism to 1.0D at 63°. The LRI would therefore have been misaligned by almost 40°. Similarly if a toric IOL was implanted at the preoperative meridian of 25° to correct 2.0D of cylinder, a postoperative surprise would have occurred as the real astigmatism correction should have been 1.0D at 63°.

Therefore, if a surgeon assumes the incision is neutral and does not place the incision along the corneal meridian, the misalignment will change both the meridian and magnitude of the astigmatism that are being treated. The amount of change will obviously depend on the amount of misalignment but also on the amount of induced flattening by the incision. Each surgeon will achieve a certain average value of corneal flattening depending on the incision size used and the orientation of the incision at the limbal meridian. Due to the ovoid shape of the cornea, incisions placed vertically have a greater flattening effect than those placed temporally as they are slightly closer to the centre of the cornea. Each surgeon ideally should track the data from previous cases to calculate their own average amount of flattening for each site of placement which can then be used when planning future cases.

The ASSORT® toric IOL calculator (freely available at www.assort.com) allows the surgeon to calculate the effect of the incision on the preoperative corneal astigmatism and incorporate this into the surgical plan, using simple vector analysis.

19.3.5 Calculating the Effect of the Incision

A patient scheduled for right eye cataract surgery has 2.0D astigmatism at 30° measured by keratometry. The surgeon intends to use a temporal (180°) clear corneal incision for cataract extraction and then use LRIs to correct the remaining astigmatism. Thus, the incision will be deliberately off-axis by 30°, so what will this do to the remaining astigmatism? From analysing their previous data, the surgeon knows the average flattening induced by their temporal incisions is approximately 0.5D. Therefore, they would expect the TIA vector (which is always perpendicular to the incision as it represents a steepening force) to be 0.5D at 90°. This is represented on the polar diagram in Fig. 19.8.

Again, we need to convert this to a mathematical construct (Cartesian co-ordinates), so we double all angles

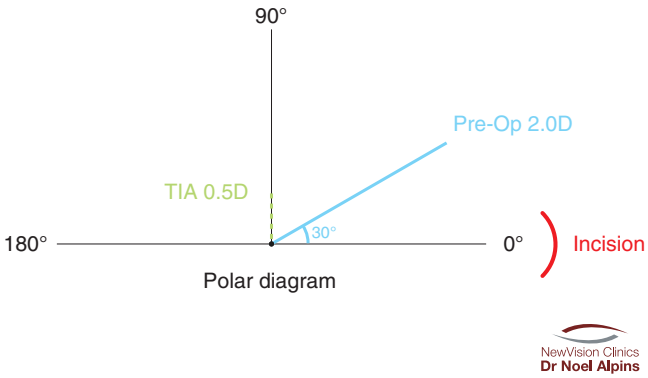

Fig. 19.8 Polar diagram representing the preoperative situation as it appears on the eye. The incision is at 180° and is expected to induce approximately 0.5D flattening. Therefore the expected TIA is perpendicular to this (as the TIA represents a steepening force)

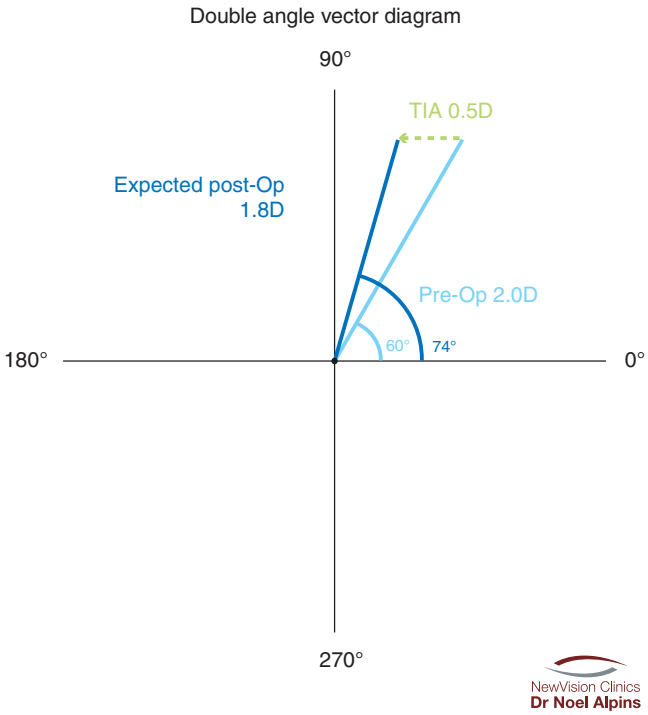

Fig. 19.9 Double-angle vector diagram to allow analysis of the expected outcome. The angles have been doubled without altering the magnitudes, and the TIA vector has been moved to the tip of the preoperative value. This allows calculation of the expected postoperative value

without altering the magnitudes to create a double-angle vector diagram in Fig. 19.9. The preoperative angle of 30° now becomes 60°, and similarly the TIA vector has doubled from 90° to 180°. This TIA vector may be moved to the end of the preoperative value without altering either the 180° angle or the magnitude as displayed in Fig. 19.9.

The expected postoperative value may now be estimated simply by drawing a line from the head of the TIA to the origin. Measuring the length and angle subtended by this line gives a value of 1.80D at 74°. To determine how

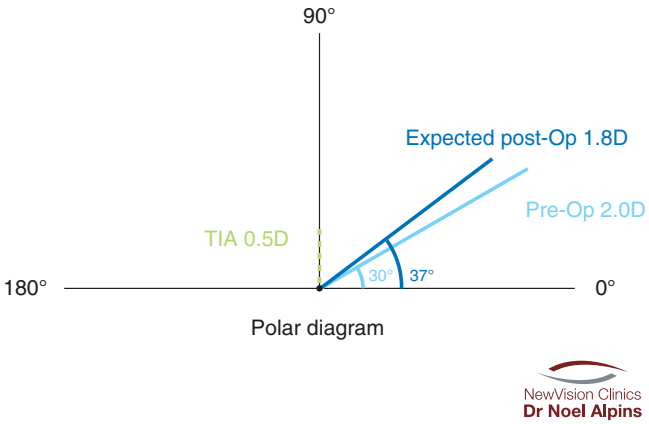

Fig. 19.10 Polar diagram representing the expected outcome as it would appear on the eye. All angles have been halved without altering the magnitudes. By simple measurement, the predicted postoperative astigmatism following the temporal cataract incision is 1.80D at 37°

this will appear on the eye, we revert back to a polar diagram by halving all angles. This is seen in Fig. 19.10, where the expected postoperative value is 1.80D at 37°. Therefore, following a temporal incision, this surgeon should centre the LRI around 37° instead of the preoperative value of 30° (free LRI calculator available at www.assort.com).

19.3.6 Refractive Surprises After Toric IOL Surgery

If there is a refractive surprise post toric IOL surgery as indicated by a significant amount of cylinder remaining in the subjective refraction postoperatively, a toric astigmatic analysis must be performed comparing the postoperative refractive cylinder (corneal plane) to the preoperative corneal astigmatism adjusted for any effect of the phaco incision. The treatment in these cases is the IOL toricity at the corneal plane allowing for the effective lens position and the spherical component of the IOL [21].

Should rotation of the IOL show significant reduction in the refractive cylinder to an acceptable level, then early intervention and rotation of the implants are advised—ideally approximately 4–6 weeks postoperatively.

There are then basically three options available to the surgeon:

1. **Rotate the existing toric IOL to reduce the refractive cylinder to a minimum**.
   Consider rotating the toric IOL when the AE is greater than 10° and the preoperative ORA is less than 0.75D (Fig. 19.11).
2. **Exchange the toric IOL as the toricity selected is too strong or too weak**.

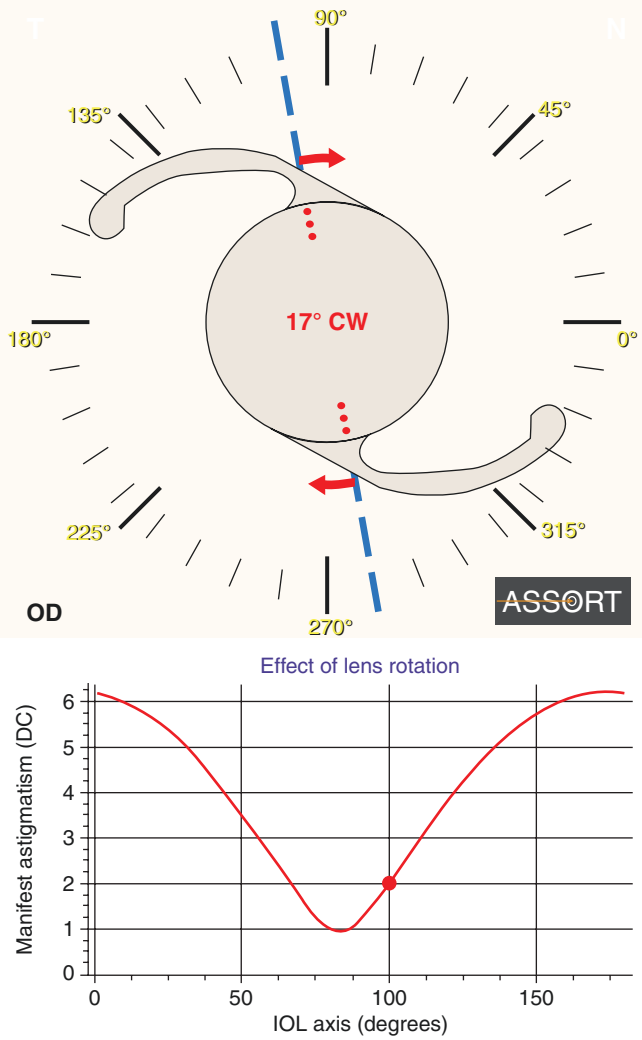

Fig. 19.11 The ASSORT® toric IOL software calculates the rotation of the implanted IOL to improve the postoperative refractive cylinder

In cases where the ME is greater than 1.00D, consider changing the toric IOL to a more suitable cylinder selection OR correcting the refractive cylinder post toric IOL implantation with an additional sulcus toric lens (Fig. 19.12).

3. **Perform excimer laser surgery to correct for any spherical and/or astigmatic error in the subjective refraction**.
   In cases where the preoperative ORA was greater than 1.25D and the AE and ME are not significant, then excimer laser surgery to correct postoperative refractive cylinder would be an option.
   The significance of postoperative corneal and/or refractive astigmatism can be determined by the steps that the toric IOL of your choice is available in – that is, if the toric IOL comes in 0.75 steps of cylinder and the postoperative corneal astigmatism has changed less than this, or the ME is less than this, changing the toric IOL may not be required.

Alpins method

SIA	2.64	Ax	50
TIA	2.69	Ax	30
Difference vector	1.83	Ax	176
Correction index	0.98		
Index of success	0.68		
Magnitude of error	–0.05		
Angle of error	20 (CCW)		

Fig. 19.12 The Alpins Method can be used to determine if the implanted toricity of the IOL is overcorrecting or undercorrecting the corneal astigmatism. Calculation of the magnitude of error (ME) should ideally be zero: greater than ±0.75D means that an exchange of the toric IOL for a more accurate toric power should be considered

Take-Home Pearls

- When marking the limbus, do so prior to surgery with the patient in the seated position before they lie down. This way it will match the preoperative keratometry or topography meridian where the patient is also seated. This meridian may actually change by 2–7° as the patient lies down due to cyclotorsion of the eyes.
- If a treatment is applied exactly at the steepest corneal meridian, the magnitude of the astigmatism is reduced, and the meridian of any remaining astigmatism remains unchanged.
- If a treatment is applied at a meridian other than the steepest corneal meridian (i.e. a misaligned 'off-axis' treatment), the magnitude of the astigmatism is either reduced or increased, and the meridian of the remaining astigmatism is changed in the opposite direction of the misaligned incision due to the force of torque.
- Many cataract surgeons place all incisions temporally or superiorly regardless of the location of the steepest meridian but then orientate the toric IOL or LRI with the preoperative corneal meridian without accounting for any change in magnitude or direction from the incision. This results in a compromised result with incomplete astigmatism reduction.
- Use vector analysis (www.assort.com) to calculate the effect of the incision on the remaining astigmatism magnitude and meridian prior to performing surgery to optimise results from toric IOLs or LRIs.
- Use vector analysis to calculate the effect of rotating the implanted toric IOL in reducing the manifest refractive cylinder. The Alpins Method of vector analysis can be used to determine if the toric power of the IOL is accurate.

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Part V

Optical Aberrations and Corneal Irregularities

Causes of Higher-Order Aberrations Induction in Excimer Laser Surgery

20

Vikentia J. Katsanevaki, Veronica Vargas Fragoso, and Jorge L. Alio

Core Messages

- Some patients may complain of optical disturbances after corneal refractive surgery.
- These optical disturbances are secondary to the increase in high order aberrations after refractive surgery; the greater the correction of the refractive error, the greater the induction of corneal aberrations.
- The most commonly induced aberrations are spherical aberration and coma.
- Customized treatments are meant to reduce the induction of HOAs.
- SMILE technique induces lesser aberrations than LASIK or PRK.

20.1 Introduction

Refractive surgery is one of the most popular surgeries in ophthalmology. Although most of the patients are satisfied with their final results, some of them complain following the surgical procedure of optical disturbances, which are caused by optical aberrations induced by the surgery.

Patients complain of blurred vision, poor image contrast, glare, halos, ghost images, starbursts, and poor night vision. A study reported that blur was the most common reason for a low subjective quality of vision after LASIK [1].

Night vision disturbances occur even after successful LASIK treatments [2].

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These aberrations are sometimes visually disabling; some patients can't drive at night because of significant glare.

In this chapter we are going to review the optical complications after refractive surgery, why they occur, and how to resolve and try to avoid them using the latest laser technology available.

20.2 Excimer Laser in Refractive Surgery

The excimer laser was first introduced in ophthalmology 25 years ago; it uses an ultraviolet radiation at a wavelength of 193 nanometers that breaks inter- and intramolecular bonds. Refractive surgery is used to reshape the corneal surface by removing anterior stromal tissue.

For treating hyperopia, it creates a doughnut-shaped annular photoablation in the periphery of the cornea, which steepens the cornea, giving a more prolate corneal shape.

For correcting myopia, it flattens the central corneal, reducing its refractive power, giving an oblate corneal shape.

20.3 Optical Corneal Changes After Refractive Surgery

The normal cornea has a prolate shape, it is steeper at the center, and it gradually flattens toward the periphery and creates an aspheric optical system.

The corneal asphericity coefficient (Q value) describes the rate of change in curvature of the cornea from its center to the periphery; if the Q value is 0, the corneal shape is a sphere, a negative Q value indicates a prolate profile, and a positive Q value indicates an oblate profile [3].

A normal cornea has a Q value equal to −0.25 [4]. Any change in Q will lead to optical aberrations [5, 6].

Since laser refractive surgery alters the corneal shape, it is expected to have changes in Q values; in myopic ablations the cornea becomes more oblate, changing the Q value to

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positive; and in hyperopic ablations the cornea becomes more prolate, changing to a negative *Q* value.

Changes in corneal asphericity values after refractive surgery induce spherical aberrations, which diminish the optical quality of vision and compromises contrast sensitivity. The patient will complain of nighttime vision problems, even if he has a total correction of the refractive error with a 20/20 vision.

Spherical aberration (SA) is a rotationally symmetric aberration in which the rays that pass through the paraxial zone of the pupil focus at a different plane than the rays that pass through the marginal pupil. For positive spherical aberrations, the central focus (paraxial) is positioned posterior to the best focus, and the marginal focus is anterior to the best focus. The opposite occurs when the spherical aberration is negative [3].

Spherical aberration plays an important role in image formation under low luminance conditions such as night driving [7]**;** glare, halos, and starburst are also associated with SA.

LASIK induces a positive change in spherical aberration after myopic ablation (Fig. 20.1) and a negative change after hyperopic ablation (Fig. 20.2). The amount of induced aberrations is related to the magnitude of the preoperative refractive error [3, 7–9].

The induction of positive spherical aberration after myopic ablation is due to laser fluence loss toward the peripheral cornea, which is also known as "cosine effect" [10].

After hyperopic ablation, the more negative values of spherical aberration are associated to more prolate corneas.

There is also an increase in coma and coma-like aberrations, although these aberrations are normally associated with decentration of the ablation procedure [6]. Even a subclinical decentration (<1.0 mm) can increase coma-like and spherical-like aberrations after refractive surgery [9, 11]. High refractive corrections tend to induce more coma aberrations since the ablation time is longer, and there is a higher risk of decentration [10].

There are two different forms of decentration described by Azar and Yeh: shift and drift.

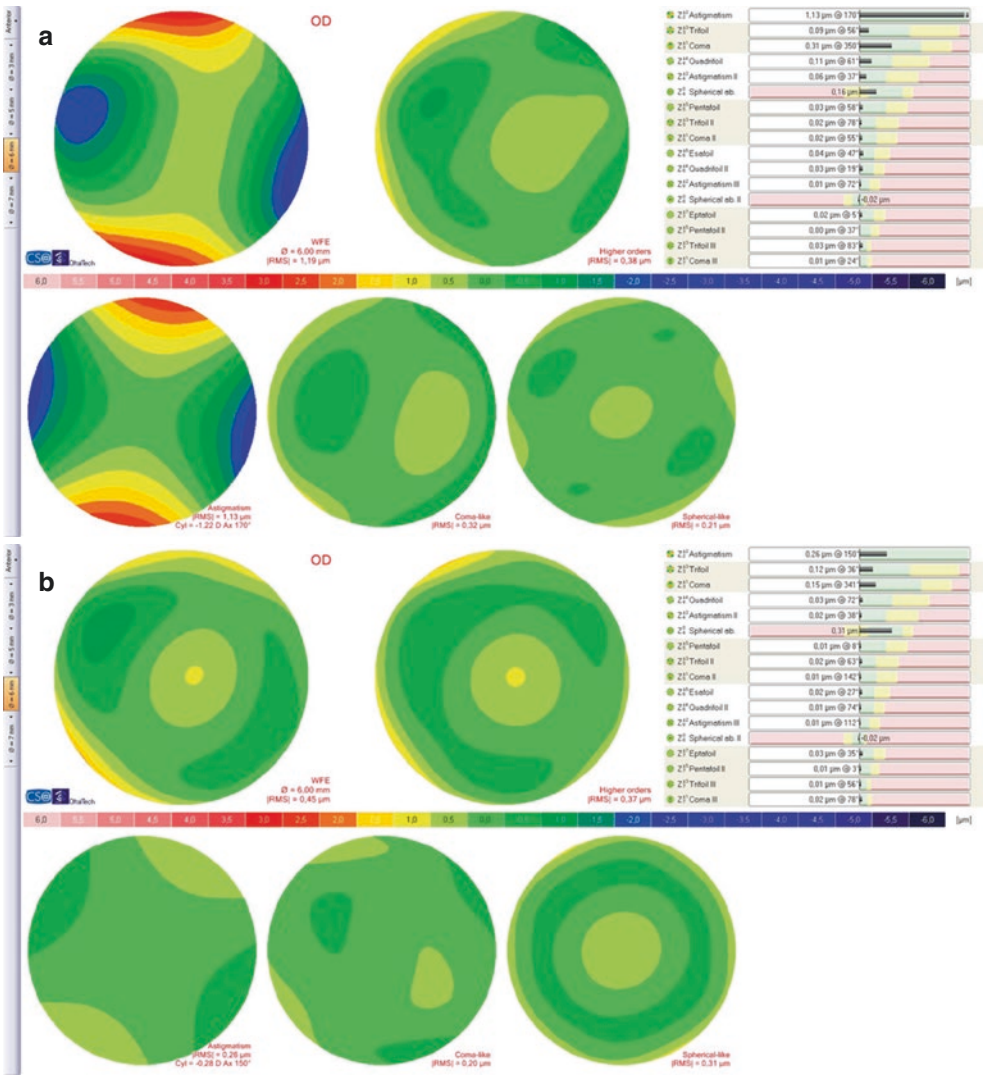

Fig. 20.1 (**a**) Myopic patient with -3.50 diopters before LASIK surgery (**b**) Same patient as figure 1a, after myopic intraLASIK with a positive change in spherical aberration.

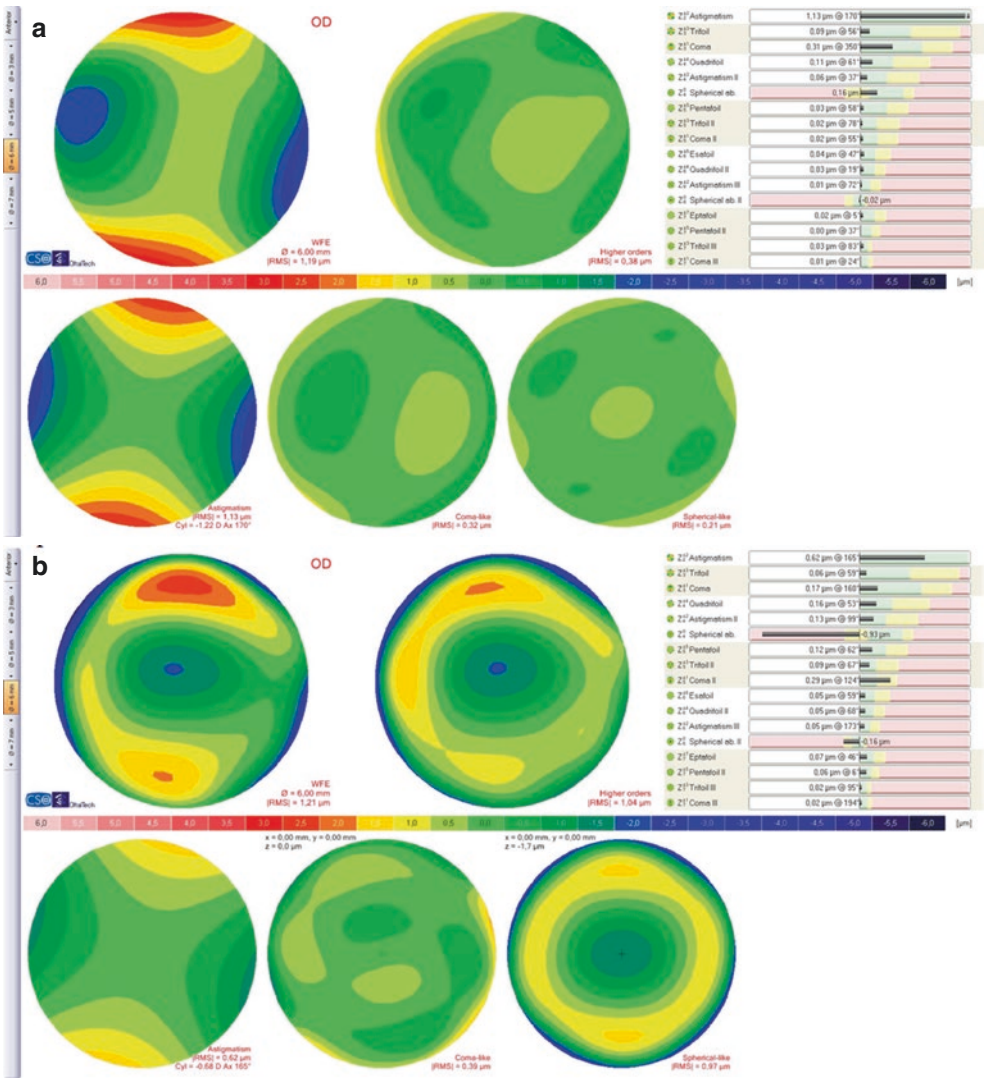

Fig. 20.2 (**a**) Patient with hyperopia of +6.00 diopters before LASIK surgery (**b**) Same patient as figure 2-a after hyperopic intraLASIK, there is a negative change in spherical aberration

Shift is secondary to a misalignment of the excimer laser, and it is a static phenomenon and causes a displaced ablation.

Drift is a kinetic phenomenon and occurs when the patient moves the eye during the procedure, causing an irregular delivery of the laser's energy [12].

A study reported that subtle levels of decentration are more sensitive when doing peripheral ablation of hyperopic procedure, and this could easily induce aberrations [8].

The diagnosis of decentration can be made either by tangential topography or a wavefront map, although in the latest a coma profile will appear, and other causes of coma have to be studied (internal coma, ectasia).

Decentered ablations can induce halos, glare, starbursts, and irregular astigmatism; this is why an accurate centration of the optical zone is very important for optimal results.

20.4 Ablation Profiles and Postoperative Aberrations

The excimer laser energy can be delivered with three different types of lasers: broad-beam lasers, scanning-slit lasers, and flying-spot lasers.

Broad-beam lasers were used in the first-generation laser platforms. These types of lasers had the disadvantage of causing of a central island (defined as a central area of steeper corneal tissue having increased refractive power [13]), leading to high levels of vertical coma and spherical aberrations [9]; the optical zones were smaller, so aberrations occurred, especially in dim light when the pupil is larger than the optical zone, and it wasn't possible to create transition zones. The refractive predictability of these lasers was reduced due to the variations in energy of the laser beam [13].

A study reported that patients that underwent laser refractive surgery with broad-beam laser had an increase in the anterior corneal optical irregularity, and the HOAs in these patients were much larger compared with patients that had flying-spot laser and customized ablation [14].

Scanning-slit lasers, instead of using an iris diaphragm to control a broad beam, use a smaller slit-shaped laser beam, and their advantage over broad-beam lasers is that the postoperative corneal surface is smoother, and larger diameters of ablation can be made, giving the patient a higher vision quality [15].

The shape of the beam is important to produce a smoother surface. The beam profile can be a Gaussian, super-Gaussian, or flat top. In the latest the energy density is equal at every area along the beam. In a Gaussian profile, the greater energy density is at the center. The beam profile varies with every excimer laser platform. [16]

The most modern excimer lasers are flying-spot lasers (a type of scanning laser) that have smaller beams (0.5–1.0 mm) and are used for more accurate results in custom ablations. The speed of these lasers varies from 400 to 1050 Hz, reducing the time needed per diopter ablation in a 6.5 mm optical zone from 7 to 10 s using older generation laser platforms to 4 s [13].

This is an important advantage since a longer treatment time might lead to further dryness of the corneal stroma and more involuntary eye movement, and these could compromise the visual outcome [14].

Scanning-slit and flying-spot systems have shown to:

- Produce predictably uniform corneal profiles
- Have lower refractive error postoperatively
- Have a lower incidence of central islands
- Have a wider mean of effective ablation area and a less steep ablation edge

Another advantage of scanning lasers is that they can be used in combination with eye tracking technology to compensate for eye movements. Early treatments with broad-beam lasers were performed without compensation for movement, resulting in decentered ablations and induction of coma aberrations.

A conventional eye tracker adjusts eye movements into an *X*- and Y-axis linear movement; modern eye trackers do not only follow these horizontal and vertical displacements of the eye but also track the cyclotorsional rotations [13]. The latency (the time required to measure the position of the eye, the time required to move the deflection mirrors, and the time difference between the tracking and the firing of the laser [11]) of the eye trackers at the sixth-generation lasers is of 3 ms, and this is important since the longer the latency, the greater the chance of decentration. Table 20.1 describes the features of the different generations of excimer lasers.

Patient cooperation and fixation are equally important. An active eye tracking system alone can not ensure good centration.

Table 20.1 Features of the successive generations of excimer lasers

First generation:	Pre-clinical (Touton, VISX, Summit)
Second generation:	Broad beam laser, fixed optical zone
Third generation:	Broad beam laser, variable optical zone, multizone treatment
Fourth generation:	Flying spot laser, built in tracker, hyperopic treatment
Fifth generation:	Customised wavefront (guided, optimised) treatments
Sixth generation:	• Faster ablation rates and tracking systems
	• lower biological interaction
	• More variables under control
	• Pupil size
	• Advanced ablation profiles
	• Ciclotorsion control
	• Online pachymetry

Original table

Another improvement is the automatic monitoring of the pupil size, as illumination is automatically adjusted in such a way that the pupil is exactly the same size at the start of the treatment as it was on the preoperative examination [13].

With all these advances in technology in laser platforms (faster laser, smaller spot size, a high-speed tracker, and pupil monitoring), visual outcomes have been improves, as reported by Alió et al., who analyzed the anterior corneal optical performance of patients who underwent LASIK for the correction of high levels of myopia (>8.50 diopters) using a sixth-generation excimer laser platform with an aspheric optimized ablation profile. There was an induction of RMS HO and RMS SA, but the results were comparable to previous reports for the correction of low and moderate myopia with other generations of excimer lasers [17].

A similar study was reported but for the correction of high hyperopia (>5.00 diopters). They used a 500-Hz excimer laser with an optimized ablation profile and found an induction of RMS spherical aberration, as previously reported by other investigators. For moderate hyperopia and smaller optical zones with older laser platforms, improvement of treatments was shown with sixth-generation lasers [18].

Another study reported an increase in spherical aberration that wasn't too far from the physiological range. No significant change in primary coma, when correcting primary astigmatism over 3.0D using a high-repetition-rate excimer laser platform with cyclotorsion control and an optimized aberration-free profile was observed [19].

20.5 Study of Corneal Aberrations Following Corneal Refractive Surgery

Wavefront analysis helps us determine the optical quality of the eye optical elements.

The Hartmann-Shack aberrometer provides information of the total eye. A ray of light is projected onto the retina, and it is reflected back through the pupil, activating the Hartmann screen that has sensors that transform the light into electrical power, which is analyzed by the sensor and determines the shape of the wavefront.

Global aberrometry is affected by accommodation and pupil size, and it is impossible to measure in very irregular corneas.

Corneal aberrometry is based in the mathematical transformation of topography; using Zernike polynomials, it gives us information about the anterior corneal surface, this can be used in irregular corneas, and it isn't affected accommodation or pupil dilation.

You have to consider that some aberrations are compensated by internal aberrations. Trying to correct them is an error, so global wavefront will help you determine if the aberrations are abnormal. Corneal wavefront alone won't provide this information, so when considering a patient for customized treatment, you should keep in mind that you have to evaluate global and corneal aberrometry.

20.6 Treatment and Prevention of Corneal Aberrations Following Excimer Laser Surgery

Conventional LASIK just corrects low-order aberrations, inducing high-order aberrations. Nowadays with new laser technology, like wavefront customized ablations, we are able to preserve peripheral asphericity to prevent induction of abnormal levels of aberrations and correct non-compensated aberrations to correct HOAs, providing a higher visual quality than conventional LASIK. There are different wavefront ablation profiles: wavefront guided, wavefront optimized, and custom *Q*.

Wavefront optimized:

It attempts to reduce the HOAs generated during the surgery [20].

The loss in ablation energy due to the angle of incidence of pulses in the periphery increases spherical aberration, and the optimized laser profile compensates this by increasing the pulse energy in the periphery. This ablation also applies a precalculated spherical aberration treatment to produce an aspheric ablation profile [21].

It doesn't take into account preoperative HOAs.

They are useful in primary treatments to prevent problems arising from ablation.

Wavefront guided:

This customized treatment is used to correct the preoperative HOAs (especially more than >0.3 μm RMS) and avoid inducing more aberrations. This treatment decreases HOAs and improves visual outcomes in decentration, small optical zones, and after corneal trauma. It also reduces HOAs that increased after an uneventful laser surgery.

In retreatments, global wavefront-guided treatment is used for low refractive errors, and corneal wavefront-guided treatment should be used when you are dealing with a higher refractive error or when the cornea has abnormal levels of aberration (preoperative >0.3 μm). Also, it is more useful when doing enhancements than global aberrometry.

Centration during wavefront-guided treatment is important, since decentration will induce a very different aberration pattern [21].

Custom Q:

This ablation allows the surgeon to select the desired target of *Q* value, so the spherical aberration can be calculated before the surgery knowing the expected change in corneal asphericity [22].

You have to take into account that not every laser platform can do customized treatments. The laser must have *X*, *Y*, and *Z* capability, active and passive cyclotorsion control, and rolling control.

These customized treatments have been used to correct preexisting aberrations and also for retreatments after conventional LASIK surgery. They are safe, predictable and effective [23], and they definitely have many advantages over conventional treatment [24].

They have some limitations especially with highly irregular corneas, which cannot be corrected because their profiles are too complex. Additionally, the excimer laser doesn't have the precision to correct these profiles, or also the corneal biomechanics, which play an uncontrolled role.

20.7 Corneal Aberrations Induction in SMILE

Since the advent of femtosecond laser, new surgical techniques have been developed such as small incision lenticule extraction (SMILE).

The femtosecond laser produces ultrashort pulses of 100 fs, a pulse repetition rate of 500 kHz, and wavelength of 1043 nm, and it delivers energy of less than 200 nJ. Its first use in keratorefractive surgery was for creating the flap; it has many advantages over the microkeratome, since certain complications (free caps, buttonholes) don't happen with FS flap creation, and fewer aberrations are induced.

Then, refractive lenticule extraction (ReLEx) was developed with two new procedures: FLEX (femtosecond lenticule extraction) and SMILE.

In FLEX a stromal lenticule is created, and a flap is used to dissect the lenticule; in SMILE the lenticule is created at a depth of 130 μm (leaving the anterior stroma untouched) with the FS laser and extracted through a 2–4 mm side cut.

SMILE is used for the correction of myopia and myopic astigmatism. Its main advantage over LASIK is that it is a flapless technique that gives the cornea more stability because the Bowman's layer remains intact, reducing the rate of refractive regression; it induces less HOAs, and, of course, there are no flap-related complications. Also there is less incidence of dry eye after SMILE because the superficial cornea preserves its innervation.

One of its limitations is that it doesn't correct hyperopia, and retreatments are more easily performed with femtosecond LASIK.

Although SMILE is a more difficult surgical technique compared to LASIK, it offers better visual outcomes, mainly because of less induction of HOAs (coma and spherical aberration). It also preserves the corneal asphericity better than corneal ablation, providing a better visual outcome [25–28].

Take-Home Pearls

- Optical disturbances after keratorefractive surgery are mainly due to corneal aberrations induced during treatment.
- The main corneal aberrations induced after excimer laser surgery are spherical aberration and coma.
- Blurred vision, poor image contrast, glare, halos, ghost images, starbursts, and poor night vision are optical symptoms secondary to corneal aberrations.
- Hyperopic correction induces a negative spherical aberration.
- Myopic correction induces a positive spherical aberration.
- Technology has advanced in a great manner. Now, with sixth-generation lasers, we can correct higher amounts of refractive errors, inducing the same aberrations that we used to do when correcting low-moderate refractive errors with previous laser platforms.
- Even with the latest eye tracker systems, decentered ablations may occur inducing coma aberration. Cooperation and education of the patient is crucial in order to avoid decentration.
- Aberrations should be corrected considering the anatomical location where they are induced (cornea, lens).
- Customized treatments have improved the visual outcome.
- The use of wavefront-optimized treatments for primary treatments is recommended.
- The use of wavefront-guided treatments for correction of symptomatic corneal irregularities recommended.
- Consider wavefront guided for the correction of decentration, small optical zones, after corneal trauma and for retreatments.
- Consider SMILE technique in myopic patients since it induces less corneal aberrations than femtosecond LASIK.
- Biomechanical response and wound healing are factors that can contribute negatively to the final visual outcome.
- Even the latest technology in lasers induces a significant amount of aberrations.

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Night Vision Disturbances Following Refractive Surgery: Causes, Prevention, and Treatment

21

Sina Bidgoli and Jorge L. Alio

Core Messages

- Night vision disturbances (NVDs) are among the most important complaints after refractive surgery. They vary from patient to patient, limiting normal activities such as night driving.
- No established gold standard clinical test exists to quantify night vision disturbances. Subjective questionnaires are the most commonly used method.
- Night vision disturbances are multifactorial caused by different factors. The existence of significant levels of higher-order aberrations after refractive surgery is one of these key factors.
- The use of optimized aspherical ablations may prevent, or reduce, spherical aberration after keratorefractive surgery.
- Topography-guided refractive surgery is the best method for minimizing higher-order aberrations that occur in symptomatic post-refractive surgery patients.
- Fortunately, most NVDs decrease with time, thus observation is the best therapeutical primary option.

21.1 Introduction

Several photorefractive surgery patients with none or minimal residual spherocylindrical error and good vision are not fully satisfied with their postsurgery quality of vision due to disturbances occurring at night, such as glare or halos. The expression *night vision* points to a large illumination range divided into two zones: scotopic (from 10^{-6} to 10^{-3} cd/m^2) and mesopic (from 10^{-3} to 3 cd/m^2). This wide range of illumination is one of the main sources of visual complaints in patients after uncomplicated LASIK surgery. Thus, in a recent study, the most common subjective visual complaint in patients seeking consultation after refractive surgery was blurred far vision (59%), followed by night vision disturbances (43.5%).

The terminology of night vision is confusing since there is a wide range of symptoms affecting the quality of vision at low illumination levels, which are all described as "night vision disturbances" or "night vision complaints." Night vision disturbances involve glare, halos, starburst, and ghosting.

Glare is the inability of looking at a light source, which appears too bright for the patient, making it difficult to see a sharp image of objects.

Halos are perceived as globes of illuminated fog surrounding light sources. This pattern is typically perceived when looking at street lamps or car lamps at night.

Starburst image refers to a radial scatter of light from a point source, like fine light filaments radiating from the light source.

Ghosting is a double perceived image seen even monocularly.

Starburst and ghosted images are related to refractive surgery, whereas glare and halos are often experienced by myopes wearing glasses and/or contact lenses without having undergone refractive surgery.

Apart from the former disturbances, some post-photorefractive surgery patients may also experience some loss in contrast under dim lighting conditions, especially when passing from photopic to mesopic or scotopic illuminations.

In the following picture, we can see a comparison of the impact in night driving with vision disturbances (glare in b, halos in c, starburst in d, ghost in e, and contrast loss in f), compared to driving without night vision disturbances (in a):

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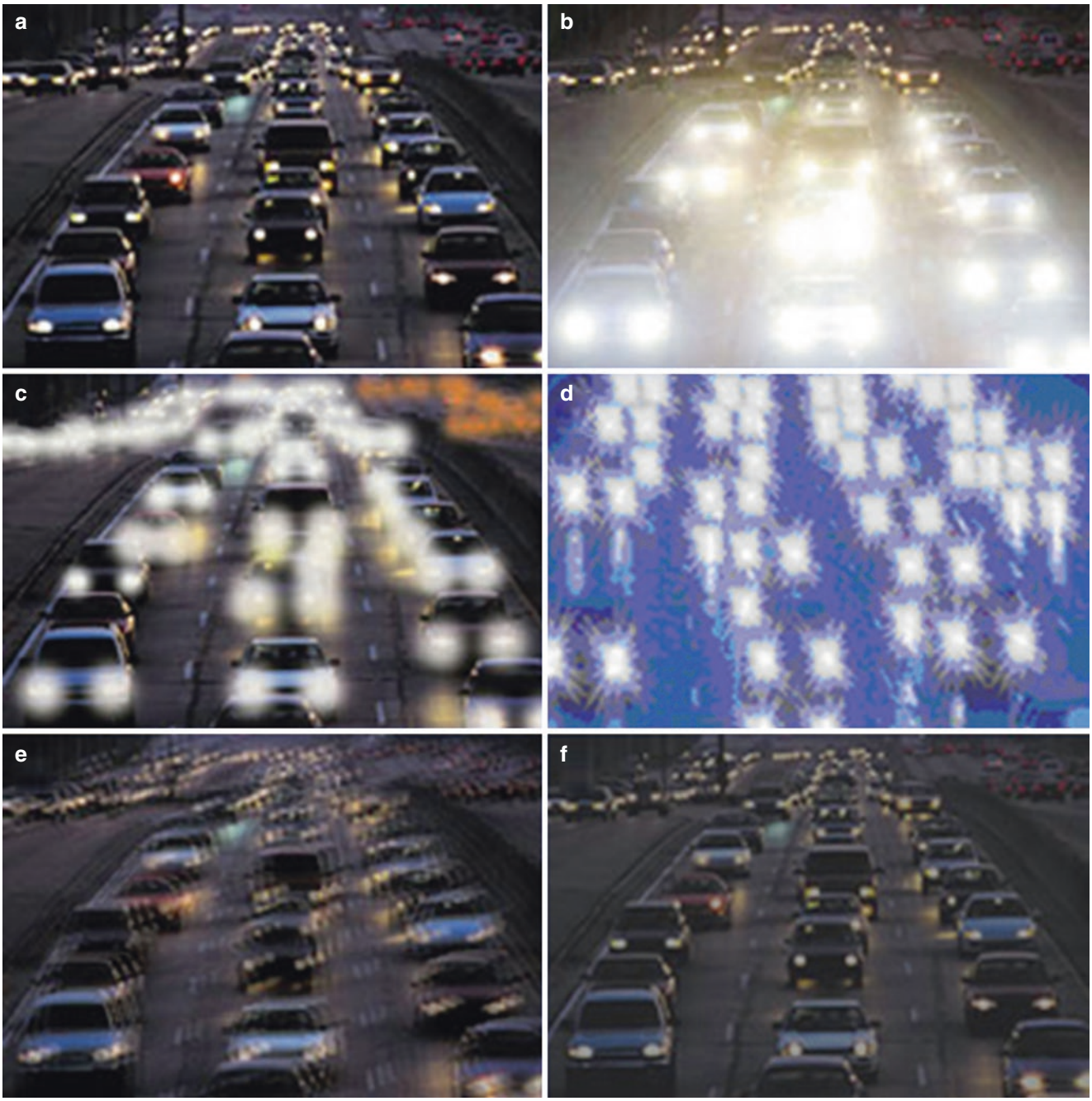

21.2 Incidence and Measurement

According to some studies, 30% of patients operated by PRK report night vision disturbances to be worse than before surgery, being glare and halos the most frequent complaints. After LASIK, almost 12% of patients experience night vision problems, starburst being the major complaint followed by halos. Other studies reported no differences in night vision disturbances 1 year after PRK or LASIK.

Night vision symptoms appear to significantly affect night driving, with almost 30% of patients experiencing worsening in their driving capabilities after photorefractive surgery.

In the immediate postsurgery recovery, the vast majority of LASIK patients experience some night vision disturbances, which may even last a few weeks, depending on several factors, such as residual refractive error, corneal swelling, and reorganization of the corneal architecture, neural adaptation, ablation diameter and profile, and pupil size.

A recent study with LASIK patients evaluated for a 12-month period revealed that overall night vision complaints considerably decreased from 25.6% at 1 month to 4.7% at 12 months postoperatively. This decrease in subjective night vision complaints can be compared to the case of multifocal intraocular lenses. Although halos do not actually disappear, the patients become more tolerant, and the neural adaptation process makes the unwanted images less noticeable.

As for contrast sensitivity and night vision, LASIK induces significant reductions under mesopic conditions only at high spatial frequencies, where the low spatial frequencies remain in the same level as in nonoperated eyes.

No established gold standard clinical test exists to quantify night vision disturbances, even though several procedures have been proposed. This leads to a dependence on the prevalence and extent of night vision complaints on the chosen methodology, which results in a wide difference of prevalence reports in night vision disturbances. The main reason for this lack of normative methodology goes back to the fact that night vision disturbances are subjective experiences that may not be easily described by some patients.

The case of CSF measurement is different since gold standard tests are recognized, as the FACT or the VCTS-1000. There may only be a low correlation between subjective quality of vision and psychophysical tests such as CST or wavefront data.

The most used measurement method for night vision disturbances is the subjective questionnaire, in which patients are asked about their symptoms which are rated on a given scale. Photos can be used in questionnaires to rate disturbances by comparing several snaps with increasing degrees of the patient's visual symptom. Another simple method to perform a subjective quantification consists of asking the patient to look at a light spot after dark adaptation and drawing any perceived disturbances (halos, starburst, etc.) using a grid (the Amsler chart can be used for this purpose). In addition, there are computer-based methods like the Starlights system, which is used to measure the extent of glare and halo. It consists of a black screen with a central light, which acts as a fixation stimulus at an angle of 0.34° and is surrounded by white light-emitting diodes (LEDs) distributed radially along 12 semi-meridians with a maximum amplitude of 30°; each of them subtends at an angle of 0.06° at a distance of 2.5 m between the observer and the screen. The luminance is about 0.17 lux or 0.054 cd m^{-2}. The device provides an index of light disturbance called the "halo disturbance index." This parameter represents the percentage of the total area explored where the peripheral stimuli are not seen due to the light distortion induced by the central source on the patient's retina under scotopic conditions. The total area can be taken as the inner circle or the peripheral circle depending on the severity of the distortion.

21.3 Etiology

The causes for night vision disturbances are undoubtedly multifactorial, including: (1) the wound healing process, (2) light scattering, (3) pupil size, (4) amount of correction, (5) ablation diameter and profile, (6) quality of the ablation, (7) quality of the flap, and (8) the individual patient's cortical adaptation.

The "simple" fact of performing an ablation in a living tissue such as the cornea, which involves a wound healing process, may lead to night vision complaints. Rays of light being refracted by a healthy human cornea with a well-organized equidistant collagen fibril structure interact in a coherent way, resulting in the reduction, even elimination of scattered light by destructive interference. Wound healing after excimer laser treatment leads to corneal haze and edema, disturbing this well-organized pattern of collagen fibrils, forming a three-dimensional array of diffraction gratings that causes light scattering. This scattered light is responsible for loss in contrast sensitivity, starburst, glare, and halo effects and is also observed in patients with cataract or keratopathy, when the loss of transparency of the optical media of the eye leads to light scattering.

The contribution of pupil size to NVD after photorefractive surgery is a matter of debate. Pupil size has two contradictory effects on the optical quality of any optical system: a larger pupil causes some image degradation in an optically aberrated system, but it also results in less diffraction and higher contrast in a diffraction-limited optical system. The effect of pupil dilation on optical aberrations is believed to be much greater after standard laser refractive surgery.

Early studies reported a high incidence of glare, haze, and halo symptoms 1 month after surgery in patients with large pupils. However, recent evidence suggests that large pupil size is not so critical than previously thought, at least with the last generation of excimer lasers. Even though pupil size is a poor predictor for night vision disturbances when considered in isolation, it seems to be a better predictor when coupled with the optical zone treatment, which is considered to be one of the main factors involved in night vision disturbances after LASIK. This is obvious since if the pupil diameter is greater than the ablation zone, two focal points are generated by the cornea, one by the central ablated zone and the second by the peripheral untreated cornea, creating a blurred image superimposed on a focusal retinal image, thus a halo.

Hence, most current refractive surgeons believe that the role of pupil size has been overrated in patients with low myopia who are treated with larger optical zone ablations.

In a recent review, no clinical study correlated a persistent relationship between pupil size and NVDs beyond 3 months when LASIK was performed with a 6.0-mm optical zone or

larger ablation. Other authors have found that scotopic pupil size is not predictive of some night vision disturbances such as halos and glare but may play an important role in others, such as ghost and starburst. On the other hand, there are some patients with very small pupils, even less than 4 mm, who have experienced night vision problems.

When patients with night vision disturbances have their pupil size pharmacologically reduced, they report a dramatic reduction in their symptoms. Although the actual role of pupil size in night vision disturbances after photorefractive surgery is still debated, we cannot entirely deny its importance, which is almost coupled with other factors.

Early PRK was performed using an optical zone of 3–4.5 mm in diameter, but a high incidence of night vision complaints was soon reported, which was reduced by extending the ablation to a 6-mm optical zone. In modern LASIK procedures, multiple regression analyses would predict that an eye with −6 D of myopia has a 4% chance of having night vision disturbances at 12 months postoperatively, using a 6.5-mm optical zone treatment. However, this chance would decrease to 1.8% if a 7.0-mm zone is used. Thus, since correcting high myopia using small optical zones would result in a higher chance of night vision complaints, it is recommended to avoid the reduction of the optical zone size to minimize corneal depth ablation in high myopic patients.

Some authors proposed that a 1-mm difference between the optical zone and the pupil size should be maintained to lower the incidence of night vision disturbances. Consequently, many surgeons recommend avoiding LASIK surgery in patients whose pupil size is greater than the possible treatment optical zone.

The Stiles-Crawford effect may also play a role in the etiology of NVDs. Described in 1933 by Stiles and Crawford, it consists in a phenomenon that a bundle of light rays entering near the center of a pupil is perceived brighter than the same bundle entering closer to the edge.

The amount of attempted correction has also been proposed as an important factor affecting night vision. It is related to the amount of ablated tissue. The higher the preoperative refraction, the higher the amount of ablated tissue and so the higher the distortion in the well-organized collagen fibril structure, resulting in a higher light scattering. But the amount of attempted correction is also related to the size of the optical zone treatment: the higher the myopic correction, the smaller the effective size of the treated area. Studies about the relationship of the amount of refraction to be corrected and the effective size of the optical zone treatment state that, even setting the same laser adjustment for an optical zone of 6.5 mm, an ablation of −10 D results in a 25% less effective treatment size zone than a − 1 D ablation.

The ablation profile is an important factor. A blend zone that smoothes the transition between the treated and the untreated cornea helps to minimize night vision complaints. This may be due to achieving a larger treatment area and a more gradual transition at the edge of ablation. The blend adjustment in photorefractive surgery has shown to reduce spherical aberration of operated eyes, which can also be one of the reasons for a decrease in night vision complaints. Hence, the newer ablation algorithms not only attempt to maximize the optical zone but also achieve a smoother transition zone to blend the principal curvature of the optical zone into the curvature of the peripheral untreated cornea. Recent studies reveal that 74% of patients perceived more glare with an eye operated with a single ablation zone than with an eye operated with a blend transition zone. The only negative feature of using a blend zone is an increase of about 20% in the required ablation depth.

Wavefront technology has an important role in the reduction of night vision complaints. Higher-order aberrations have been observed to increase after both PRK and standard LASIK and may be responsible for night vision problems. Since optical aberrations generally increase with increasing pupil sizes, aberrations can misdirect light into the eye and can result in symptoms such as glare and haze affecting night vision, when the pupil dilates. Improvement in ablation profiles to reduce higher-order aberrations, especially coma and spherical aberration, can reduce these complaints and improve the quality of vision and increase satisfaction in postoperated patients.

The qualities of the flap and stromal bed are also important parameters to be taken into account. Halos, starburst, and ghosting can occur when the corneal flap does not adhere correctly to the eye after it is replaced. In such cases, there can be areas in the cornea in which the imperfect adherence can act as a sort of plane-parallel plate, creating a double image or ghosting.

In summary, refractive surgeons should not rely solely on the pupil size as the predictor of night vision problems since recent literature finds little or no correlation with night vision complaints, at least with modern laser algorithms that optimize optical and transition zone sizes. A large treatment zone and a small pupil can lead to halos when there are significant residual HOA.

Neural plasticity must be considered as a factor for night vision complaint acceptance, and patience must be considered, in some cases, as the best method to treat some night vision disturbances.

21.4 Treatment

Different options are possible to reduce NVDs including conservative methods and surgical re-treatments. Observation is the best option for early symptoms as the patient's own neural processing and adaptation come into play.

Other conservative methods consist of creation of artificial pupils with contact lenses or constricting pupils by overcorrective negative optical prescriptions, leaving the car's dome light on while driving at night and pharmacological miosis.

As it has been pointed before, one of the main causes of night vision disturbances, such as halos or glare, after refractive surgery using the excimer laser, is the induction of higher-order aberration with the surgery itself. These aberrations make the retinal image more distorted with a clear lack of focus. From all the aberrometric components, the primary spherical aberration and coma are annoying errors that occur more frequently in the eye after refractive surgery. The coma aberration is related to decentered treatments, where an asymmetry is present in the cornea. This is one complication that can be seen in some cases after refractive surgery, and it could be due to a lack of fixation from the patient, a wrong selection of the point of centration, or a poor control of the fixation of the patient by the surgeon. This produces an enlargement of the image light distribution along an axis, generating a comet-like image of a point light object.

In uncomplicated eyes after refractive surgery, the most frequent aberration is the spherical aberration. The primary spherical aberration is a higher-order aberration corresponding to the fourth order of the Zernike decomposition. Basically, this error +10is due to the difference of refractive power between the central and the peripheral area of the optical ocular system (between the ablated and the non-ablated area), where all the light rays passing through the system do not focus at the same point. Several light rays will be focused in front of the retinal plane, whereas others will be focused behind it. This phenomenon generates a concentric circle of blurred light around the focused point or halo. The halo generated is more significant with higher aperture of the system (the pupil diameter), because the aberrated peripheral area has a greater impact on the retinal image. Obviously, this optical situation induces significant disturbances and discomfort in the patient, especially under scotopic conditions.

The ablation shape performed by the excimer laser in order to compensate a refractive error, following the Munnerlyn's equation or algorithms derived from it, unavoidably induces positive spherical aberration. This effect is produced by the flattening of the corneal curvature without taking into account the preoperative aspherical shape of the cornea. There is a significant reduction of the central refractive power of the optical ocular system but an increment in the periphery (Fig. 21.1a and b). This effect is magnified when the degree of myopia to correct is larger, because the refractive difference between center and periphery is more acute, as commented before.

On the other hand, the ablation for the compensation of hyperopia is peripheral. The laser removes tissue in a concentric peripheral area in order to achieve an increase of the central corneal curvature. Then, in an opposite situation, with this kind of ablation, an increase of the negative spherical aberration is produced. Therefore, there will be a significant difference in refractive power between the central and the peripheral area of the cornea. Specifically, the central area of the ocular optical system has greater refractive power than the peripheral (Fig. 21.2a and b). Obviously, this also induces the presence of a disturbing halo which is magnified under scotopic conditions (larger pupil size).

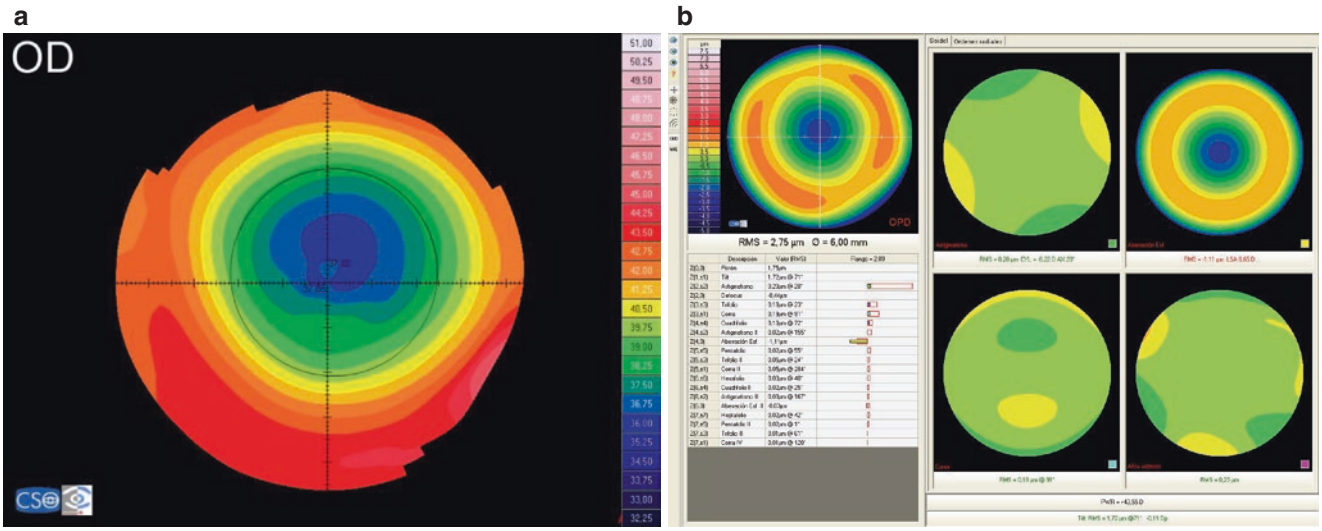

Fig. 21.1 Corneal topography and aberrometry after a myopic LASIK, performed with a classic ablation profile. (**a**) Corneal topography. The difference in curvature can be clearly seen between the central and the peripheral area. (**b**) Corneal aberrometry. *Top left*, total wavefront map. To the *right* of the image the decomposition, in components, of the total wavefront is shown. From *left* to *right* and from *top* to *down*, the astigmatism map, the spherical aberration map, the coma map, and the residual higher-order error map can be seen. All maps are calculated for a pupil of 6.0 mm. The spherical aberration map shows a greater deformation of the wavefront in a peripheral concentric area

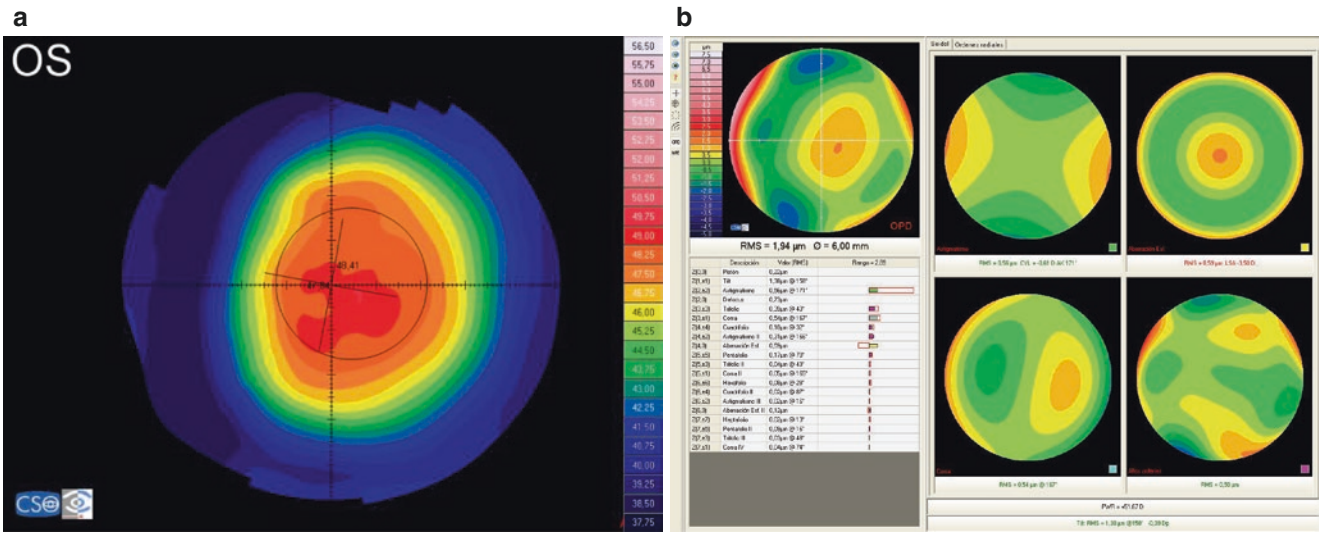

Fig. 21.2 Corneal topography and aberrometry after a hyperopic LASIK, performed with a classic ablation profile. (**a**) Corneal topography. The difference in curvature can be clearly seen between the central and the peripheral area. (**b**) Corneal aberrometry. *Top left*, total wavefront map. To the *right* of the image the decomposition, in components, of the total wavefront is shown. From *left* to *right* and from *top* to *down*, the astigmatism map, the spherical aberration map, the coma map, and the residual higher-order error map can be seen. All maps are calculated for a pupil of 6.0 mm. The spherical aberration map shows a greater deformation of the wavefront in a central area

We must take into account other factors, more difficult to analyze, that contribute to the induction of spherical aberration. Some of these factors could be the loss of efficiency when the laser ray comes into contact with the peripheral cornea, the epithelial healing, or the biomechanical response of the corneal structure.

21.4.1 Optimized Ablation Profiles

The optimized ablation profiles have become a standard way to proceed when refractive surgery with excimer laser is performed. It is a method for minimizing the induction of spherical aberration inherent in ablation profiles based on classic algorithms (such as the Munnerlyn equation).

It is well known that the anterior corneal surface is not spherical. There is a progressive flattening of the cornea toward the periphery. It is an aspherical surface. Therefore, it has no sense to use an ablation profile based on the generation of a spherical surface. A profile like this will theoretically create a spherical cornea in the optical zone but with a significant abrupt transition step between ablated and non-ablated areas (oblate profile). New designs of the ablation have been developed in order to avoid this effect. These designs are aspherical, and they try to reproduce the physiologic prolateness of the cornea, providing a gradual and progressive transition between ablated and non-ablated zones.

Nowadays, there are several commercially available refractive surgery platforms with specific software for generating aspherical ablation profiles (Fig. 21.3a and b). Different studies have proved the efficacy and safety of these kinds of treatments. Examples of these commercially available systems are the following: CATz from Nidek, CRS-Master from Zeiss, ORK-CAM from Schwind, Custom-Q from Wavelight, etc.

21.4.2 Customized Ablation Profiles

The use of an optimized aspherical profile is a first level of customization, because we are taking into account the prolateness of the cornea. However, when we talk about customized treatments, usually we are referring to tailored treatments with a high level of customization. In these cases, the distribution of the excimer laser energy is asymmetric in order to ablate more tissue from specific corneal areas. The final objective is to decrease the optical aberrations to a physiological level. This way, the patient will reach a high quality of vision increasing the level of satisfaction. Several studies have showed the applicability and the benefits of using these customized systems.

There are two methods for customizing the ablation: ocular and corneal customization. For ocular customization, it is necessary to measure the aberrations of the entire ocular optical system, taking into account the cornea and the lens. With this data and the corneal topography, an ablation for minimizing the second- and the higher-order aberrations could be designed.

This approach is less effective in patients with large amounts of corneal aberrations due to previous refractive surgery, whether uncomplicated classic algorithms or following

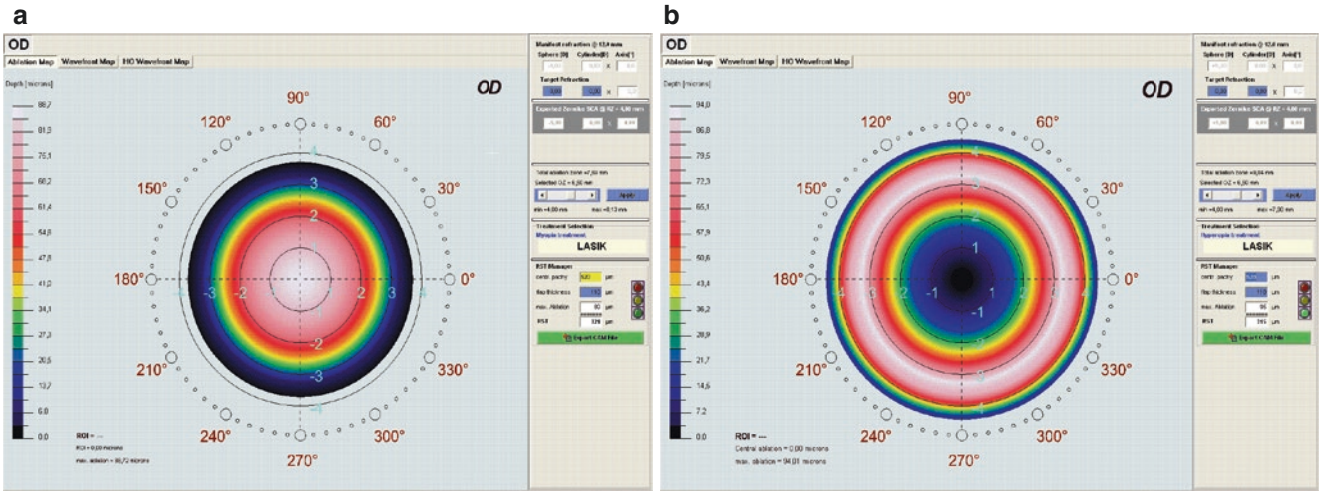

Fig. 21.3 Aspherical profile designed by means of the ORK-CAM software from Schwind. (**a**) Myopic aspherical ablation profile. (**b**) Hyperopic aspherical ablation profile

surgical complications during LASIK, corneal scars or wounds. One explanation for this fact is the inability of some wavefront sensors or aberrometers to accurately measure high levels of aberrations. This is especially true for wavefront sensors that subdivide the wavefront and take the measurements simultaneously. Crowding or superimposing of the light spots associated with different parts of the wavefront is produced when we are analyzing a highly aberrated eye. In such cases, the reliability of the measurements is reduced. In addition, with some kind of sensors, it is assumed that the slope of the wavefront in each portion analyzed is locally flat. This approach induces significant errors in the final calculated results. Then, it is a better option in highly aberrated corneas to retreat using ablation based on corneal customization or topography-guided. In these cases, we must take into account that the anterior corneal surface is the aberrated element, normally by a previous surgical procedure, and additionally this surface supposes the greatest refractive contribution to the total refractive power. There are different topography systems, with specific software, that calculate and show the aberrations associated to the anterior corneal surface. The elevation data from topography is transformed into aberration components by means of the decomposition of Zernike polynomials. Nowadays, several topography systems have the option of providing the corneal aberrometry as the CSO system (CSO) or Keratron (Optikon).

One of the commercially available software for the calculation of customized ablations is the ORK-CAM software from Schwind (Schwind eye-tech-solutions, Kleinostheim, Germany). This tool allows us to design and program different kinds of customized ablations by previously loading the topography data from the CSO. The treatment designed is loaded in the Esiris excimer laser machine (Schwind) in order to perform the treatment. This laser is a flying-spot system with a para-Gaussian spot of 0.8 mm of diameter, and it is combined with a very fast eye tracker system with a frequency of 330 Hz. For these customized systems, the use of small spots for ablating small selective corneal areas is crucial, as well as an ultrafast "eye tracker" system in order to avoid the improper orientation of the laser beam and the inadequate ablation of some zones.

The procedure for calculating ORK-CAM ablations is very simple: the corneal topography is acquired and exported, and then the file created is imported to the ORK-CAM software. Some clinical data must be introduced as the age of the patient, the subjective spherocylindrical refraction, the central corneal pachymetry, and the flap pachymetry. An ablation profile is generated with all this data, and this can be modified by the specialist to reach the best adequate profile for a specific case. The optical zone could be modified according to the pachymetry. Additionally, specific terms from the Zernike decomposition could be chosen for the treatment (Fig. 21.4). Modifying the optical zone and the number of Zernike terms treated, the ablation profile could be customized in order to get the more appropriate profile according to the corneal shape and the refractive error.

In the following section, we show the results obtained by us with this surgical option in patients with high levels of positive spherical aberration.

A total of 40 eyes (27 patients) previously operated with a primary spherical aberration coefficient (Z_4^0) equal or higher than 0.5 underwent LASIK surgery using the excimer laser Esiris and a topographic-guided customized ablation designed by means of the ORK-CAM software. All of them complained of night vision disturbances or lack of visual quality with and without optical correction of the residual error.

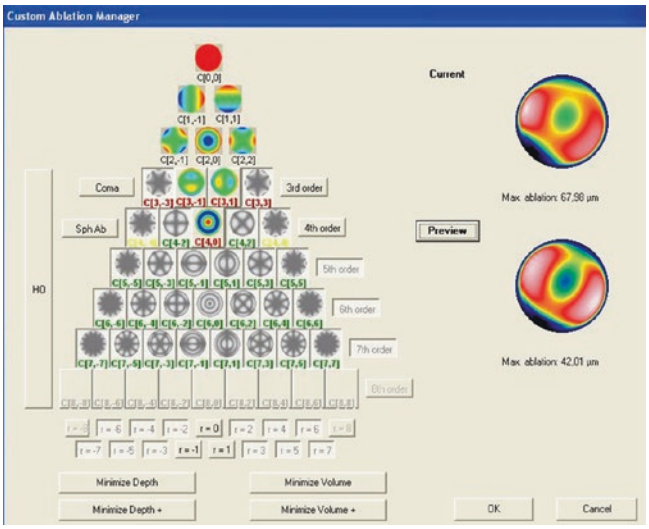

Fig. 21.4 Selection in the ORK-CAM software (Schwind) of the Zernike components for treatment during the ablation design process. We have observed that the correction of the combination primary coma and spherical aberration is highly effective and very satisfying for the patient in almost 100% of cases

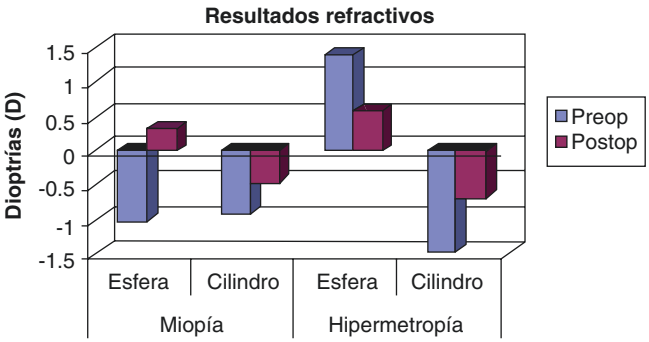

Fig. 21.5 Summary of the refractive outcomes obtained in patients with high levels of primary spherical aberrations and treated with a topographic-guided ablation designed with the ORK-CAM system (Schwind). We have divided the results in myopic and hyperopic patients

Figure 21.5 shows a summary of the refractive results obtained with this procedure. No complications occurred during and after the surgery. The efficacy and safety levels achieved were excellent, 0.87 ± 0.23 and 1.00 ± 0.25, respectively.

Statistically significant reduction of the primary spherical aberration 3 months after surgery ($p < 0.001$) (Fig. 21.6) is observed. This reduction was significantly greater in the hyperopic patients. This is logical because the ablation itself for correcting the hyperopia induces a compensation of the positive spherical aberration, because the ablation is ring-shaped and concentric. However, the myopic ablation itself produces positive spherical aberration, making the efficacy of the ablation not so effective.

Concerning the negative spherical aberration, we have few cases (12 eyes) with high levels of this defect, and all of them are myopes. In these cases, after the treatment, there is a very slight reduction of the primary spherical aberration, and it is not statistically significant. No clear improvement of the visual quality was observed, and it seems that improvements in the algorithms for these cases are necessary. Anyway, we must take into account that the number of eyes treated is small and a larger sample is necessary for obtaining firm conclusions.

Several studies have compared the quality of vision after wavefront-guided and wavefront-optimized treatments in patients undergoing primary photorefractive surgery, and it seems that there is no difference between the two profiles. Further investigation will define guidelines for each profile. At this stage, primary customized treatments may be suggested for patients with increased level of preoperative HOA or those likely to get a significative increase of their initial level. However, they are well indicated for re-treatments particularly in decentered ablations and seem to be effective in improving subjective night vision symptoms.

21.4.3 Example of Topographic-Guided Customization

A patient underwent LASIK surgery 1 year ago for correcting moderate myopia in both eyes. He complains of lack of clarity in his vision and difficulties for night driving. He has worn glasses for driving, but he felt awkward.

These are the results of the ophthalmologic examination:

Preoperative exam:

- UCVA: OD, 0.7; OS, 0.9
- Subjective refraction and BSCVA:
  OD: +1.00 −1.00 × 45°; BSCVA 1.0
  OS: +1.25 −0.50 × 150°; BSCVA 1.0
- Corneal topography: see Fig. 21.7a and b
  Corneal asphericity (Q) over the central 4.5 mm: OD, 1.70; OS, 1.24
- Corneal aberrations (Fig. 21.8a and b): significant level of primary spherical aberration
  Primary spherical aberration coefficient (Z_4^0): OD, 0.82 µm; OS, 0.68 µm
  Primary coma RMS: OD, 0.52 µm; OS, 0.34 µm
  Residual higher-order RMS: OD, 0.37 µm; OS, 0.32 µm
  Strehl ratio: OD, 0.11; OS, 0.14
- Scotopic pupil (Procyon): OD, 6.75 mm; OS, 6.82 mm
- Biomicroscopy: LASIK both eyes, anterior segment OK

Surgery:

- Treatment plan: see Fig. 21.9a and b. The correction of the primary coma and spherical aberration is programmed in the right eye, whereas in the left eye the correction of the primary spherical aberration is only

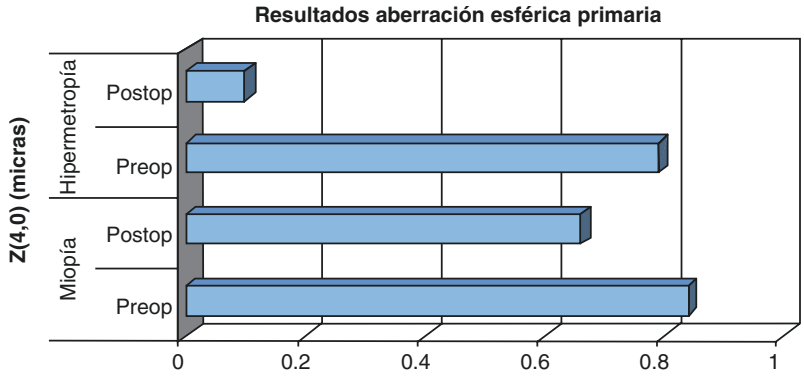

Fig. 21.6 Changes in the primary spherical aberration coefficient after refractive surgery with corneal customization. We have divided the results in myopic and hyperopic patients

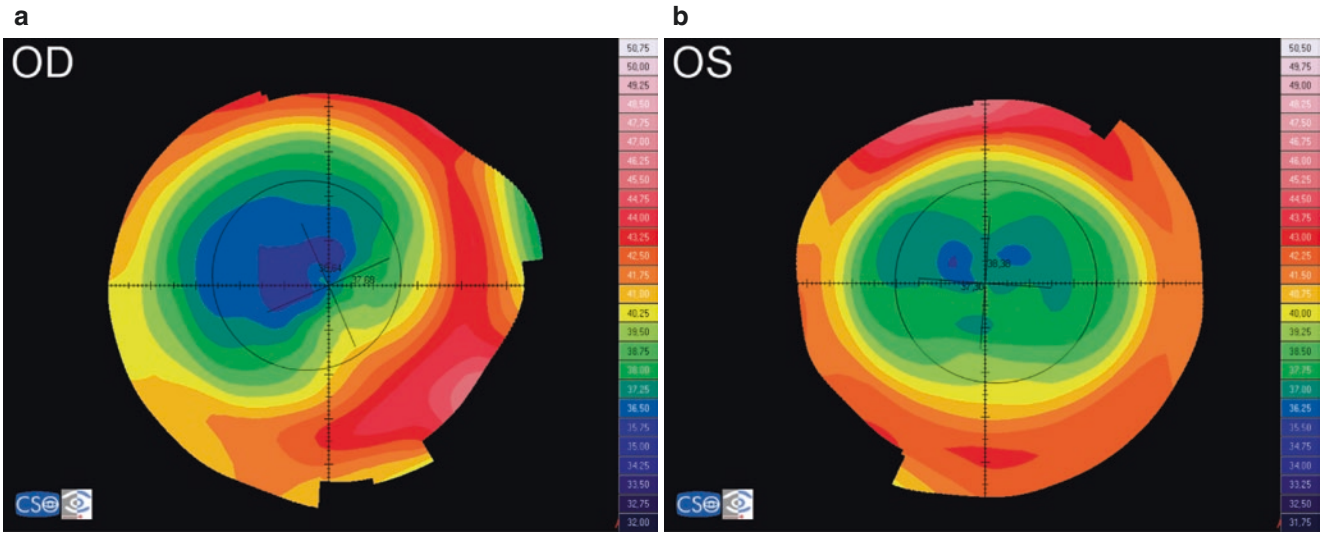

Fig. 21.7 Clinical case: preoperative corneal topography obtained by the CSO system. (**a**) Right eye. (**b**) Left eye

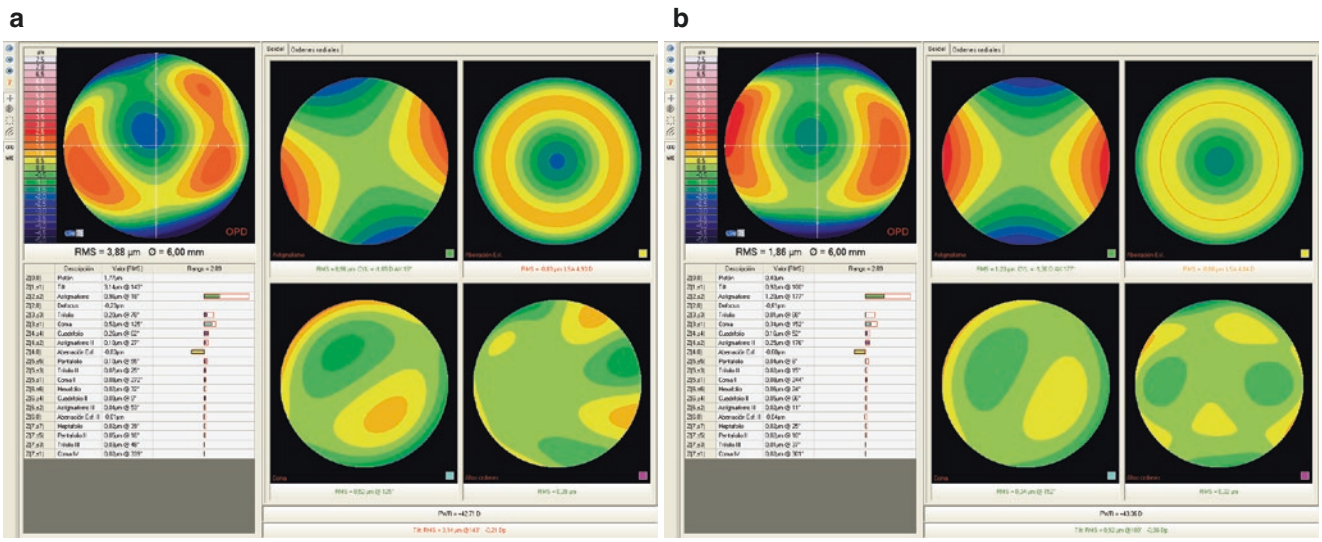

Fig. 21.8 Clinical case: preoperative corneal aberrometry obtained by the CSO system. (**a**) Right eye; significant level of primary coma and spherical aberration. (**b**) Left eye; significant level of primary spherical aberration, although smaller than corresponding to OD

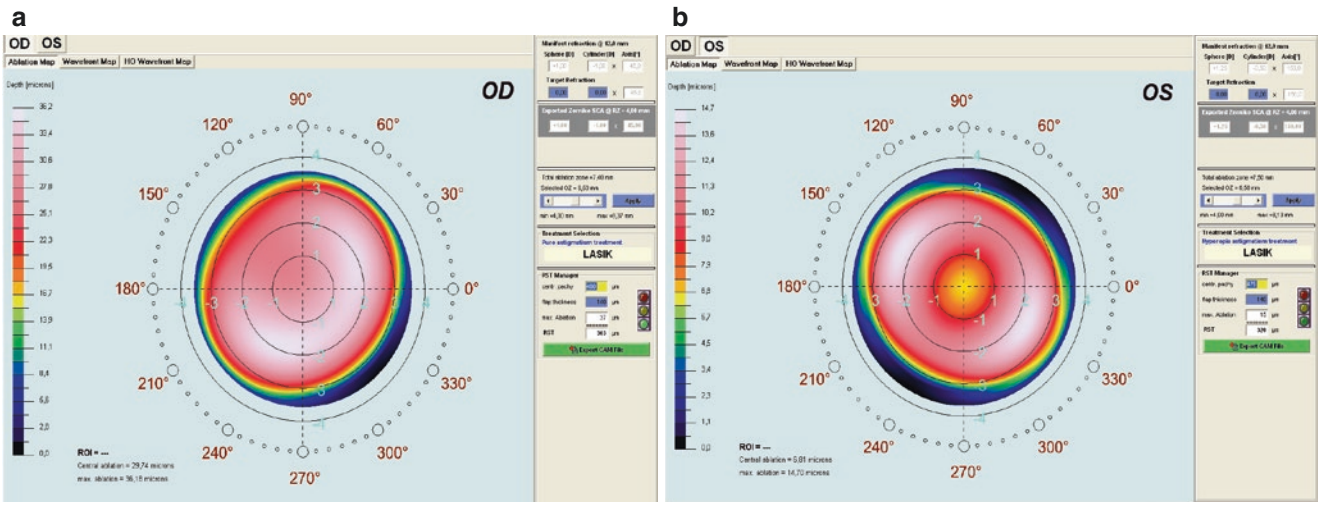

Fig. 21.9 Clinical case: ablation profiles obtained by the ORK-CAM software. (**a**) Right eye; correction of the primary coma and spherical aberration. (**b**) Left eye; correction of the primary spherical aberration; it can be seen that the ablation is circular and peripheral in order to reduce the excessive refractive power of that area

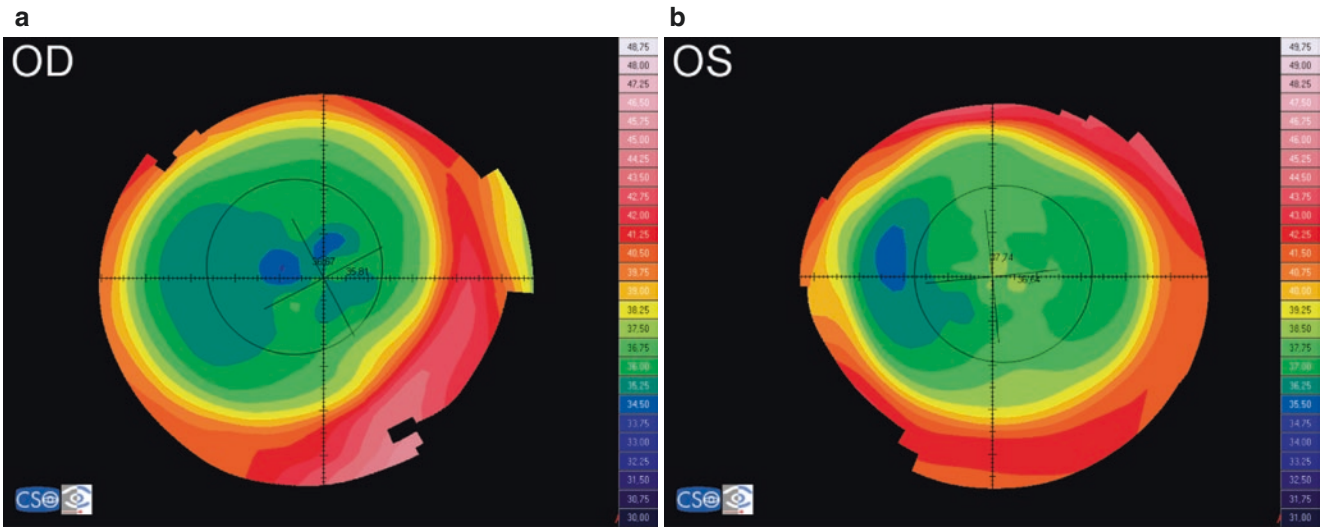

Fig. 21.10 Clinical case: postoperative corneal topography obtained by the CSO system. The widening of the optical zone can be seen with the non-ablated area out from the pupilar area. (**a**) Right eye. (**b**) Left eye

programmed. In addition, in both eyes the spherocylindrical error was planned for correction.
- The lift of the flap and the laser re-treatment is performed with the following parameters:
  Optical zone: OD, 7.0 mm; OS, 7.0 mm
  Total ablation diameter: OD, 7.92 mm; OS, 7.98 mm

Three months postoperatively:

- UCVA: OD, 0.95; OS, 1.0
- Subjective refraction and BSCVA:
  OD: +0.50 −0.50 × 110°; BSCVA 0.95
  OS: +0.50 sph; BSCVA 1.0
- Corneal topography: see Fig. 21.10a and b
  Corneal asphericity (Q) over the central 4.5 mm: OD, 0.94; OS, −0.20
- Corneal aberrations (Fig. 21.11a) and b: no significant level of higher-order aberrations.
  Primary spherical aberration coefficient (Z_4^0): OD, 0.37 μm; OS, 0.17 μm
  Primary coma RMS: OD, 0.10 μm; OS, 0.33 μm
  Primary residual higher-order RMS: OD, 0.33 μm; OS, 0.32 μm
  Strehl ratio: OD, 0.13; OS, 0.15
- Biomicroscopy: LASIK both eyes without problems, anterior segment OK

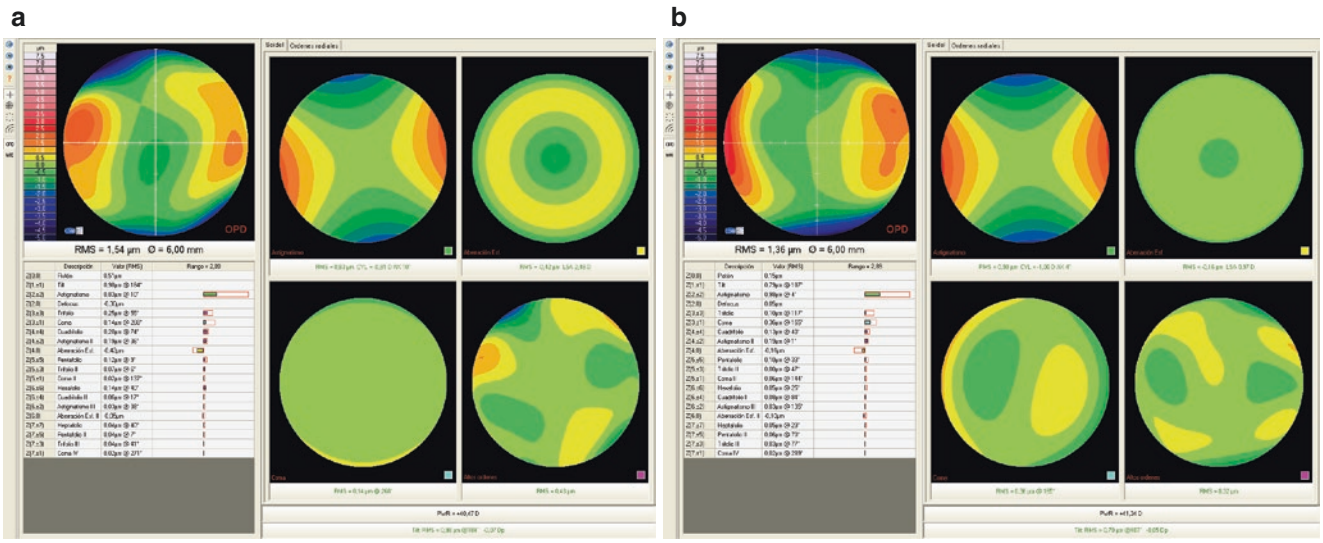

Fig. 21.11 Clinical case: postoperative corneal aberrometry obtained by the CSO system. Physiologic levels of higher-order aberrations. (**a**) Right eye. (**b**) Left eye

An improvement in UCVA and quality of vision was observed. Reducing the positive spherical aberration increased the corneal asphericity and provided the cornea with a more prolate shape. The patient is satisfied, reporting a significant subjective improvement.

21.4.4 Pharmacological Management of NVDs

Pupil size reduction is possible by blocking the sympathetic system (with adrenergic agonists) or by stimulating the parasympathetic system (with miotics).

Brimonidine tartrate ophthalmic solution (Alphagan), an α2 adrenergic agonist, has shown to be efficient in reducing NVDs. The problem with its chronic use is ocular allergy. Among miotics, aceclidine has been evaluated because of its minor side effects and seemed to be effective and safe at concentrations of 0.016% or 0.032%.

Take-Home Pearls

- One of the most common subjective complaints following refractive surgery with the excimer laser is night vision disturbances.
- These night vision disturbances include glare, halos, starburst, and ghosting, and they could dramatically affect common tasks such as night driving.
- The generation of these night vision disturbances is multifactorial, including the wound healing process, pupil size, amount of correction, and existence of significant levels of higher-order aberrations or decentration.
- The use of optimized aspherical ablation profiles is a way of preventing the induction of significant amounts of spherical aberration.
- Cases with very high levels of spherical aberrations could be corrected by means of a topography-guided ablation, which attempts to distribute the laser energy in order to ablate specific tissue areas.
- Fortunately, most NVDs decrease with time; thus, observation is the best primary option.

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Decentration

22

Jonathan H. Talamo and Dimitri T. Azar

Core Messages

- Prevention is easier (and more effective) than treatment.
- The accurate centration technique is important: Intraoperative vigilance is needed even with eye tracking.
- Thorough understanding of laser technology and calibration is essential to prevent errors.
- Be certain to exclude abnormal wound healing as a cause.
- Do not rush re-treatment.

22.1 Description of the Problem

22.1.1 Definition of Centration

Decentration of ablation effect after laser vision correction or other refractive surgical procedures can occur when the effect of surgery results in an unintentional asymmetric alteration of the eye's optical system, which results in increased higher-order aberrations and causes what was often described in the past as irregular astigmatism. In order to describe decentration after keratorefractive or lenticular refractive surgery, it is important to first define a center of the eye's optical system. As described in the classic paper by Uozato in Guyton in 1987 [1], corneal refractive surgical procedures can be centered by using either the corneal light reflex or the pupil center, which represents the line of sight (the line connecting the fixation point with the pupil center and corresponds to the chief ray of the bundle of light rays passing through the pupil and reaching fovea) [2]. While there remains some controversy as to which approach is correct (some surgeons advocate for centration based on patient fixation rather than pupil center for patients with large angle kappa measurements), the consensus at this time is that all procedures (corneal or lenticular) should be performed with the goal of centration over physiologic pupil. Especially, in cases of eyes showing large temporal pupil decentration, pupil-centered ablation seemed to induce less coma, resulting in a reduced loss of BCVA in comparison to the vertex-centered patients [3]. Additionally, it is now widely recognized that for astigmatic or wavefront-derived custom laser treatments, the eye should not only be centered with respect to the *x*–*y*-axis but also with respect to the cyclotorsional position of the globe in the upright position, as there may be shifts in this parameter when moving the patient from the upright position used for clinical testing to the supine orientation needed during laser treatment [4]. The major exception to this approach is, of course, the treatment of decentered prior treatments, which is the subject of this chapter. Due to space considerations, we cover only decentration of laser vision correction procedures.

22.1.2 Centering Technique

For the purpose of this chapter, we discuss technique primarily with respect to laser vision correction procedures, but such an approach can be viewed as valuable for any corneal or lenticular procedure. As the best treatment for decentered laser treatment remains prevention, we first discuss appropriate centering technique.

To most accurately center a corneal laser treatment over the pupil, the patient should be fixating on a target with physiologic pupil with the head and eye in an orthogonal position with respect to the laser optics and fixating on a target that is coaxial with the examiner's sighting eye through the surgeon microscope [5]. To ensure appropriate orientation to the globe from a cyclorotational perspective during treatment, the limbus should be marked at the slit lamp with the patient

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fixating a target coaxial with the microscope's optics. Generally, marks at 3 and 9 or 6 and 12 o'clock are most helpful. With the advent of wavefront-sensing devices with iris or limbal registration techniques, it may not be necessary in many instances to manually mark the globe, as these devices will allow transmission of information to the excimer laser's eye-tracking system that enable automatic cyclorotational centering, but it is still advisable to mark in case these functions fail to perform during surgery.

Another important consideration for centration is the position of the pupil centroid. As lighting conditions vary, the pupil's centroid shifts along with changes in diameter [6]. If wavefront capture occurs under dimly lit conditions and centration during surgery under bright illumination, then the pupil centroid may shift, usually nasally. This phenomenon may lead to a decentration of the laser treatment with respect to the pupil centroid in mesopic lighting conditions, under which symptoms such as glare, halo, and starburst are most pronounced following surgery. Although no data yet exist to prove clinical significance of such an approach, it may be important to control ambient lighting during surgery to mimic mesopic conditions whenever possible if the eye-tracking system being used does not correct for pupil centroid shifts.

22.2 Causes of Decentration or Decentration-Like Effect (Pseudo-Decentration)

It is important to distinguish a truly decentered laser ablation from other etiologies (pseudo-decentration), as the appropriate treatment may vary. The various entities that may lead to decentration or pseudo-decentration are discussed below.

22.2.1 Misalignment of Reference Point: Static or Dynamic

As discussed above, improper alignment of the pupil/line of sight, cyclorotational axis of the globe, and pupil centroid may all lead to decentration. While it is crucial for the surgeon to be certain such alignment is present at the initiation of treatment, it is also crucial to maintain alignment during photoablation. It is common for the globe or head to drift off center or cyclorotate during surgery. Tense or sedated patients are particularly apt to allow the chin to drift down toward the chest during surgery, with a corresponding Bell's response to maintain fixation on the target light inside the laser microscope. The presence of an eye-tracking function will not protect against a decentration effect: The tracking function will continue to work in a two-dimensional *x*–*y* plane, while parallax is introduced between the laser optics and the corneal dome, resulting in an asymmetric distribution of laser energy with respect to the pupil center. No excimer laser system exists to correct for this phenomenon, so it is critical to monitor patient position during surgery and verbally encourage the best compliance possible. If the patient is unable to control eye movement during photoablation, then the globe can be manually fixated with a toothed fixation ring or microkeratome suction ring with a low vacuum setting to regain control of the situation. This is not ideal but better than allowing the ablation to proceed. If the surgeon cannot gain control over the tendency toward excessive eye or head movement, then it is better to stop the procedure or try again later.

22.2.2 Uneven Uptake of Laser Energy

Uneven corneal hydration may lead to a decentration of ablation effect due to uneven uptake of excimer laser despite appropriate ocular alignment during surgery. The corneal topographic appearance in this setting is often that of an asymmetric peninsula-shaped area of reduced ablation effect (Fig. 22.1). Central islands can also occur, but these are most distinctive and hard to mistake for a decentration. To avoid such problems, it is critical to minimize the amount of fluid on the surgical field. For surface ablation procedures, this is easily accomplished by placing a cellulose sponge drain or similar material on the globe if excess moisture is present. If alcohol is used to remove the epithelium, then it is important to irrigate the cornea to remove excess alcohol prior to removing the epithelium and to try the surface to be ablated in a uniform fashion. During epi-LASIK or LASIK procedures with blade microkeratomes, large amounts of balanced salt solution are sometimes used for irrigation as the instrument is

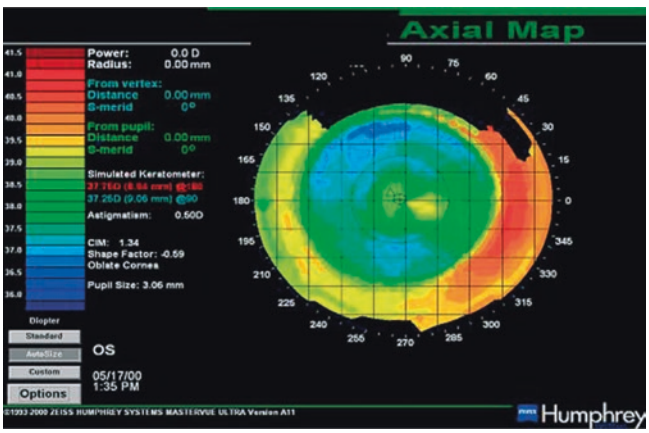


Fig. 22.1 "Peninsula" of decreased effect following myopic photorefractive keratectomy. This axial topographic map shows an ablation that is well centered over the physiologic pupil but with differential flattening effect

passed across the cornea, so it is critical in these settings to dry the stromal bed to be treated quickly and uniformly. When performing all-laser LASIK with a device such as the IntraLase femtosecond laser, it is not necessary to use a large amount of moisture to mobilize the corneal flap, and fluid should be used sparingly during flap dissection/lifting.

Another cause of uneven laser energy uptake is the presence of localized corneal scarring or, in the case of surface ablation, residual corneal epithelium within the ablation zone. Corneal scars ablate at a slower rate than normal stroma and can result in a pseudo-decentration effect similar to that seen with uneven hydration.

22.2.3 Uneven Emission of Laser Energy

Much like the situation described above for corneal dehydration, pseudo-decentration can occur if the distribution of laser energy is uneven. While flying spot lasers using a small beam profile (1 mm) to deliver energy via a pattern of many overlapping pulses tend to have a fairly homogeneous energy profile, broad-beam excimer lasers can develop an irregular beam profile usually detectable by calibration devices. This most commonly occurs when solutions used during surgery are splashed up into the laser microscope and coat the laser optics. For such systems, the laser optics should be carefully inspected between cases, and, where possible, frequent calibration using a test ablation in plastic should be made.

22.2.4 Asymmetric or Abnormal Wound Healing

If evidence suggestive of decentration is present, then the presence of abnormal wound healing should be excluded. Epithelial ingrowth often creates the appearance of localized corneal flattening, which may seem to shift the position of ablation effect (Fig. 22.2). Stromal tissue melting of the flap or deeper tissue may result in the appearance of localized flattening or steepening depending upon its location. Careful clinical examination should be performed to ensure that a laser treatment that appears decentered by topography is in fact not due to problems related to corneal wound healing, as the correct treatment will differ.

Rarely, corneal ectasia may create the appearance of decentration. To rule out this unlikely but serious cause of pseudo-decentration, analysis of corneal shape with Orbscan (Bausch and Lomb, Rochester, NY) or Pentacam (Oculus, Heidelberg, Germany) technology is essential prior to proceeding with additional laser treatment. Optical coherence tomography (OCT) may also become useful, but the ability of this technology to detect more than qualitative evidence of ectasia is limited at present.

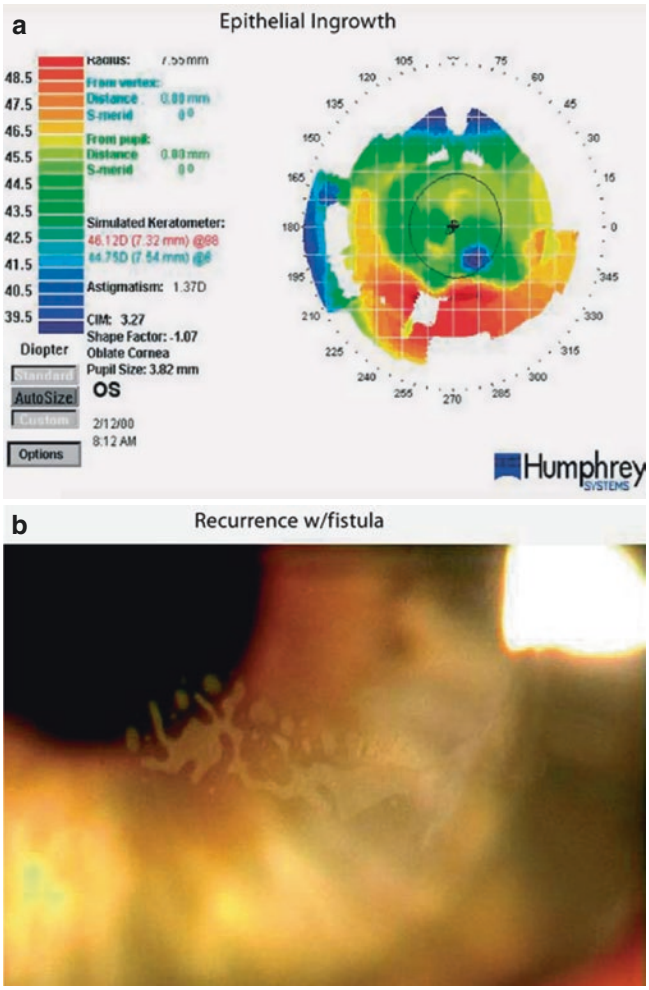


Fig. 22.2 Epithelial ingrowth-induced localized flattening following LASIK. (**a**) Asymmetric flattening after LASIK, but the ablation is well centered over the physiologic pupil. (**b**) This area of flattening corresponds to epithelial ingrowth visible at the slit lamp

22.3 Clinical Manifestations of Decentration

22.3.1 Symptoms

The most common symptoms of decentered laser treatments include:

- Blurred vision
- Ghosting
- Poor vision in low light
- Glare or halo, often asymmetric around point sources of light

Because symptoms associated with decentered laser ablations increase as the pupil dilates, patient complaints often

relate to lighting conditions. During the early weeks or months after surgery, such symptoms may be explained away as normal, but one should be particularly suspicious of complaints that lateralize to one eye or the other.

22.3.2 Signs

The most common clinical signs of decentration include:

- Decreased uncorrected and BCVA
- Visual acuity results that vary with ambient lighting
- Difficult refraction or wavefront capture
- Scissors reflex during retinoscopy suggestive of irregular astigmatism
- Significantly increased higher-order aberrations of the ocular wavefront versus before surgery, especially horizontal vertical coma [7] (Figs. 22.2 and 22.4)
- Abnormal corneal topography

When analyzing corneal topography, it is important to distinguish between true ablation decentration (Figs. 22.3 and 22.4) and pseudo-decentration (Fig. 22.2), as the treatments may vary if the problem is due to abnormal wound healing. The most powerful tool for doing this is the difference map function on topography devices, which allows analysis of surgically induced changes in corneal curvature. Without a difference map, it is very difficult to quantify the degree of decentration. Axial maps are useful, but some investigators feel tangential corneal topography is the most sensitive means for evaluating such changes [8]. Four kinds of scenarios can arise during laser treatment. Two terms—displacement (shift) and drift—are used to describe these scenarios where displacement (shift) refers to the initial lack of centration resulting from the involuntary eye movement during the procedure or due to lack of rectification, ultimately resulting in a decentered treatment. Drift refers to the correction of decentration while ablation continues or to the recognition of the decentration by the surgeon and an attempt to correct the initial decentration during treatment. The first scenario is low displacement (shift) (≤ 0.4 mm) and low drift (≤ 1.0 mm) (group I), where the vision outcome is excellent. Azar et al. [8] reported a mean logMAR best-corrected visual acuity (BCVA) of 0.91 for such patients, which was statistically significantly better than the patients with high displacement and high drift ($r = 0.64$, $P = 0.09$). Before, they had measured drift index that showed a statistically significant, positive correlation with BCVA ($r = 0.58$, $P < 0.001$) (Fig. 22.5). The high displacement (>0.4 mm) and high drift group (>1.0 mm) (group IV) had the worst vision. The remaining two scenarios are that of high displacement and low drift (group II) where the vision outcome is also excellent and low displacement and high drift (group III) where the vision outcome is intermediate. Figure 22.6 shows the tangential topographic maps of all of these four scenarios. Figure 22.7 shows the tangential topographic maps comparing the effects of laser drifts on BCVA in two patients who show similar amounts of initial treatment decentration (displacement).

Irregular astigmatism and reduction of BCVA following PRK result from intraoperative drift due to a less homogeneous distribution of surface powers within the treatment zone. Reliable and reproducible patient fixation is important to allow meaningful analysis of tomographic changes, as small shifts in fixation can create the appearance of decentration where none exists.

After conventional photoablation treatments using spherocylindrical treatments, topographic decentrations of 1 mm or greater are widely considered to be clinically significant [9], although differences in BCVA have been demonstrated if topographic decentration exceeds 0.5 mm [8]. Lee et al. reported of ablation decentration greater than 0.30 mm from the center of the entrance pupil associated with greater induction of total HOA, coma, and spherical aberration after PRK, as compared to the ablation decentration less than 0.15 mm. Ablation decentration was also found to have a more significant influence on coma-inducing effects [10]. Buhren et al. modeled decentration with real wavefront error (WFE) changes which showed irregularities of decentration effects for rotationally symmetric treatments. Coma, astigmatism, and defocus were the main aberrations instigated by decentration [11]. However, as pointed out above, if a patient exhibits symptoms of decentration despite the lack of significant decentration with corneal topography measurements, then increased higher-order aberrations may be responsible, hence the importance of wavefront analysis for all patients with persistent or unusual visual symptoms after refractive surgery.

For custom ablations, the allowable degree of lateral translation error in the x–y plane to prevent degradation of wavefront correction effect is less forgiving, ranging from 0.2 to 0.7 mm for small (3 mm) and large pupils, respectively [12]. This degree of control is difficult to maintain during photoablation, which may be one reason why reductions in higher-order ocular aberrations are not consistently seen after photoablation and why patients with larger pupils could

be more likely to develop symptoms after lesser degrees of ablation decentration. Furthermore, if one is contemplating laser re-treatment with a wavefront-driven ablation, then great care should be taken to ensure that patient fixation is optimized and eye movement minimized during subsequent surgery.

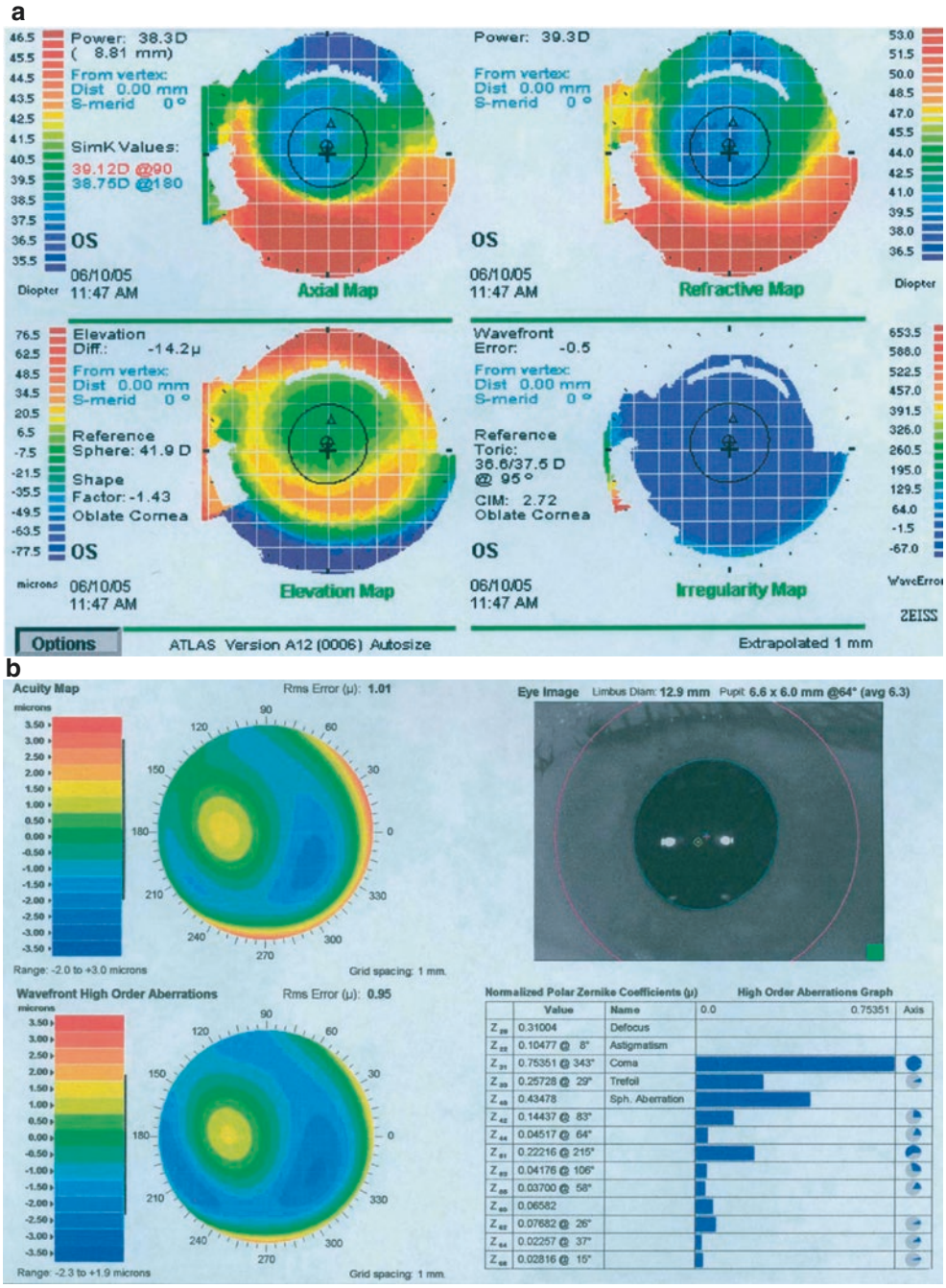
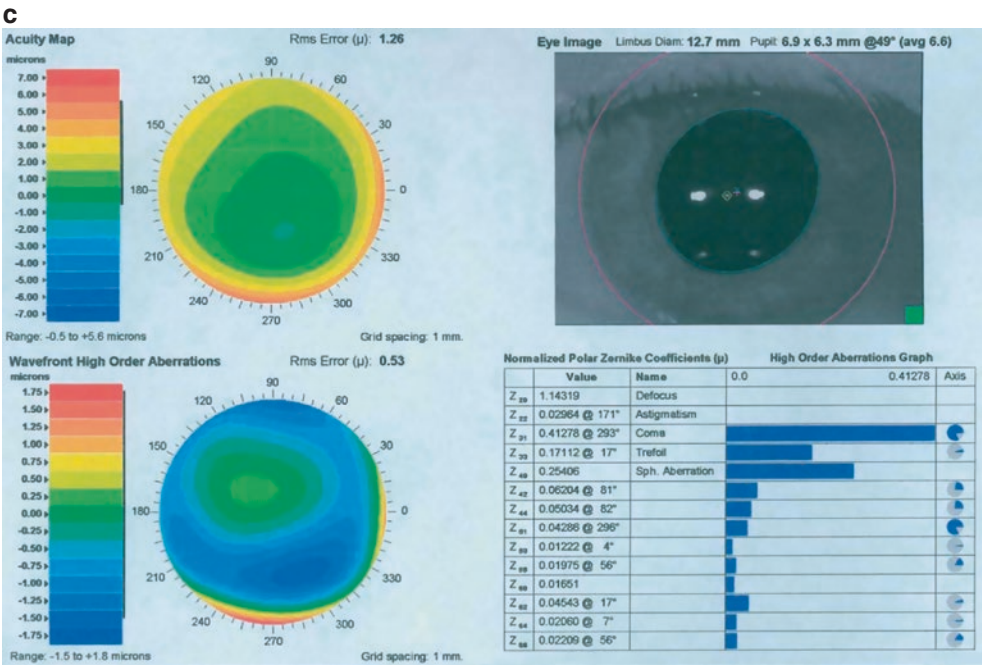


Fig. 22.3 Higher-order aberrations (HOA) after ablation decentration and wavefront-guided re-treatment. This patient sustained a superotemporally decentered myopic ablation and overcorrection after LASIK (**a**) and complained of vertical light scatter and ghosting at night. Uncorrected visual acuity was 20/60, improving to 20/25 with +2.00 sphere on manifest or cycloplegic refraction. Note the significant reduction in total HOA (44%), coma (44%), and spherical aberration (42%) when comparing before (**b**) and after custom hyperopic/astigmatic laser re-treatment (**c**). After re-treatment, UCVA was 20/25 and 20/15 with a manifest refraction of −0.25 to −0.50 × 120

Fig. 22.3 (continued)



22.4 Prevention of Decentration

The well-known Revolutionary Era scientist–politician Benjamin Franklin was notably known to say, "An ounce of prevention is worth a pound of cure." This dictum holds firm when it comes to the management of decentered refractive surgical procedures. While medical and surgical treatments do exist, the physical effects of a significantly decentered laser ablation are difficult to reverse completely. Fortunately, there are many precautions that the surgical team can take, and serious decentrations are quite rare with current laser technology.

Preoperative data should be carefully scrutinized before surgery to endure that the data being utilized are for the correct patient, correct eye, and correct axis. Furthermore, if custom ablation is being performed, then it is essential to validate the quality and reproducibility of either the raw and processed wavefront or topographic data. If inaccurate custom data is entered because the ocular wavefront was distorted by a dry eye, eye movement [12], or excessive accommodation, an asymmetric ablation may be delivered, resulting in the appearance and effect of a decentration even if the treatment is appropriately centered on the pupil.

The role of patient education should not be underestimated. If patients understand ahead of time what is expected of them during surgery and what they will experience, it will be easier for them to cooperate fully during treatment by maintaining fixation and a stable head position under the laser. A prepared patient is a less anxious and a more cooperative patient, and as such, it is worth the time for the surgeon and operating room staff to ensure that the patient is as prepared as possible when he or she is readied for surgery. Many surgeons use small doses of anxiolytic medications such as diazepam or alprazolam by mouth prior to surgery to aid in patient relaxation. While helpful in low doses, an oversedated patient may be less cooperative, and it may be difficult to control involuntary Bell's response of the globe that often occurs in this situation.

Calibration of laser centering and tracking devices is also of paramount importance to prevent decentered laser treatments. Even the most cooperative patient may end up with a bad result if the excimer laser being used for treatment is allowed to slip out of calibration. All laser systems have both internal and external means for calibrating these functions, and it is important to follow manufacturer's instructions religiously in this regard.

Once in the operating room, positioning of the patient, head, and eye are critical to provide for proper alignment of laser photoablation as energy strikes the cornea. Ideally, the globe should be positioned so that the corneal apex is orthog-

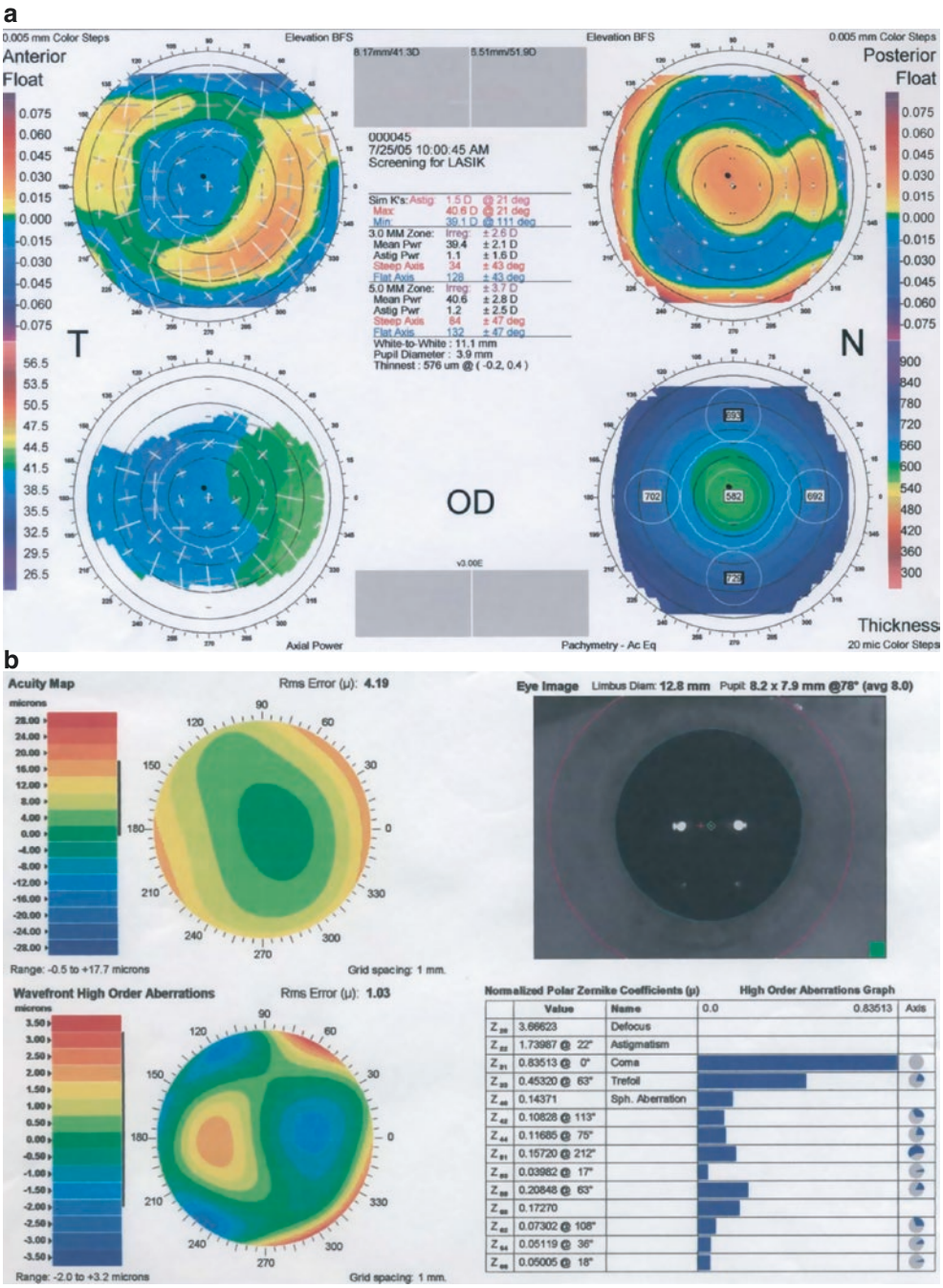
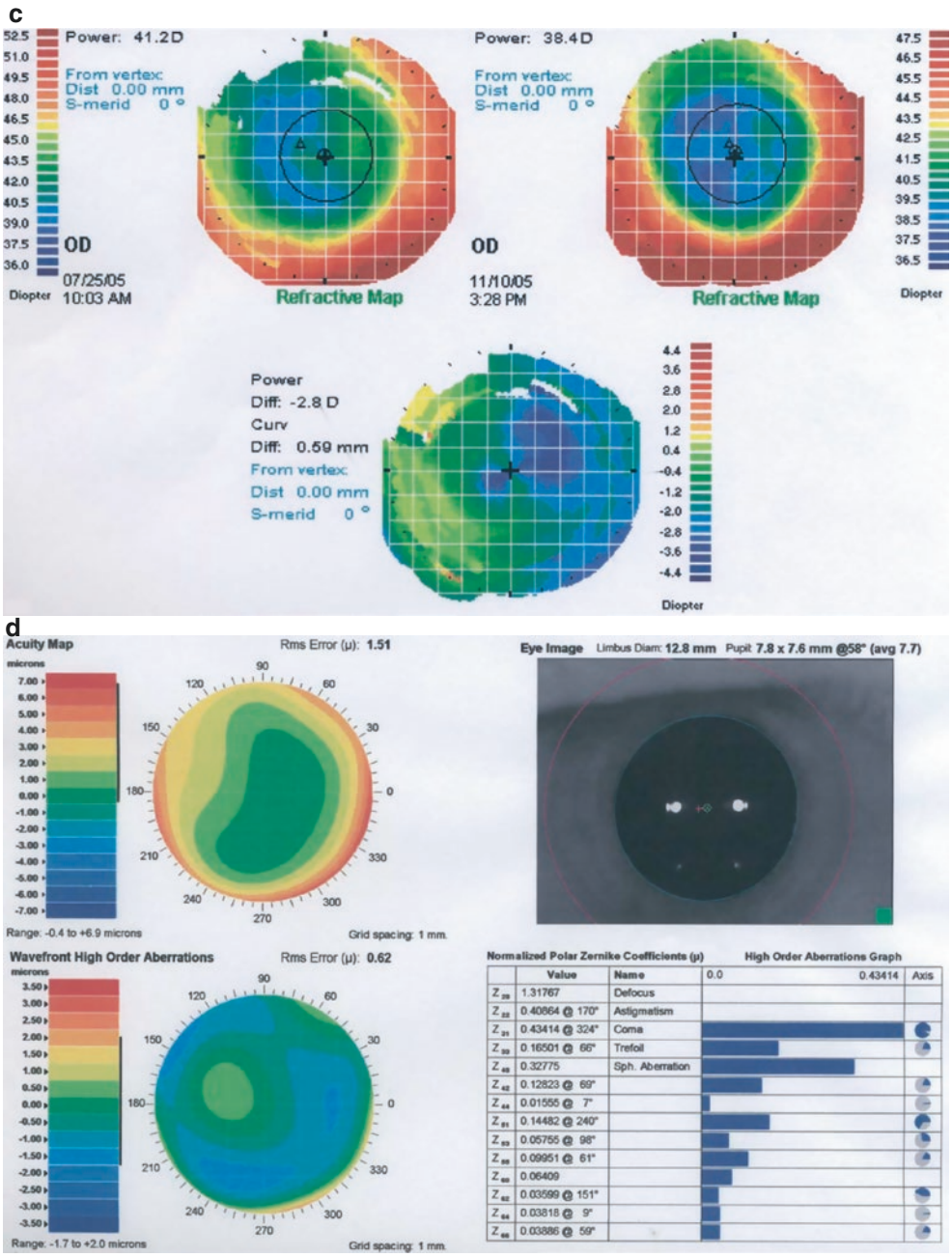


Fig. 22.4 Corneal topography after ablation decentration and wavefront-guided re-treatment. This patient complained of significant glare disability and monocular/ghosting due to temporal ablation decentration with respect to the pupil center seen on Orbscan testing after LASIK approximately—5.00 D (**a**). UCVA was 20/40, and BCVA was 20/25, with a manifest refraction of −0.25 to −0.75 × 94. Wavefront analysis showed a profound degree of horizontal coma (**b**). Eight months after wavefront-guided custom re-treatment, UCVA improved to 20/25 and 20/20, with manifest refraction using plano −0.50 × 80 and complete resolution of glare/ghosting symptoms. As expected, ablation centration as assessed by corneal topography also improved dramatically (**c**, *upper right*) when compared with preoperative topography (**c**, *upper left*). The pTake-Homential flattening achieved nasally by custom re-treatment is depicted in the difference map (**c**, *below center*). Wavefront sensing showed reduction in horizontal coma of almost 50% (**d**)

Fig. 22.4 (continued)



onal (or very close to orthogonal) to the incident laser beam. The corneal limbus should be marked in the upright position to avoid off-axis astigmatic ablation [4], which can be considered a decentration of sorts. If manual centering of the laser's optical path is used, then care should be taken to avoid parallax error by following manufacturer's instructions for each laser's microscope. If an automated eye-tracking system is utilized, then it is important to activate the tracking function with the eye in the correct position (i.e., with the patient fixating on the appropriate target within the laser microscope).

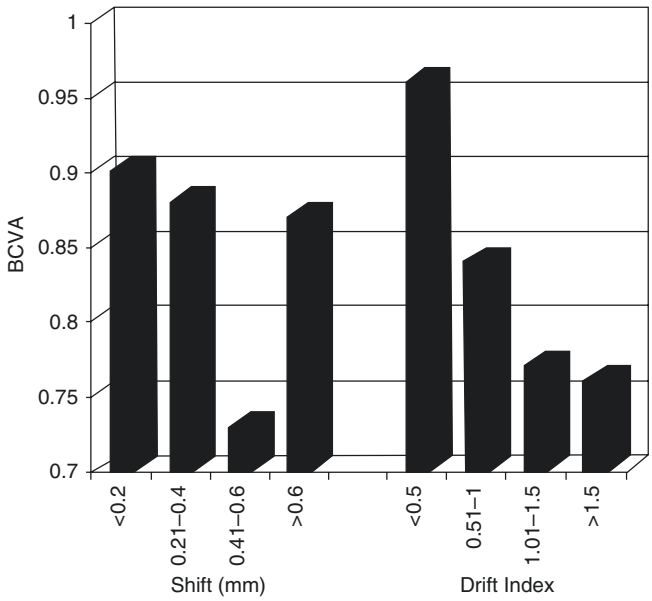


Fig. 22.5 A bar graph showing the relationship between best-corrected visual acuity (BCVA) and treatment shift and drift index. No statistically significant correlation was found between the best-corrected visual acuity and the axial or the tangential decentration ($r = 0.23$, $P = 0.14$). However, there is a positive, inverse correlation between the amount of drift and best-corrected visual acuity ($r = 0.58$, $P < 0.0001$)

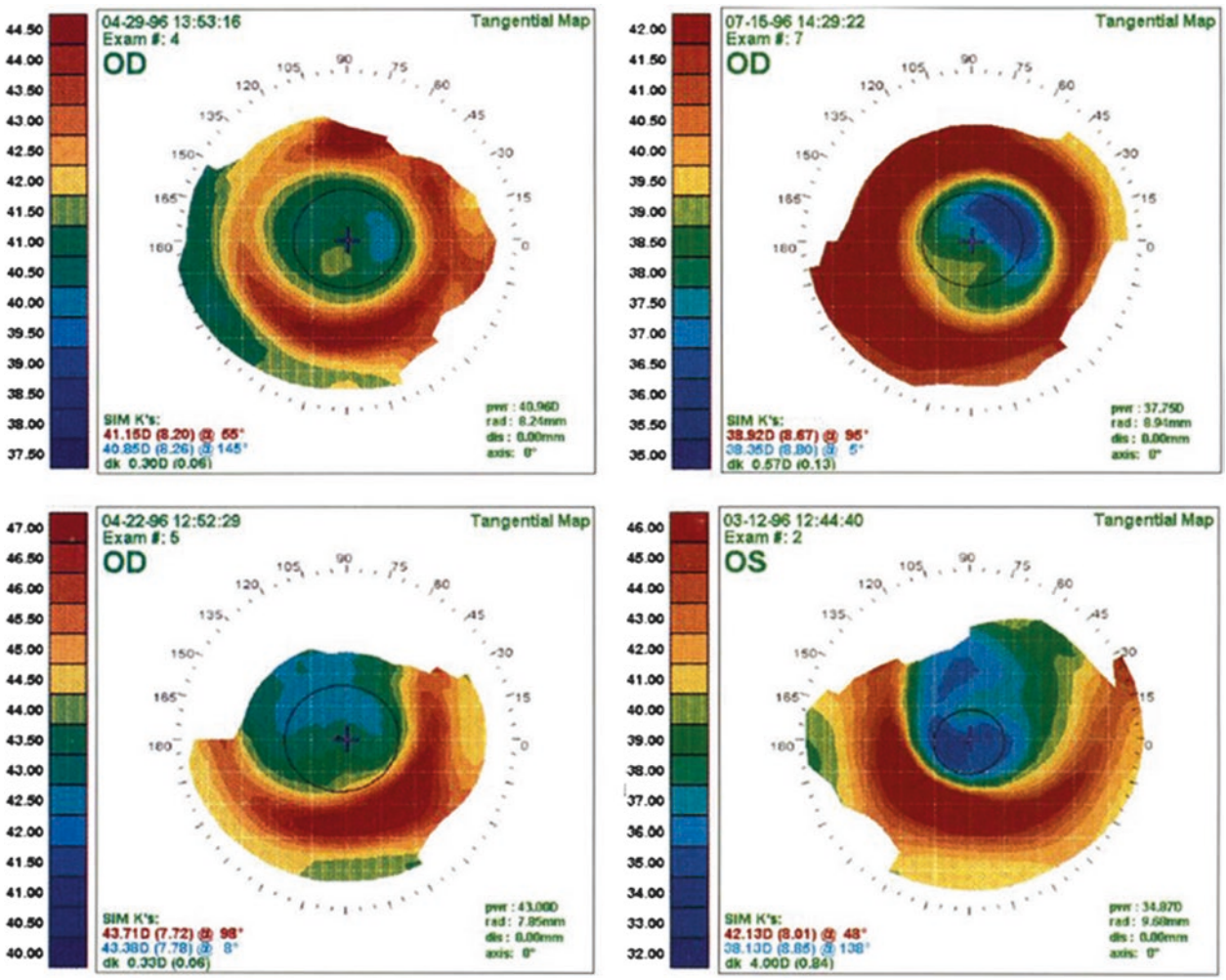


Fig. 22.6 (*Top left*) Tangential topographic map showing low displacement ($r = 0.10$ mm) and low drift index (0.23). Visual acuity of 20/15 was achieved 1 month after photorefractive keratectomy (PRK). (*Top right*) Tangential topographic map showing low displacement ($r = 0.20$ mm) and high drift index (1.30). Postoperative visual acuity was 20/30. (*Bottom left*) Tangential topographic map showing high displacement (0.67 mm) in the superotemporal direction and low drift index (0.00). Visual acuity of 20/20 was achieved. (*Bottom right*) Tangential topographic map showing high displacement (0.95 mm) superotemporally and high drift index (3.27), resulting in 20/40 postoperative visual acuity. In each map, the contour and center of the entrance pupil are, respectively, indicated by the *black circle* and *black cross*

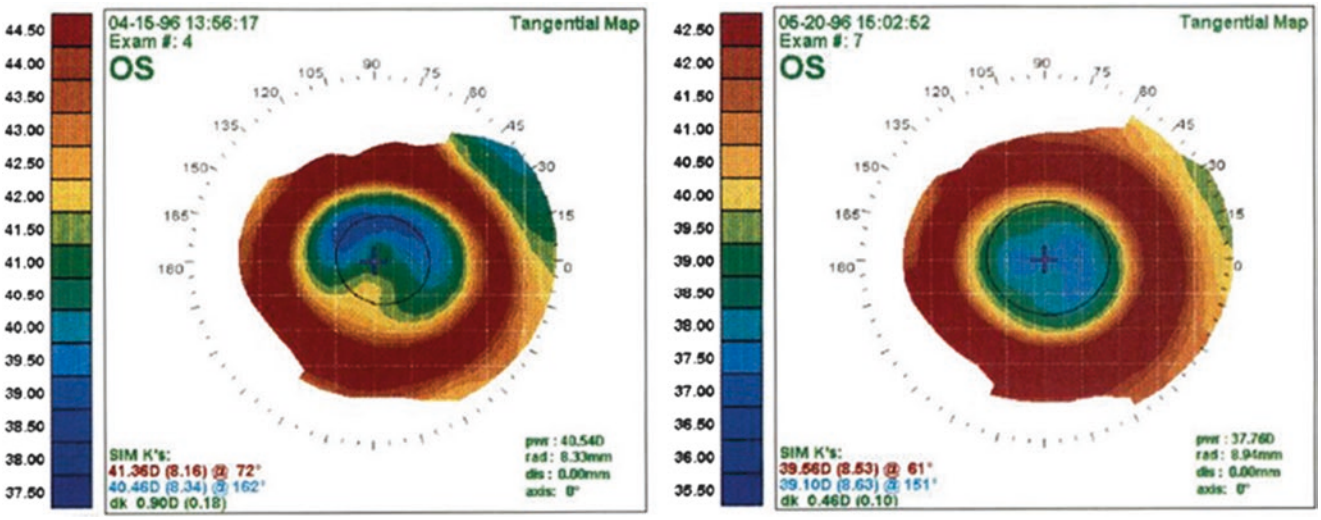


Fig. 22.7 Comparison of laser drift in two patients with similar amounts of treatment decentration (displacement). The contour and the pupillary center are represented by the *black circle* and *black cross*, respectively. (*Left*) Tangential topography showing a laser drift effect in the superior direction. The treatment, with an intended myopic correction of −6.20 diopters, was slightly shifted inferotemporally (r = 0.31 mm). Note the area of greatest ablation (*blue*) was drifted upward, resulting in a nonuniform central ablation power. The change in central ablation power in the central 4 mm^2 relative to the pupillary center was 3.00 diopters, and the arc of the second flattest area was 3.07 radii. The shortest distance from the center of ablation to the flattest area was 1.00 mm. The drift index was 0.98. The best-corrected visual acuity 1 month after photorefractive keratectomy was 20/40. (*Right*) Tangential topography of a left eye with an intended myopic correction of −5.50 diopters with similar degree of displacement as in the map at left (0.31 mm). Compared with the panel at *left*, the central power is more homogeneous, without gross drift effect (drift index = 0.03). Visual acuity of 20/20 was achieved

22.5 Medical Treatment of Decentration

Symptoms of decentered laser ablations can often be treated with medical intervention alone. If the degree of disability is mild, then correction of the residual refractive error with spectacles or soft contact lenses is often sufficient to minimize or eliminate the increased ghosting or glare that may be worst under mesopic lighting conditions.

Miotic agents are also useful adjuncts. Alpha agonists such as Alphagan P (Allergan, Irvine, CA) cause a transient, mild pupillary miosis of 1–2 mm lasting 2–3 h in duration, which is often enough to minimize mesopic symptoms while driving at night or at the movies. Tachyphylaxis is a problem with these agents, and the duration of effect may decrease with prolonged or frequent usage, so patients should be encouraged to use these drugs sparingly to maintain good effect. More pronounced symptoms might require the use of dilute (0.5–1%) pilocarpine, a much more potent muscarinic agent. May patients, however, experience a decline in visual function when the pupil is less than 2 mm in diameter, limiting pilocarpine's utility in this situation. When used three times daily, a permanent miotic effect can be maintained, but chronic usage of this drug has attendant complications, such as a high incidence of allergic reaction as well as increased risk of iris cyst formation and retinal detachment.

When decentration is profound (generally greater than 1 mm from the pupillary center), significant irregular astigmatism with decreased spectacle corrected visual acuity often results. Rigid gas permeable (RGP) contact lenses can be helpful in this setting, restoring visual acuity and minimizing irregular astigmatism and its symptoms. For patients whose corneal thickness is insufficient to allow further photoablation, RGP lens fitting may be the only option short of lamellar or penetrating corneal transplantation. While patients who have a history of RGP lens use may tolerate this type of treatment, most laser vision correction patients are poorly disposed toward this type of solution to the problem.

22.6 Surgical Treatment of Decentration

Decentered ablations may be treated using manual calculations and laser offsets to administer transepithelial PRK and phototherapeutic keratectomy (PTK) ablations (usually based on interpretations of corneal topography) [13–15], custom ablations mathematically derived and programmed into a laser from corneal topography [15, 16], ocular wavefront data [17], or numerical non-wavefront-guided algorithm for expansion or centration of optical zone [18, 19]. Astigmatic keratotomy (AK) and single Intacs segments have been used as well but with unpredictable results (Jonathan H. Talamo 2006, personal communication). With the arrival of reliable ocular aberrometry to measure the ocular wavefront, surgical therapy for laser decentration has become greatly simplified for all but the most severe cases. In the United States, wavefront- or topography-guided re-treatment of decentered laser

ablations is an off-label, non-US Food and Drug Administration (FDA)-approved procedure, and appropriate informed consent should be obtained.

Most decentrations symptomatic enough to require laser re-treatment are displaced 0.75 mm or more from the pupil center. In general, wavefront-guided re-treatment is the preferred method, as this approach allows the higher-order ocular aberrations induced by the decentered corneal optics to be treated with less likelihood of a large residual refractive error than if topography is used. Recently, Ang et al. reported a first case of the ability of the wavefront-guided treatment to reverse the Supracor LASIK presbyopic procedure while still maintaining the hyperopic correction [20].

If the decentration is very severe or there are significant corneal opacities, then wavefront sensing may not be possible, but for the vast majority of cases, it is the preferred modality (Figs. 22.3 and 22.4).

Prior to laser re-treatment of decentered ablations, it is important to exclude other causes of visual symptoms and to demonstrate refractive stability. In particular, ocular surface dysfunction from dry eye and blepharitis should be treated aggressively, as symptoms may be magnified and the ability to measure the ocular wavefront compromised by an unstable tear film. Careful slit lamp biomicroscopy should be performed to exclude the presence of incipient cataract, and if the patient has undergone recent intraocular surgery (such as phakic intraocular [IOL] implantation or refractive lensectomy patients undergoing planned bioptics procedures), then the presence of cystoid macular edema (CME), posterior capsular opacification, or IOL subluxation should be excluded. A hard contact lens over-refraction is crucial to demonstrate a reduction in symptoms to the patient and to confirm that the etiology is corneal.

Wavefront measurements must be reproducible and of sufficient quality to reliably calculate a custom treatment. If imaging is not possible with one type of aberrometer, then it may be easier with another. It is important to maximize the pupil diameter during measurement, since the diameter of the custom ablation will only be as wide as the capture wavefront (6 mm or greater is usually sufficient). As wavefront-guided laser systems using Hartmann–Shack (VISX, Alcon, Bausch & Lomb), Tserning (Wavelight), and Scanning Slit-Skiascopy (Nidek) are all available, it may be worth imaging with more than one system if data is difficult to capture. The MEL 80 CRS-Master TOSCA II software appears to be an effective treatment for decentrations, optical zone enlargement, and reduction of higher-order aberrations [21]. Where possible, it is very useful to cut a "test lens" in polymethylmethacrylate (PMMA; available with the VISX CustomVue System) and have the patient test his or her vision in a trial frame with an over-refraction to establish (1) if improvement in symptoms occurs and (2) if the target spherical equivalent is accurate.

When calculating wavefront-guided custom treatments, it is important to be mindful of tissue-removal depth requirements. In general, wavefront-derived re-treatments require significantly greater tissue ablation depths than either conventional spherocylindrical or primary custom treatments. To avoid insufficient residual stromal bed thickness in a LASIK patient, it may often be necessary to re-treat with surface ablation. Single-application, low-dose intraoperative topical mitomycin C (0.01–0.02% for 12–15 s) is useful in this setting (also off-label, non-FDA approved in the United States).

For the unusual cases where wavefront-guided re-treatment cannot be performed, topography can be used to generate a custom ablation algorithm (Fig. 22.8). As noted above, addi-

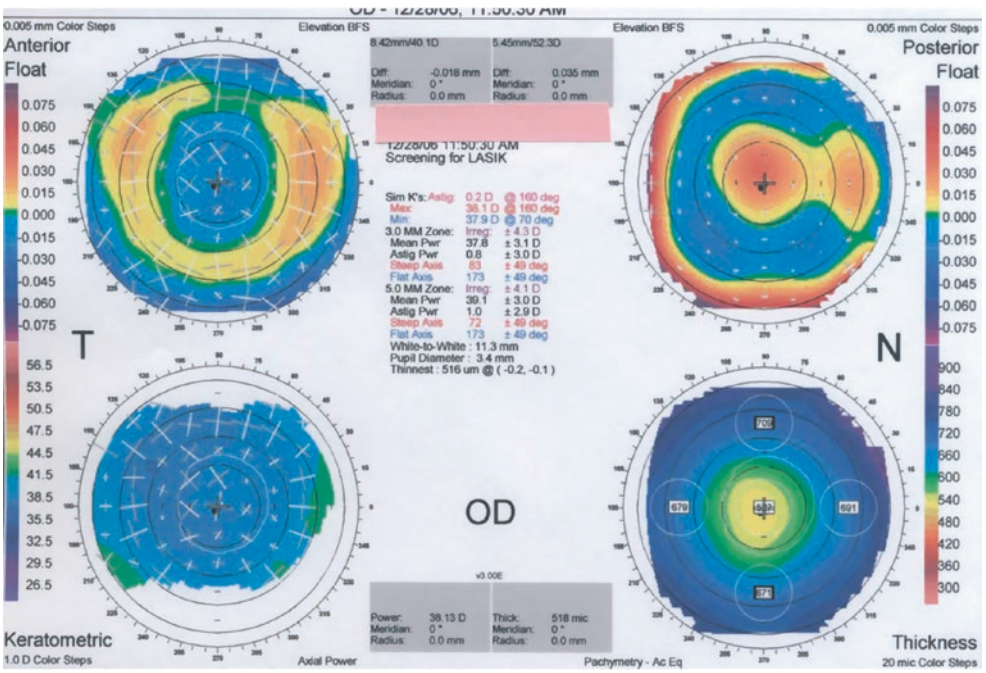


Fig. 22.8 Custom-contoured ablation for irregular cornea. This figure depicts the ability of VISX excimer laser system to program and precisely decenter topography-derived, custom-programmed photoablation (using C-CAP software) with respect to the pupil center after capture by an active eye-tracking system. Intentional decentration allows applications of asymmetric ablations to improved corneal topographic symmetry

tional refractive surgery is often indicated to adjust further the spherical equivalent to a level compatible with comfortable uncorrected vision. Additionally, in the cases of huge aberrations where wavefront sensing cannot give precise measurements, non-wavefront-guided numerical algorithm may prove to be inexpensive and simpler way to re-center the optical zone and to correct the refractive error with minimal tissue removal. In this method, a target ablation is calculated based on the reconstruction of the ablation achieved on the first surgical procedure, whereby the later ablation has adequate centration and an optical zone sufficient enough to envelope the achieved ablation. Inducing centration helps to correct coma and broadening the optical zone helps to correct spherical aberrations. Further, the minimal tissue removal in this method benefits the patients with critical residual corneal thickness [20]. This is important, especially since the central corneal thickness in the patients who undergo LASIK treatment has been proved to be statistically significant parameter associated with decentration [22].

While dramatic progress has been made in both the diagnosis and therapy of decentered corneal laser ablations over the 22 years the excimer laser has been in widespread use, surgical correction remains a challenging problem. As technology and surgeon skill continue to improve, perhaps decentration will become even more infrequent and treatment less complex.

Take-Home Pearls

- The best defense system is a good offense—have a system for preventing decentration.
- Leave enough stromal tissue after primary treatment to re-treat unexpected problems, as there are no good surgical options for decentered ablation in a too-thin cornea.
- Do not overlook medical treatment options.
- Before re-treatment, clearly establish refractive stability and that the etiology of symptoms is corneal.
- Wavefront-guided re-treatments, when possible, offer the simplest and most accurate method of surgical correction.
- Informed consent should underscore off-label nature of any surgery.

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Corneal Irregularity Following Refractive Surgery: Causes and Therapeutic Approaches

23

Jorge L. Alio and Jorge L. Alio del Barrio

Core Messages

- Corneal irregularity is the most frequent complication of corneal refractive surgical procedures.
- Corneal topography and corneal aberrometry are both important in understanding the challenge of corneal irregularity.
- Macro- and micro-irregular components may appear individually or associated, depending on the case.
- A comprehensive approach and grading of the clinical characteristics and impact of the symptoms in the patient's quality of life are important in the management of each case.
- Consecutive approaches can successfully treat most of the cases, avoiding corneal grafting.

23.1 Concept

Corneal irregularity is one of the most frequent complications that appears as a consequence of refractive surgery. Corneal irregularity leads to unacceptable visual symptoms and the loss of best-corrected vision. Its role in corneal refractive surgery outcomes was previously misdiagnosed and underestimated in its frequency. In the last decade, with the massive use of aberrometers, most corneal refractive surgery cases end with a different profile than normal at the anterior corneal surface, changing the aberrometry pattern of the cornea [1]. The consequence of this is a change in the visual perception and in vision quality. To a certain extent, the neuroprocessing role of the brain is able to compensate these changes. However, when the corneal optical dysfunction reaches high levels, such as with the loss of best-corrected vision, it frequently becomes a complication that is difficult to solve. In this situation, an adequate clinical examination and surgical expertise can lead to the correction of the irregularity with restoration of acceptable or normal levels of vision [1, 2].

Corneal irregularity, also called irregular astigmatism, appears when the principal meridians of the anterior corneal surface are not 90° apart, without a progressive transition from one meridian to another. This optical system is impossible to correct by conventional spherical or cylindrical lenses. The refraction in different meridians conforms to a nongeometric plane, and the refractive rays have no planes of symmetry [3].

Corneal irregularity causes a variety of unpleasant symptoms in patients. It can be studied with modern examination techniques which lead to an adequate therapeutic decision-making process in the benefit of the disabled patient.

23.2 Symptoms

The irregular or aberrated cornea causes visual distortion with night and/or day glare. Patients describe halos, dazzling, monocular diplopia or polyopia, either in night or daylight conditions. A decrease in best-corrected vision is also perceived by most patients.

The subjective feeling that a patient may describe depends, to a great extent, on the ocular dominance, the severity of the irregularity and the type of corneal aberrations that are more abnormally deviated.

23.3 Clinical Examination and Classification

Prior ophthalmic history and refractive surgical procedures should be traced in eyes with corneal irregularity. If possible for example, in the case of lamellar surgery, the physician

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should know details about flap construction and flap complications that might have occurred, the preoperative best spectacle-corrected visual acuity of the patient and the changes in the quality of life. Previous medical reports and adequate clinical documents to support previous patients' history are mandatory at this stage. Then, a complete ocular examination should be performed including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), pinhole visual acuity, cycloplegic refraction, retinoscopy, keratometry, ultrasonic pachymetry, corneal topography, corneal aberrometry and global aberrometry examination. Pupil size in high and low mesopic conditions, if possible, should also be recorded. Best overcorrected vision over a rigid contact lens is important to ascertain the role of corneal irregularity in cases where other problems, such as corneal opacity, may play a role in visual loss. Other visual findings that could be related to loss of best-corrected vision, such as lens changes and macular problems, should be also highlighted in a medical examination.

Clinically, corneal irregularity will present a typical retinoscopy pattern with spinning and inscissoring of the red pupil retinoscopy reflex. On keratometry, the mires and rings will appear distorted. Modern corneal topography (Figs. 23.1 and 23.2) shows certain patterns and numerical indexes of corneal irregularity that can be useful for the follow-up. However, today, the most useful clinical examination technique is corneal aberrometry (Fig. 23.3). Corneal aberrometry is a mathematical transformation of the corneal topography data that can obtain up to 8.5 mm of the cornea diameter, which is independent of pupil size; analyses the anterior corneal surface, usually the one affected by the previous refractive surgery; and can be analysed by different mathematical approaches such as the Zernike polynomials, Seidel equations or Fourier analysis [1, 2, 4, 5].

Global wavefront examination with the pupil in mydriasis (test dependent on the pupil size and accommodation) can also be performed. However, in highly aberrated corneas with irregular astigmatism, it is often not possible to obtain a wavefront map, at least of a minimum quality. Also we should consider that global aberrometry is affected by the intraocular aberrations (lens and posterior corneal surface) and can be masqueraded by residual accommodation, making this examination not ideal for the assessment of such cases [6]. An

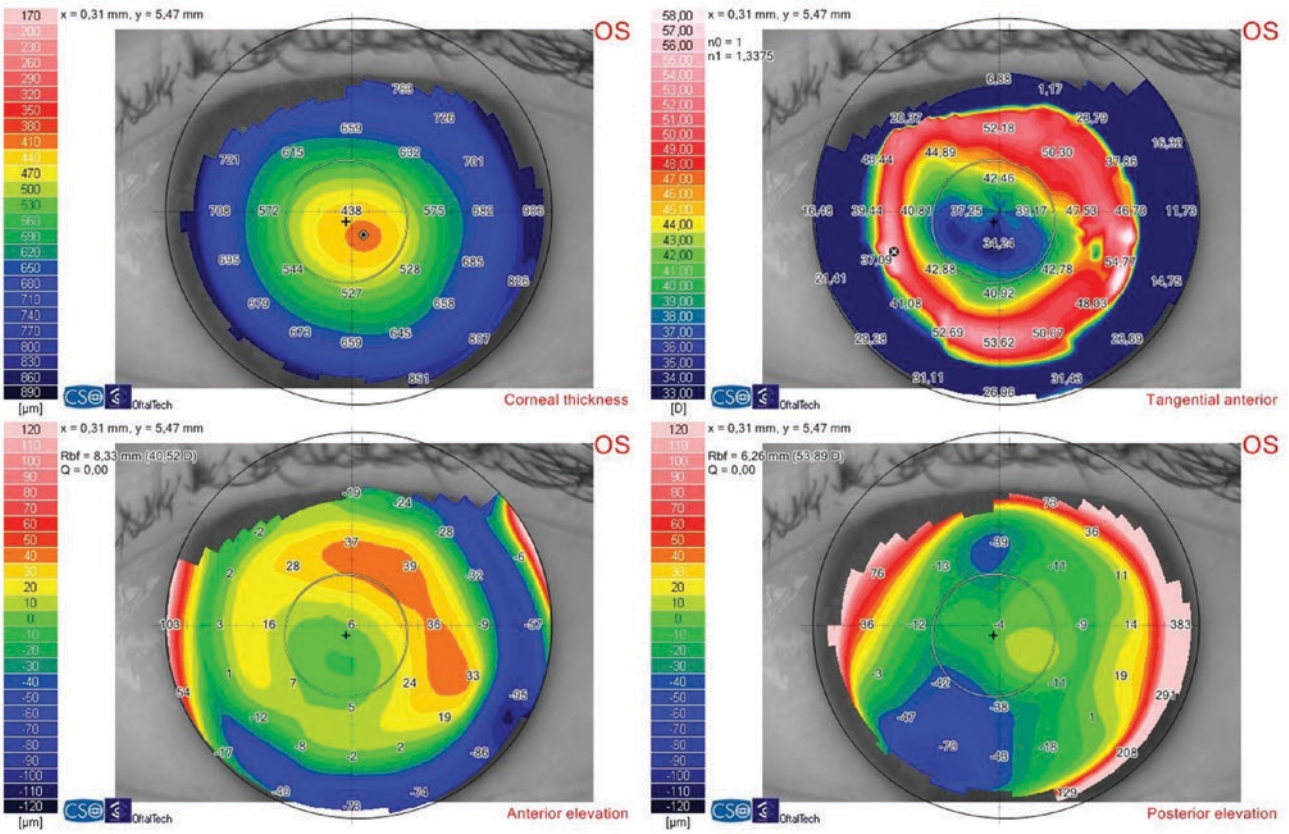

Fig. 23.1 Corneal topography of a post-LASIK decentred myopic treatment with a secondary decrease in the unaided and spectacle-corrected visual acuities due to the irregularity of the anterior surface of the cornea

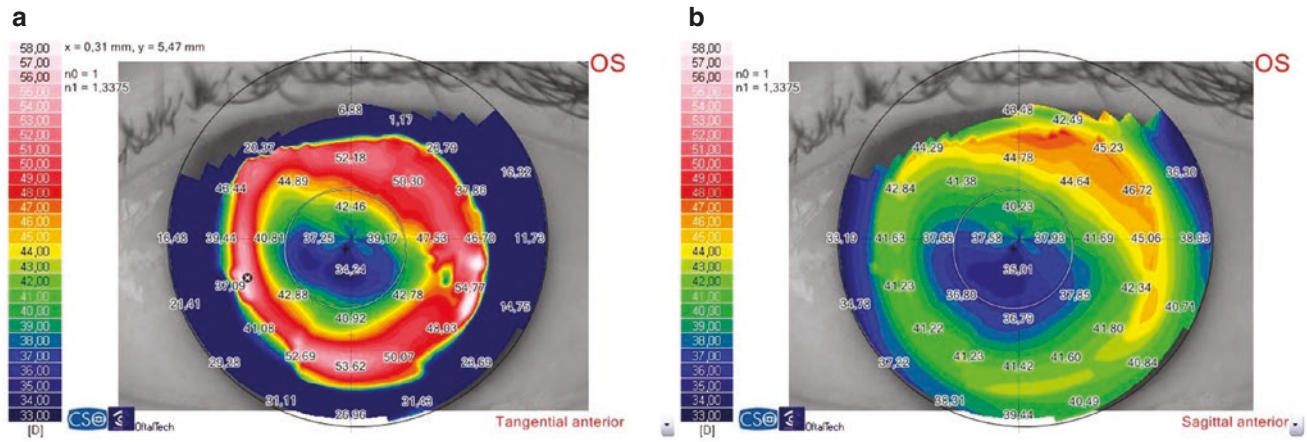

Fig. 23.2 The different appearance that the same case of Fig. 23.1 may have on corneal topography: tangential (**a**) versus sagittal maps (**b**). The clinicians should be aware of these differences, not to have misunderstandings in the clinical interpretation of the topography. Tangential maps give more precise and accurate information regarding the shape of the anterior corneal surface, although they are more vulnerable to artefacts

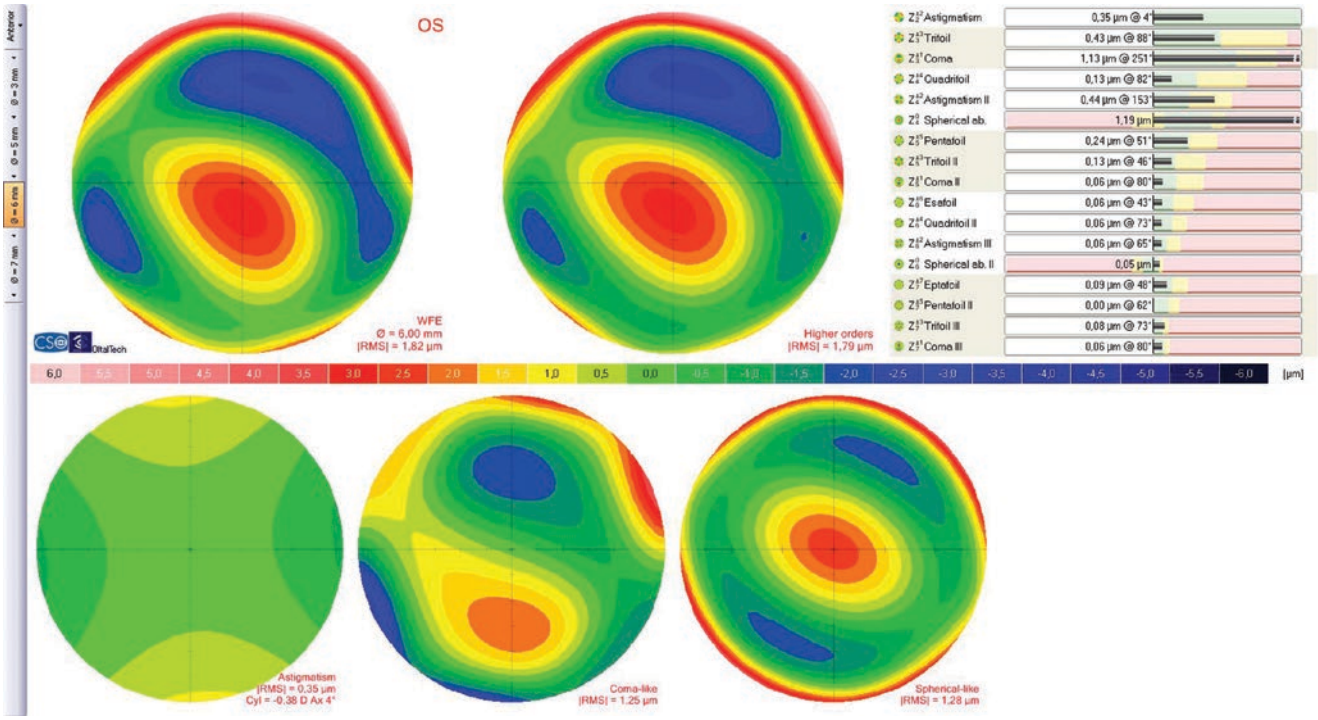

Fig. 23.3 Corneal aberrometry of the same case as in Figs. 23.1 and 23.2. Corneal aberrometry represents the numerical optical value of the corneal topography and indeed is the most important examination tool for the understanding of irregular astigmatism

important difference is that in wavefront measurements, the Zernike expansion is calculated from the entrance pupil centre, while topographic measurements of the cornea are centred on the corneal vertex, which approximates better to the visual axis [7]. However, the latest wavefront aberrometers like the Osiris aberrometer (CSO—Costruzione Strumenti Oftalmici, Italy) use a pyramid wavefront sensor that provides greater accuracy on sensing total eye aberrations in very irregular corneas, providing very valuable information for the treatment plan and detecting corneal irregularities that usually are not seen in the commonly used tangential and sagittal topographic maps (Fig. 23.4) [8].

Other examination techniques, such as ray-tracing [9], in which a laser beam is delivered parallel to the optical axis of the retina sequentially through different pupil locations, can be useful. The ray-tracing technique is able to analyse separately the corneal, intraocular and global aberrations.

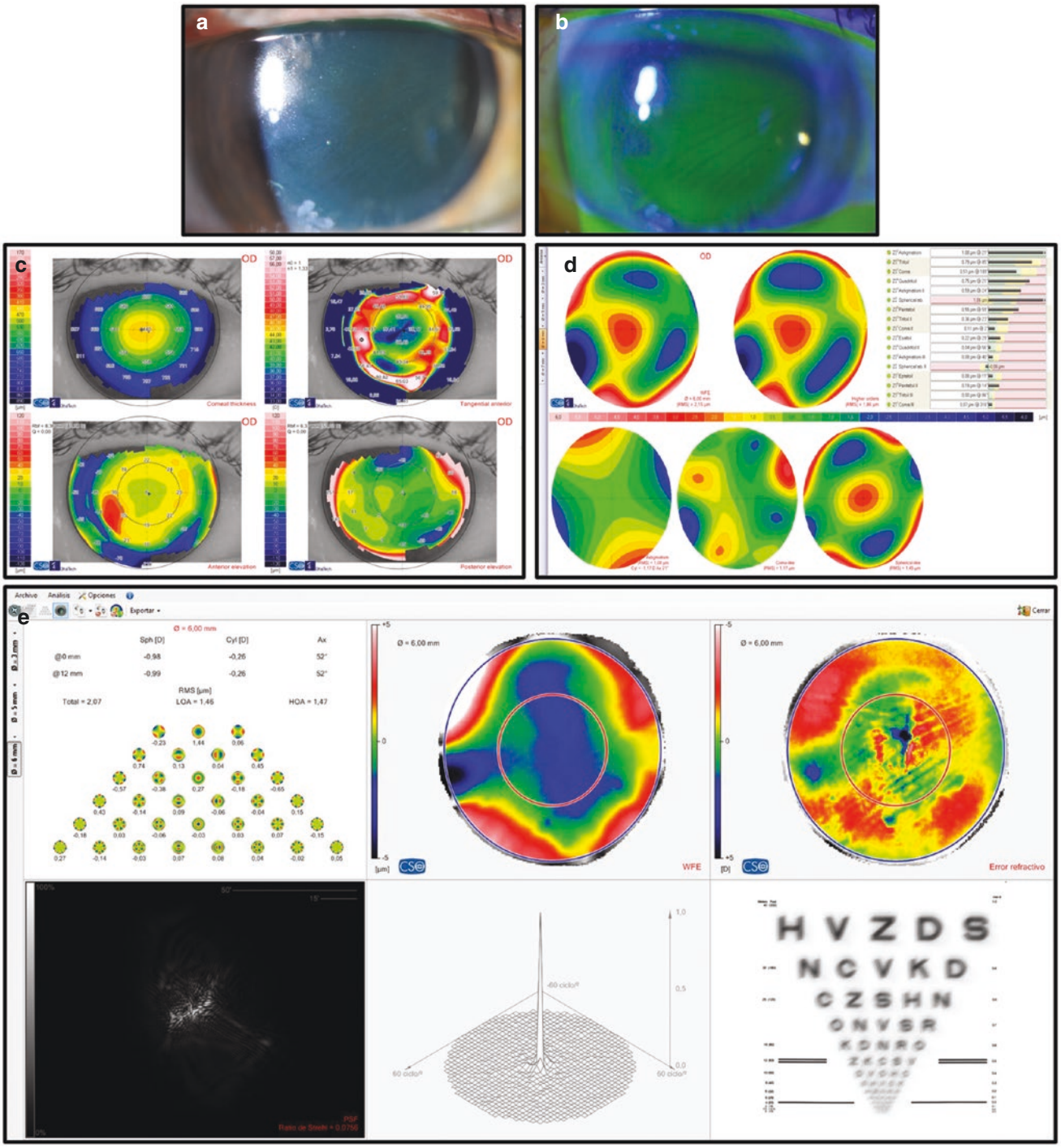

Fig. 23.4 Flap macrofolds 10 years after myopic LASIK: the macrofolds are easily seen by slit lamp biomicroscopy (**a**), although its visualization can be enhanced by fluorescein instillation (**b**). In the corneal topography, it can be observed the flattening of the central cornea in relation with the myopic ablation (**c**) but not an obvious irregularity that justifies the highly aberrated cornea seen in the aberrometry (**d**). The Osiris total eye wavefront analysis shows perfectly the severe irregularity induced by the flap macrofolds, delineating accurately their shape and location, and also provides an overview of the quality of vision that in this case is severely affected with a low PSF (**e**)

Other clinical examination techniques can also give useful information: anterior segment optical coherence tomography (OCT), very high-frequency (VHF) ultrasound bioimaging of the anterior segment of the eye and corneal confocal microscopy. Diagnostic imaging techniques such as anterior segment OCT and VHF ultrasound are, at this moment, capable of globally analysing the corneal profile. The Artemis very high-frequency digital ultrasound arc scanner (ArcScan Inc., Morrison, CO) can be used to obtain layered corneal thicknesses including epithelial thickness profile. With this information stromal surface height can be then calculated by subtracting epithelial thickness data from corneal front

surface elevation data and used to calculate the ablation profile applied to the eye [10–12]. This is important in difficult cases where data on the type of complication that the patient suffered from during surgery is lacking. Similar information, even though less precise, is offered today by anterior segment OCT (Visante, Carl Zeiss, Germany). Corneal confocal microscopy is relevant in measuring light scattering and analysing the degree of corneal scarring that is present at the central cornea, which is important in certain cases.

23.4 Clinical Classification of Corneal Irregularity

23.4.1 Macro-irregular and Micro-irregular Patterns

When the main reason for visual disability is a steeper or flatter area of the cornea larger than 2 mm, the case can be classified as macro-irregular [1]. When a disperse irregularity, not specifically creating a well-defined elevated or flatter area of the cornea, then the case can be termed as micro-irregular. This initial classification is obtained from the corneal topography map and has important clinical implications in the therapeutic decision-making process for the case. Also, mixed patterns with a macro-irregular area associated to some degree of micro-irregularity are frequently present.

Typical macro-irregular patterns are those caused by decentrated ablations. Micro-irregular patterns are found frequently in cases with flap complications.

23.4.2 Measuring Corneal Irregularity by Higher-Order Aberration Analysis

Probably the most specific way to analyse and grade corneal irregularity is the mathematical transformation of the topography analysed by corneal aberrometry. In the normal eye, more than 90% of the eye aberrations are derived from the cornea, and the proportion is larger when corneal irregularity is present [7]. This makes corneal aberrometry a very precise and comprehensive method to globally analyse the optical profile of the anterior corneal surface. The Zernike decomposition of this analysis, precisely the measurement of the higher-order aberrations from the third to the eighth order from the maximum area of the anterior corneal surface, offers us global data about the irregularity. This information will be very important in the decision of how to treat such cases [5].

23.4.3 Clinical Classification

We have defined a scale to classify corneal irregularity in four grades based on (1) patient symptoms, (2) loss of lines of best-corrected visual acuity, (3) quality of life changes and (4) objective data such as aberrometry. This classification is displayed in Table 23.1. In medical legal terms, it is important to offer objective data about how severe the corneal irregularity is and how much the patient's life is affected by the problem.

Table 23.1 Grading of irregular astigmatism

Grade 1	– Mild symptoms at night or daylight conditions – Loss of 1–2 lines of BCVA – Useful vision for reading, driving and walking – No disability for normal life, but with discomfort – No monocular diplopia – Ray-tracing abnormal. Distortion = 2–8 μm – Aberrometry: RMS = 2–3 μm
Grade 2	– Moderate disability – Loss of 3–4 lines of BCVA – Reading and driving partially affected, especially in dim light conditions – Some patients prefer not to use the eye – Moderate monocular diplopia – Ray-tracing affected. Distortion = 8–14 μm – Aberrometry: RMS = 3–6 μm
Grade 3	– Severe disability. Eye not useful for visual performance – Loss of >5 lines of BCVA – Patients prefer not to use the eye – Reading and driving affected, all light conditions – Severe monocular diplopia or polyopia – Ray-tracing disaster. Distortion >14 μm – Aberrometry: RMS > 6 μm
Grade 4	– Eye not useful, legally blind – BCVA =20/200 or less – Aberrometry, ray-tracing and topography not possible to capture due to the severity of irregularities

23.5 Correction and Treatment of Corneal Irregularity

No surgical correction should be attempted prior to 6 months of follow-up of the case from the causing surgery. In many mild cases, corneal irregularity improves with time thanks to the role of the corneal epithelium remodelling. Visual symptoms somehow are improved by neuroprocessing, and for this reason, some cases become less symptomatic with time. This time interval is also important, as some changes related to the corneal wound healing process may need time to improve or to worsen and an adequate perspective on the case cannot be obtained prior to this time in many cases.

23.5.1 Contact Lens Adaptation

During this waiting period, contact lenses can be very helpful in relieving the patient's symptoms, as the patient accepts that this is a temporary solution. Corneal contact lens adaptation is not easy in these cases due to (1) lack of patient motivation, (2) frequent concomitant existence of ocular surface syndrome related to the previous corneal surgery (especially following LASIK), (3) prior patient history of contact lens intolerance and (4) intolerance related to the corneal surgical

process. All types of contact lenses can be used in these patients: hard (polymethylmethacrylate, PMMA), gas permeable (silicon fluoromethacrylate and silicon acrylate), hybrid (Sinergicon Soft Perm CibaVision) and hydrophilic. Preoperative corneal topography, fluorescein pattern and topographic pattern of the corneal irregularity should be used to select the contact lens trial. Some companies manufacture customized contact lenses depending on the corneal topography for severely disabled corneal irregularity. These types of contact lenses are becoming very helpful when available and also in mild cases.

When adapting contact lenses, the diameter of the lens should depend on the choice of the diameter of the flap. The lens should lean on the zone not affected by the previous refractive surgery (or to the corneal periphery). In cases of incisional surgery, such as RK, toric hydrophilic lenses and soft perm are preferred because these lenses have larger diameters and they rest on the scleral ring, avoiding the corneal periphery usually affected by the healing effect of the incision and poor stability of the lens [13]. Contact lens adaptation should be performed by a contact lens specialist, as these are very demanding cases. An adequate follow-up should be offered during the waiting period in cases in which visual disability is high enough not to allow normal patient's quality of life with glasses and contact lenses.

23.5.2 Wavefront-Guided Excimer Laser Surgery: Global Wavefront Versus Corneal Wavefront

As discussed previously, global wavefront analysis used to have limited value in the understanding and correction of the irregular cornea. The reasons for these limitations were the following:

(1) Most global wavefront sensors couldn't measure highly aberrated corneas.

(2) Global wavefront analyses were restricted to pupil size.

(3) Most global wavefront sensors limited their analysis to 1 mm inside the pupil diameter, which further limited the knowledge of the corneal irregularity: in many cases, corneal irregularity is outside these limits and cannot be rightly understood. On the other hand, corneal wavefront analysis can measure up to 8 or 8.5 mm diameter of the cornea (Fig. 23.3), is not limited by pupil size and measures a much larger amount of points, which renders much more accurate information of the corneal irregularity.

Also corneal wavefront analysis can be obtained in almost any case of corneal irregularity even in highly aberrated corneas. Corneal wavefront analysis is a mathematical analysis of corneal topography by measuring the abnormality of the anterior corneal surface. As most of the corneal irregularity following refractive surgery comes from problems in the anterior surface of the cornea, corneal wavefront analysis comes to be much more useful than any other tool in the analysis that helps in planning the treatment of an irregular cornea [14].

Corneal wavefront analysis is not interfered by accommodation or intraocular aberrations and offers adequate, specific and precise information about the corneal problem as a larger number of points are studied on the cornea. This allows more precise information to build the customized programme required for the correction of such cases. Macro-irregular patterns can be analysed and treated based on this information and also to some extent the micro-irregular component. The use of corneal topography to guide excimer laser surgery has been used in several investigations that have concluded that the macro-irregular components can be rightly treated by topography-guided treatments [7, 15–17].

To correct an irregular cornea using the corneal wavefront analysis, we capture and analyse the corneal aberration map up to the seventh Zernike order, and we process this data with the software of the Esiris-Schwind technology (Frankfurt, Germany), which transforms corneal aberration data into an adequate ablation profile. To correct the irregular cornea, especially in severe cases, the software enables the surgeon to take an active part in the decision-making process, selecting the best solution for each patient based on corneal pachymetry, mesopic pupil size and total ablation thickness. The optical ablation zone can be adjusted, and specific aberrations can be selected or discarded in the resulting ablation profile in order to adjust the ablation thickness and achieve the best visual outcome for the patient without compromising corneal integrity. The specific surgical criteria to choose the optical zone with transition zones and the exclusion of specific aberrations from the treatment might be decided by the surgeon.

As discussed before, the Osiris aberrometer (CSO—Costruzione Strumenti Oftalmici, Italy) provides greater accuracy on sensing total eye aberrations in very irregular corneas [8]. With this platform we can simulate the expected change in visual acuity and quality of vision by correcting each specific aberration in the Zernike polynomial, thus assisting in the elaboration of the treatment plan in order to discard those aberrations that are not relevant, or even their correction may deteriorate the optical quality of the eye, adjusting then the ablation thickness to the minimum necessary (Fig. 23.5). This simulation still needs to be validated and its reliability demonstrated with large prospective studies but starts a new encouraging way of treating these patients knowing "what we are doing", "why" and "what result we can expect".

Using this surgeon's corneal wavefront-guided methods, total higher-order aberrations can be reduced significantly, increasing the best-corrected visual acuity and decreasing patients' symptoms (Fig. 23.6a–d) [7, 18]. As it is shown in other chapters of this book, corneal wavefront-guided methods are especially valuable in the correction of hyperopic and myopic decentrations and to enlarge the optical zone in

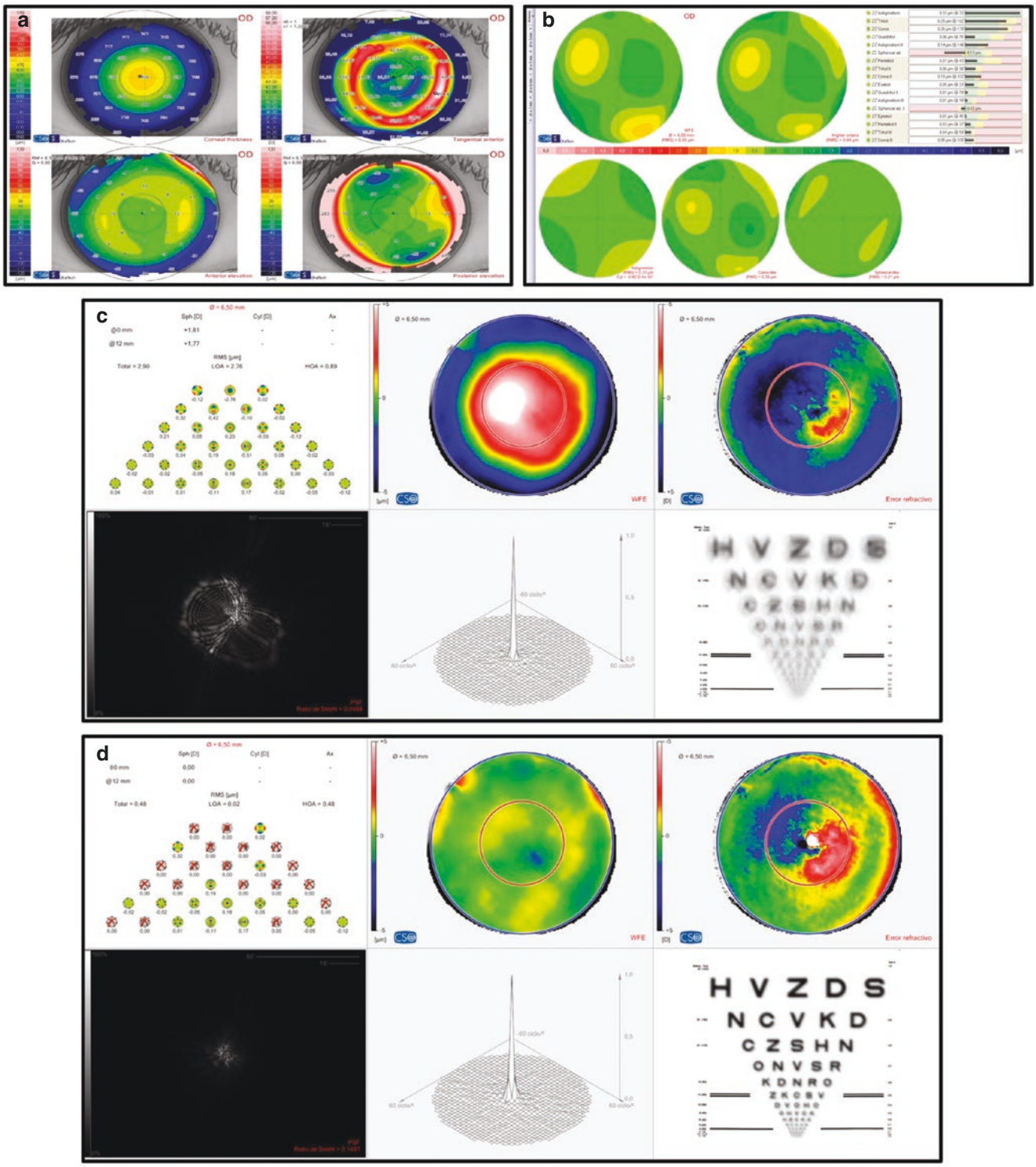

Fig. 23.5 Patient referred due to a decreased UVA and CDVA after SMILE on her right eye. Bad collaboration reported during treatment: the cornea appears unremarkable on slit lamp examination. At the corneal topography, it can be observed the expected flattening of the central cornea in relation with the myopic treatment (**a**) but not an obvious irregularity that justifies the highly distorted corneal aberrometry (**b**). The Osiris total eye wavefront analysis shows clearly a focal paracentral area that induces a significant distortion of the quality of vision, compatible with a retained fragment from the SMILE intrastromal lenticule (**c**). The simulation offered by the platform shows that a significant ablation (treating up to the seventh Zernike polynomial aberrations) is required in order to improve the quality of vision (**d**). The not relevant aberrations can be easily detected and excluded from the treatment plan

symptomatic patients with night vision problems related to a small optical zone.

Compensatory epithelial remodelling masks anterior stromal irregularities from the corneal surface, as it is seen in keratoconus where the epithelium becomes thinner in the area of the cone, masking partially its irregularity. Reinstein et al. have published the advantages of the Artemis epithelial mapping (ArcScan Inc., Morrison, CO) in irregular corneas in

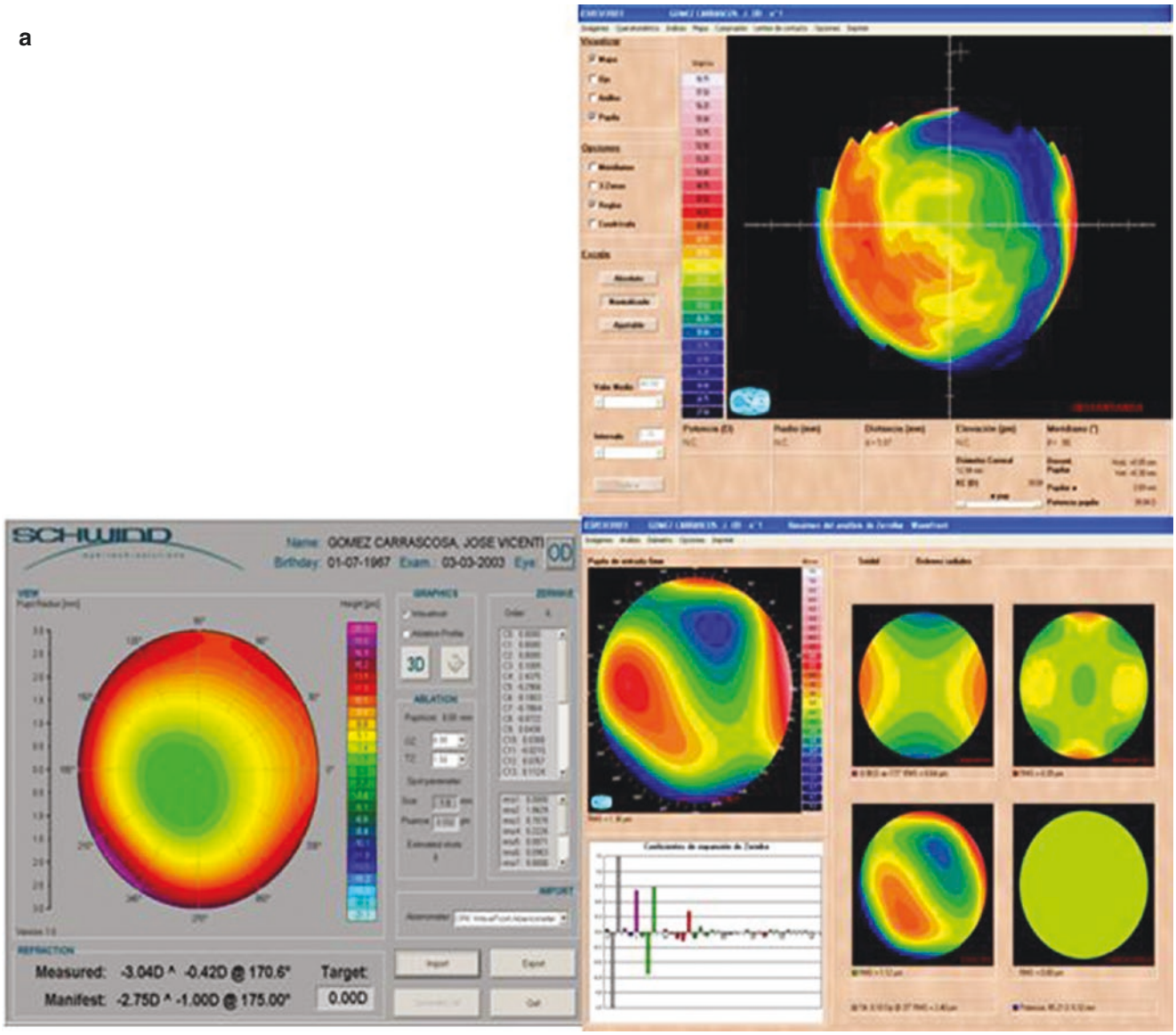

Fig. 23.6 This figure shows the evolution of a case (**a**) treated with topography-guided excimer laser ablation (the Esiris-Schwind technology), with the evolution of corneal topography (**b**) and corneal aberrometry (**c**). This figure corresponds to the following clinical case:Figure **a**: Patient history:
A 33 year old white male came to our clinic with an ocular history of refractive surgery in both eyes. He complained of poor quality of vision, ghost images and halos especially at night in his right eye. He had his first standard LASIK treatment in March 2000. His previous ocular history was:
BCVA OD: 1.0
Rx OD: −3.75 to 1.00 cyl ×115
After we examined the patient his ocular history was as follows:
UCVA OD: 0.6
BCVA OD: 0.7
Rx OD: −1.75 to 0.75 ×170
Pachymetry: 482 μm
Biomicroscopy: within normal limits
Figure **b**–**c**:
1 month POSTOP evaluation:
Patient reported that vision in his OD improved and he was not perceiving ghost images.
UCVA OD: 0.8
BCVA: 0.8
Rx OD: −0.50 cyl ×30
3 month POSTOP evaluation:
UCVA OD: 0.9
BCVA: 1.0
Rx OD: −0.50 cyl ×180°
6 month POST OP evaluation:
UCVA OD: 1.0
BCVA: 1.0
Rx OD: −0.50 cyl ×180°

b

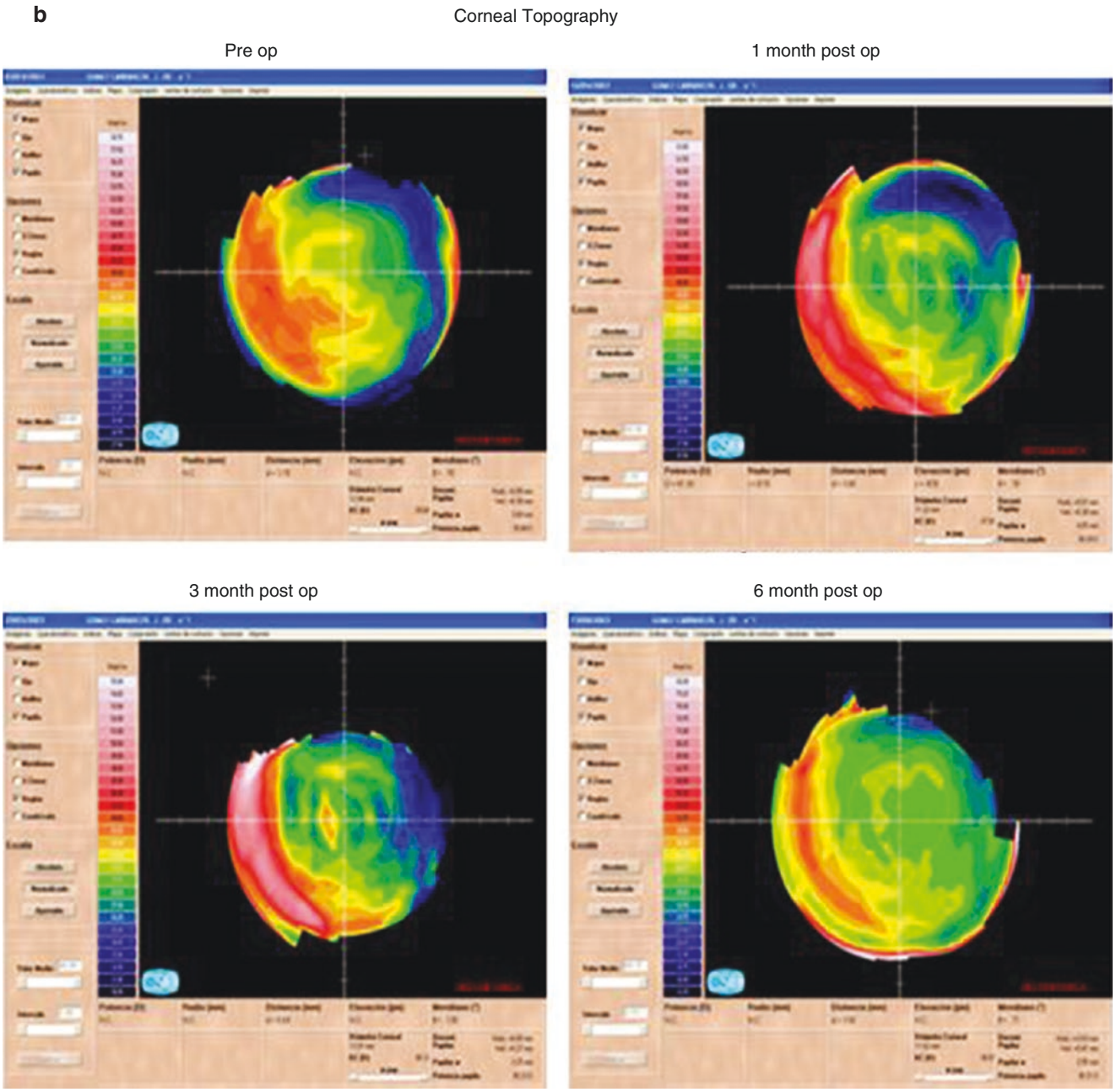

Fig. 23.6 (continued)

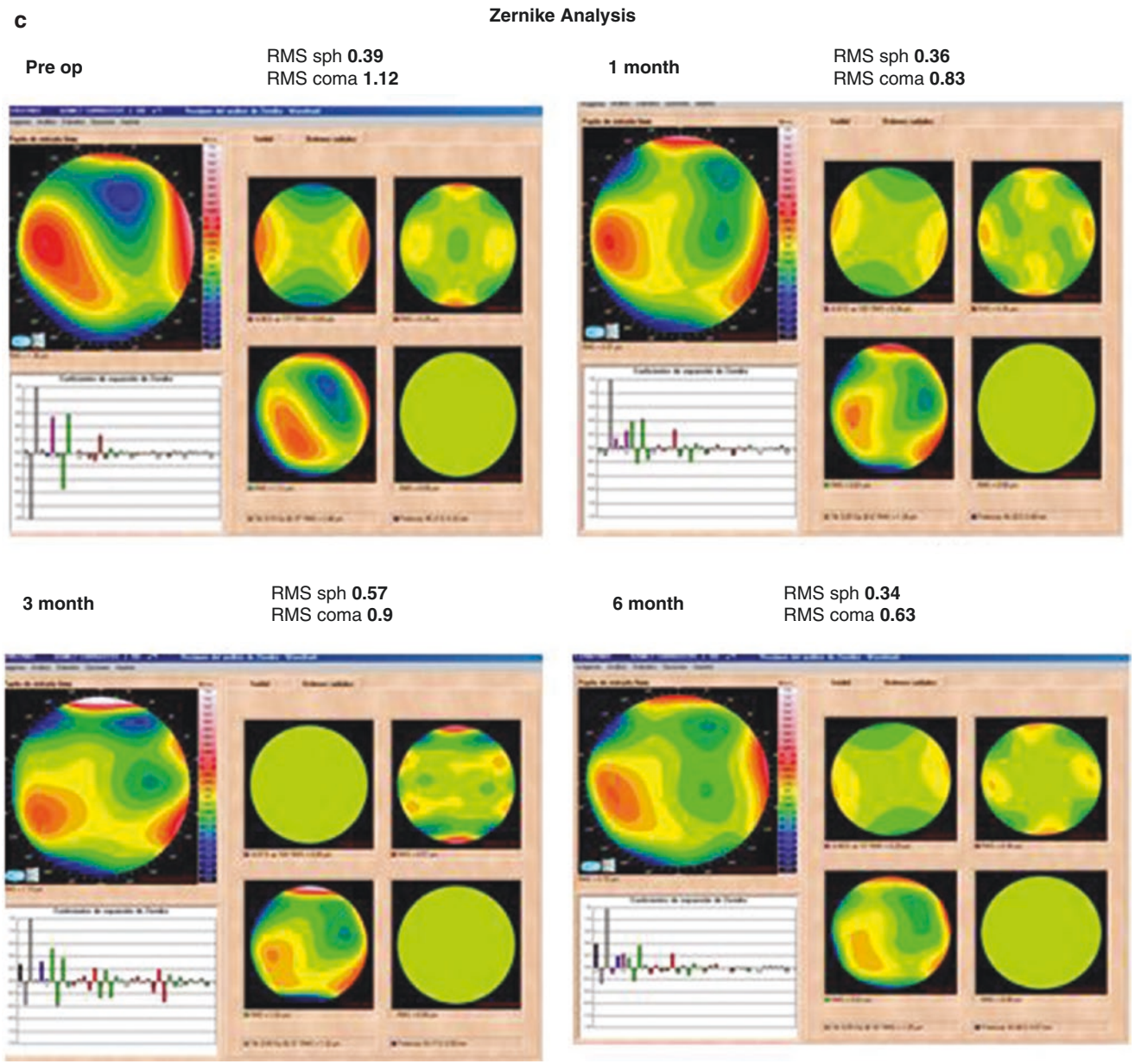

Fig. 23.6 (continued)

order to identify properly the anterior stromal surface irregularities and perform a stromal surface topography-guided procedure instead of a standard topography-guided ablation to target the stromal irregularity masked by epithelium [9–11]. They demonstrated that the epithelial thickness profile is highly irregular in such corneas, masking a significant proportion of the true stromal irregularity from front corneal surface topography. In this scenario, a topography-guided (or wavefront-guided) ablation may result in significant inaccuracies and may potentially worsen the irregularity.

23.5.3 Masking Solutions

The use of a viscous masking agent during the ablations of an irregular cornea aims to protect the valleys between the irregular corneal peaks, leaving these peaks of pathology exposed to laser treatment. Of the different masking agents that have been evaluated, methylcellulose is the most commonly used and is available in different concentrations. However, it turns white during ablation due to its low boiling point and thus was not ideal for treatment [19]. Other attempts to improve irregular astigmatism with a masking substance were made by Pallikaris et al., applying their PALM technique to smoothen the corneal surface [20]. However, this technique was abandoned due to its lack of reproducibility. Alió and coworkers described a new technique using sodium hyaluronate 0.25% as the masking solution, the so-called excimer laser assisted by sodium hyaluronate (ELASHY) [21]. The physical characteristics of sodium hyaluronate confer important rheological properties to the product, and the photoablation rate is similar

to that of corneal tissue, forming a stable and uniform coating on the surface of the eye, filling depressions on the cornea and effectively masking tissues to be protected against ablation by the laser pulses in PTK mode. They performed a prospective clinically controlled study performed on 50 eyes of 50 patients with induced irregular astigmatism. The safety index was equal to 1.1, and the efficacy index was 0.74. The ray-tracing parameters improved, and most of the patients (89.3%) subjectively noted improvement of the visual acuity and disappearance of the visual aberrations that previously impaired their quality of vision [21].

The clinical indications for this procedure include irregular astigmatism caused by irregularity in flap or in the stromal bed induced by laser in situ keratomileusis (LASIK).

23.5.4 Corneal Excision (Superficial Lamellar Keratectomy)

Corneal excision has been successfully used to eliminate superficial corneal irregularities following flap complications and severe decentrations. Automatic mechanical methods have been used for this purpose successfully [22]. Corneal excision can be safely performed leaving corneal thickness reduced up to 320 mm successfully without creating corneal ectasia [22]. Mechanical microkeratomes usually leave a rough surface that requires at least 30–40 microns of excimer laser ablation assisted by masking substances (ELASHY). Recently, the use of femtosecond laser technology may allow a more precise calculation of the excised corneal thickness with more successful outcomes. Up to this moment, there is no adequate knowledge about the limit of corneal thickness compatible with adequate recovery of best-corrected vision. All these cases will be left with a residual ametropia that should be corrected with a phakic IOL, usually a toric design. It is very advisable to complete the corneal excision with 30 microns of masking solution excimer laser ablation in PTK mode (ELASHY) as the smoothness of the corneal surface is increased. Superficial lamellar keratectomy or corneal incisions should be used as a last resource prior to corneal lamellar grafting.

23.5.5 Non-laser Corneal Surgery

23.5.5.1 Automated Anterior Lamellar Keratoplasty

This technique was originally designed to treat superficial stromal disorders, but it has also been used in the treatment of difficult cases of irregular astigmatism, with variable results [23]. The surgeon performs phototherapeutic keratectomy or a microkeratome or femtosecond laser lamellar resection to 250–400 μm stromal depth, followed by transplantation of a donor lamella of the same dimension and thickness on to the recipient bed. It is a good option for patients with thin corneas, and with the preservation of the Descemet's membrane, the complications of rejection should be minimized. Results seem to be better if lenticules are over 300 μm. Visual recovery is fast, occurring between 2 and 4 months. Sutures are removed during the third month, and astigmatism can be retreated with LASIK or better surface ablation techniques. Although complications are rare, some epithelial invasion has been observed with thin tissues that have been inadequately sutured.

23.5.5.2 Deep Anterior Lamellar Keratoplasty (DALK)

DALK is an alternative surgical technique in which the optically abnormal corneal tissue is substituted by a normal donor cornea, leaving untouched the corneal endothelium and Descemet's membrane (DM) of the recipient cornea. This allows a large decrease in the risk of immunological rejection [24]. An incomplete stromal dissection and the not fully baring of the DM create a wound healing surface and optical irregularities that have a negative impact in the visual outcomes [25].

Many of these patients still needed hard contact lens fitting to achieve 20/20 vision, so DALK is therefore reserved for those patients who suffer from post-refractive surgery irregular astigmatism that cannot be managed with other forms of treatment or from astigmatism combined with scarring, near or within the optical axis.

23.5.5.3 Penetrating Keratoplasty

Penetrating keratoplasty (PK) is the first option in the management of irregular astigmatism associated with full-thickness corneal opacities (including the DM and endothelium). The difficulty lies in deciding when a PK is the only solution, which may spare both the patient and the surgeon frustration and energy invested in ineffective attempts with milder techniques.

Take-Home Pearls

- Astigmatism is defined as irregular if the principal meridians are not 90° apart. This is usually because of an irregularity of the corneal curvature, which cannot be completely corrected with spherocylindrical lenses.
- The most common clinical symptoms of induced irregular astigmatism are decreased in best-corrected vision and visual distortion, together with night and/or day glare.
- Clinically, irregular astigmatism will present with a typical retinoscopy pattern, the most common being spinning and scissoring of the red reflex.
- The best analysis of post-refractive surgery-induced irregular astigmatism is by corneal wavefront aberrometers.

- Corneal wavefront-guided excimer laser surgery; superficial corneal excision either mechanical, femtosecond or controlled by masking solution; anterior lamellar corneal graft techniques; or penetrating keratoplasty can be used to solve moderate to severe cases of corneal irregularity.

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Part VI

Optic Nerve, Retinal and Binocular Vision

Optic Neuropathy and Retinal Complications After Refractive Surgery

24

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Core Messages

- It is important to adopt preventive measures for optic neuropathy after LASIK.
- Vitreoretinal stress is induced at the posterior vitreous base during a posterior vitreous detachment after LASIK.
- Macular diseases may be a relative contraindication to LASIK in:
  - Patients with high myopia and lacquer cracks.
  - Patients with angioid streaks and traumatic choroidal ruptures.
- Macular holes may develop in myopic eyes after LASIK or photorefractive keratectomy.
- LASIK may be associated with uveitis.
- LASIK may be a safe and efficient option for treating refractive errors in eyes with previous retinal detachment surgery.
- Cryopexy, laser retinopexy, pneumatic retinopexy or vitrectomy without a scleral band tend not to change the shape or length of the globe and should be preferred to repair rhegmatogenous retinal detachments (RRD).
- Prophylactic treatment of vitreoretinal pathology before LASIK does not guarantee the prevention of post-LASIK vitreoretinal complications.
- It is very important to inform patients that LASIK only corrects the refractive aspect of myopia and that vitreoretinal complications after LASIK although infrequent may occur.
- Reasons for poor VA after surgery for RRD after LASIK include delayed referral to a vitreoretinal specialist.

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24.1 Introduction

The prevalence of myopia in the United States ranges from 25% to 46.4% of the adult population [1–3]. In Asian populations, these proportions may be much higher and much lower in African and Pacific Islander groups. The global prevalence and severity of myopia have increased significantly in the past three decades and are primarily attributed to environmental factors with some contribution from genetic predisposition [3, 4]. The market for refractive surgery has a very high potential for people with low (less than −5.00 diopters (D)) and moderate myopia (−5.01 to −10.00 D), and most patients fall into one of these two groups [2].

Refractive surgery has become popular for correcting ametropias; however, this procedure may lead to complications. Hofman et al. [5], Sanders et al. [6], and Feldman et al. [7] have described cases of retinal detachment (RD) after radial keratotomy. Rodriguez and Camacho [8] reported 14 eyes (12 patients) which had either asymptomatic or symptomatic retinal breaks, subclinical and clinical rhegmatogenous RD, or both after corneal refractive surgery. Seven of these eyes had automated lamellar keratoplasty (ALK), and seven had radial keratotomy. Rodriguez et al. [9], Barraquer et al. [10], and Ripandelli et al. [11] have reported retinal detachments after clear lens extraction for myopia correction. Ruiz-Moreno and associates [12] reported the results of a clinically controlled study to investigate the rate of retinal detachment after implantation of phakic anterior chamber intraocular lenses. The implantation of a phakic anterior chamber intraocular lens, as a procedure for the correction of severe myopia, had a 4.8% incidence of retinal detachment.

Laser-assisted in situ keratomileusis (LASIK) has become one of the most popular options for the correction of low to moderate myopia worldwide [13–15]. However, complications including optic neuropathy [16], undercorrections and overcorrections [17], flap displacement [18], epithelial ingrowth [19], flap melting [20], keratitis [21], retinal tears [22], retinal detachments [23], retinal phlebitis [24], corneoscleral perforations [25], retinal hemorrhages

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[25], macular hemorrhages [15], macular holes [26], serous macular detachments [27], choroidal neovascular membranes [25], reactivation of ocular toxoplasmosis [28], and irregular astigmatism have been reported.

The objective of this chapter is to review optic neuropathy and retinal complications that may occur after refractive surgery with an emphasis on LASIK.

24.2 Optic Neuropathy After LASIK

24.2.1 History and Mechanism of Optic Nerve Damage

Most cases of anterior ischemic optic neuropathy (AION) are due to either arteriosclerosis or temporal arteritis. There is also a large variety of systemic, local, vascular, and ocular disorders that can lead to anterior ischemic optic neuropathy. The relationship between AION and LASIK was first reported by Lee et al. [29] with four cases of optic neuropathy and an onset of visual loss ranging from the day of surgery to 3 days after LASIK. Since that report, some studies have described the relationship between LASIK and the compromise of vascular supply of the posterior ciliary arteries such as in optic nerve ischemia (Fig. 24.1) [30], cilioretinal artery occlusion associated with ischemic optic neuropathy [31], appearance or progression of visual field defects in ocular hypertensive patients and normal tension glaucoma [16, 32], and choroidal infarcts [33].

Can all these conditions be explained by the same pathophysiologic principle? In 1975, Hayreh [34] explained in detail that partial occlusion of the posterior ciliary arteries due to any cause is responsible for the development of AION because they supply the lamina cribrosa, prelaminar,

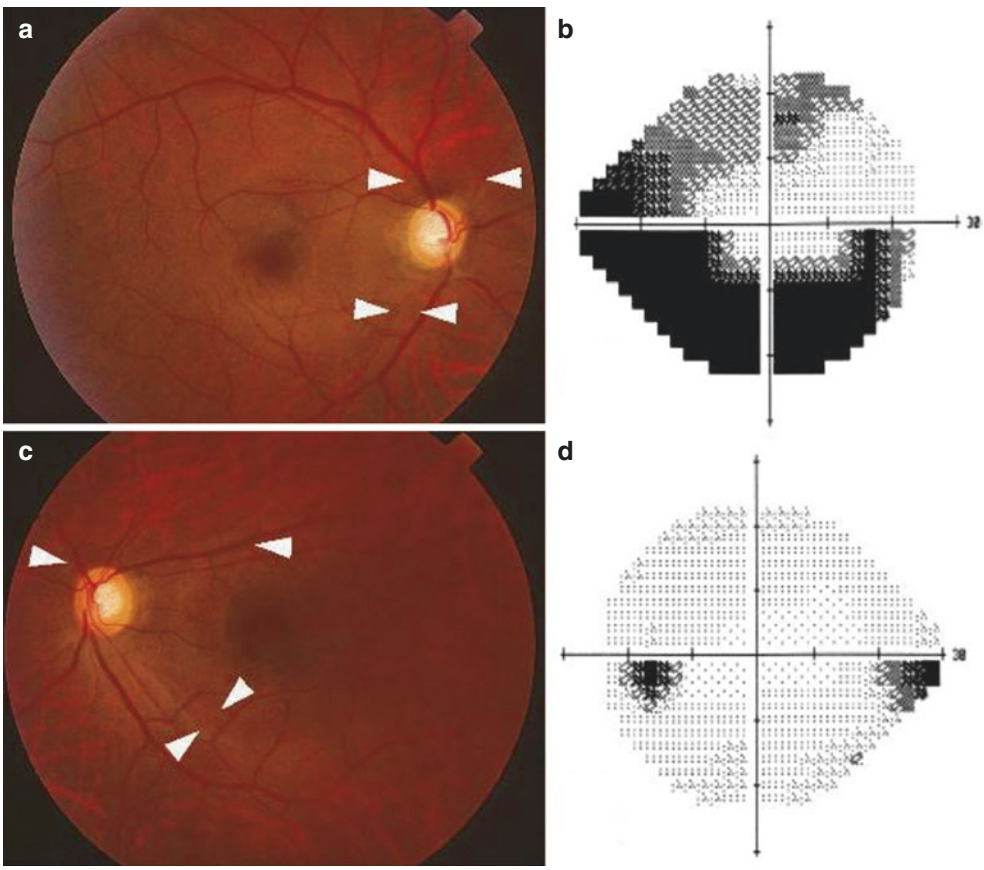

Fig. 24.1 A 39-year-old man had loss of vision on day 1 after bilateral LASIK. He described a hazy quality of vision in both eyes immediately after LASIK. His medical history had no other risk factors for optic neuropathy. Examination revealed a visual acuity of 20/20 in both eyes, normal color vision, increased cupping of the optic nerve, and a relative afferent pupillary defect in the right eye (RE). (**a**) Fifty-degree fundus photo of the RE shows diffuse loss of retinal nerve fiber layer (RNFL) at the superior pole of the disc and early wedge defects in the RNFL at the inferior pole of the disc (*arrows*). (**b**) Visual field shows a dense inferior nerve fiber bundle-type scotoma and a moderate superior nerve fiber bundle-type scotoma corresponding to the disc and RNFL defects in the RE. (**c**) Fifty-degree fundus photo of the left eye (LE) shows diffuse loss of RNFL at the superior pole of the disc and a wedge defect in the inferotemporal RNFL corresponding to the notch in the inferior neuroretinal rim (*arrows*). (**d**) Visual field shows an early inferior nerve fiber bundle-type scotoma corresponding to loss of superior RNFL in the LE (Modified and reprinted from Cameron et al. Laser in situ keratomileusis-induced optic neuropathy. Ophthalmology 2001;108:660–665, with permission from the American Academy of Ophthalmology)

and retrolaminar regions of the optic nerve. Anterior ischemic optic neuropathy, glaucoma, and low-tension glaucoma are manifestations of ischemia of the optic nerve head and retrolaminar optic nerve due to interference with posterior ciliary artery circulation as a result of an imbalance between the perfusion pressure of the posterior ciliary arteries and the intraocular pressure. If the process is sudden, it produces anterior ischemic neuropathy with infarction of the optic nerve head and retrolaminar region. If the process is chronic, as in high-tension glaucoma and low-tension glaucoma, it produces slow degeneration of neural tissue in the optic nerve head and retrobulbar region, resulting in cupping of the optic disc and cavernous degeneration of the retrolaminar optic nerve.

When imbalance is produced between perfusion and intraocular pressure, either by lowering perfusion pressure or raising intraocular pressure, the susceptibility of intraocular blood vessels to obliteration varies considerably. The optic disc circulation is the first to become compromised, then the peripapillary choroid, and finally the rest of the choroid. This explains the frequent presence of anterior ischemic optic neuropathy without a chorioretinal lesion. However, since a chorioretinal artery arises from a posterior ciliary artery, a cilioretinal artery occlusion may be associated with AION as described in the case reported by Ahmadieh and Javadi [31]. Finally, in AION, the visual fields defects can be extremely variable and mimic many ocular and neurologic conditions. In fact, nerve fiber bundle defects with an arcuate scotoma may be seen in AION and would simulate a glaucomatous defect as in the case reported by Weiss et al. [32] and Bushley et al. [16] after LASIK. Therefore, occlusion of the supply of one of the small subdivisions of the posterior ciliary arteries could involve a sector of the prelaminar, lamina cribosa, or retrolaminar regions of the optic nerve [34].

In LASIK, the creation of a corneal lamellar flap requires placement of a suction ring on the anterior segment of the eye, which transiently elevates the intraocular pressure (IOP) to levels exceeding 65 mmHg [35]. Experimental studies in animal eyes have found that the IOP can increase to between 80 mmHg and 230 mmHg during this vacuum phase with the microkeratome. Other studies have suggested that an even greater increase in IOP of 140–360 mmHg may occur during the lamellar cut itself [29]. Recent advances utilizing the femtosecond laser may serve as an alternative to the mechanical microkeratome, with a low-pressure suction ring. Femtosecond lasers emit short-duration pulses of 10^{-15} s, which produce precise intrastromal dissection using photodisruption, with minimal neighboring tissue damage [36]. In studies using porcine eyes, the IOP during the suctioning or laser application phase reached a maximum of 135 mmHg using the femtosecond laser, lower than pressures reached with a traditional microkeratome, but for a longer duration of time [36, 37]. In studies with human donor eyes, the IOP may reach up to 195 mmHg [38]. The use of femtosecond laser LASIK may be preferred in patients with risk factors for AION or glaucoma, although AION has been previously reported to occur in this context [39].

Intraocular pressure elevation during LASIK may cause a reduction in the perfusion of the retina and optic nerve head, posterior displacement of the lamina cribosa, and a decline in ocular perfusion pressure of the posterior ciliary arteries. Although this IOP elevation is temporary, the potential for ischemic or pressure-induced damage to the optic nerve head and the retinal nerve fiber layer exists [35]. Therefore, LASIK-induced damage to the optic nerve could be ischemic as a result of transient interruption of blood flow in the short posterior ciliary arteries when the IOP is greater than the arterial perfusion pressure. Although less probable, LASIK-related optic neuropathy could be due to barotrauma, with compression of the ganglion cells, nerve fiber layer, and lamina cribrosa. This would lead to posterior cupping of the optic nerve and damage to the nerve fibers, with resultant visual defect.

Chan and colleagues studied a group of patients with glaucoma and glaucoma suspect and induced transient elevation of intraocular pressure up to 67 mmHg for 30 s [40]. Pre- and post-procedure visual field testing did not demonstrate a statistically significant decline in mean deviation. Transient post-procedure decline in mean deviation with no change in pattern standard deviation was attributed to corneal superficial epitheliopathy [40]. This negative finding may be due to a moderate increase in intraocular pressure for a shorter duration, sensitivity of visual field testing, as well as a delayed effect of visual field loss in optic neuropathy. However, this study does reveal that even in patients with optic nerves susceptible to damage from high intraocular pressure, optic neuropathy is likely a relatively rare event post-LASIK.

In patients with risk factors for glaucoma, a full preoperative eye examination including baseline documentation of gonioscopy, axial length, IOP, status of optic nerve, and visual fields is particularly important [41]. Multiple imaging modalities of the optic nerve and retinal nerve fiber layer (RNFL) are available, including fundus photos, optical coherence tomography (OCT), scanning laser polarimetry RNFL analyzer, and Heidelberg retinal tomography (HRT) [41]. It is important to note that scanning laser polarimetry measurements of RNFL may be influenced by alterations in corneal architecture [42]. Measurements obtained with variable corneal compensation before surgery may be used for future comparisons [43].

24.2.2 Optic Neuropathy Risk Factors

Optic neuropathy after LASIK surgery is an extremely rare, while important, vision-threatening complication because the visual acuity and visual field loss may be permanent. Furthermore, ophthalmologists should be aware of the poten-

tial for an acute anterior or retrobulbar optic neuropathy following LASIK and should perform a comprehensive eye examination before and immediately after LASIK surgery to identify risk factors and promptly treat any complications.

Risk factors for ischemic optic neuropathy include personal and family history of glaucoma, previous optic neuropathy, severe cardiovascular disease such as hypertension or a tendency toward systemic arterial hypotension (congestive heart failure, myocardial ischemia, anesthesia, and surgical or nonsurgical shock), any tendency toward elevated intraocular pressure or glaucoma, and structural changes in the optic disc such as a structural small "disc at risk" and optic nerve head drusen. Finally, risk factors include systemic conditions such as diabetes, hyperlipidemia, and heterozygous factor V Leiden mutation [16, 29, 34, 44].

A rapid steroid response may occur post-LASIK, resulting in high intraocular pressure and fluid accumulation in the flap interface, known as pressure-induced stromal keratopathy (PISK) [45]. Applanation tonometry tends to underestimate IOP centrally, and peripheral measurements tend to be more accurate [45]. Glaucomatous field loss may occur if PISK is not recognized early and therefore can cause or worsen consequences of post-LASIK ischemic optic neuropathy [46–48].

Hayreh has suggested that nocturnal arterial hypotension is an important risk factor for the development and progression of nonarteritic anterior ischemic optic neuropathy (NA-AION). Potent antihypertensive drugs, when used aggressively and/or given at bedtime, are emerging as an important risk factor for nocturnal hypotension, and there is some evidence that NA-AION may be occurring iatrogenically in some individuals [49].

24.2.3 Clinical Findings

At the onset of optic neuropathy after LASIK, the patient can present postoperatively with a decline in visual acuity and color vision, relative afferent pupillary defect, variable swelling of the disc, and optic nerve-related visual field defects. Deep cupping of the optic nerve, focal changes in the neuroretinal rim, and decreased thickness of the retinal nerve fiber layer can be seen as soon as 6 weeks to 2 or 3 months after the onset of AION [29, 30, 34].

24.2.4 Management

There are no proven effective treatments for AION, and options are considered controversial. Steroid treatment for the nonarteritic type of AION has been proposed. A number of reports suggest that systemic corticosteroids given during the very early stages of the disease may help to improve visual function in some patients [50, 51]. Hayreh has found definite evidence of a significant visual improvement with steroids in a small group of patients, particularly those with incipient nonarteritic AION when treated early [34, 50, 51].

Surgical treatment including optic nerve fenestration was advocated for AION until the completion of the ischemic optic neuropathy decompression trial (IONDT). This study conclusively showed no beneficial effect of the surgical procedure [52]. Optic neurotomy has been used for nonarteritic AION [53]. In this procedure, a radial cut is made through the entire thickness of the optic nerve head. This procedure not only cuts thousands of nerve fibers in the optic nerve head but also severs the blood vessels supplying it—both of which likely lead to more loss of vision without any beneficial effect [49].

24.2.5 Prevention

Due to the lack of an effective treatment for this condition, it is extremely important to adopt preventive measures. Prevention should include:

1. Avoiding any sudden decline in systemic arterial blood pressure (hypotensive anesthesia, congestive heart failure)
2. Improving systemic circulatory hemodynamics by medical therapy
3. Preventing any sudden rise in intraocular pressure (angle closure and intraocular surgery such as cataract extraction)
4. Keeping intraocular pressure as low as possible with topical medical therapy [19, 34, 50, 54]

Patients with personal or family history of AION, systemic diseases or ophthalmic risks such as a small optic nerve, glaucoma, and a family history of glaucoma, as well as glaucoma suspects, should be counseled about the possibility of LASIK-associated visual field loss prior to the procedure. For many of these patients, photorefractive keratectomy, intrastromal corneal ring segments, or continued use of contact lens or eyeglasses may offer satisfactory vision without subjecting the optic nerve to the small but real risk of pressure-associated visual field loss [32].

24.2.6 Retinal Detachments and Retinal Breaks

A number of studies have been reported in the literature regarding retinal detachments after LASIK [22, 55, 56]. Ozdamar et al. reported a case of bilateral retinal detachment associated with giant retinal tear after LASIK [55]. Stulting

and associates reported a case of rhegmatogenous retinal detachment after LASIK for the correction of myopia [56]. Faghihi et al. reported an incidence of 0.082% [57], while Ruiz-Moreno and coworkers reported an incidence of 0.25% in myopic eyes after LASIK and a mean best-corrected visual acuity of 20/45 after retinal surgery [23]. Aras et al. described ten retinal detachments (an incidence of 0.22%) in myopic eyes after LASIK [58]. Farah and colleagues reported four eyes that had early rhegmatogenous retinal detachment within 3 months of LASIK for correction of high myopia [59]. One case report details the development of an inferior retinal detachment due to two inferior horseshoe tears diagnosed 14 hours post-LASIK surgery in a patient with −13 D myopia [60].

No cause-effect relationship between LASIK and retinal detachment can be stated from these studies, LASIK may be associated with retinal detachment, particularly in highly myopic eyes. In myopic eyes, the yearly incidence of retinal detachment has been estimated to range from 0.015% to 0.075% and thought to be related to premature vitreous liquefaction and earlier posterior vitreous detachment [61].

We have previously reported a 2-year study of 29,916 eyes after LASIK for the correction of ametropias (myopia and hyperopia). The incidence at 24 months of vitreoretinal pathology in our study was 0.06%, including 14 rhegmatogenous retinal detachments (RRD) (Fig. 24.2) [25]. The incidence of RRD after LASIK in our previous studies ranges between 0.04% and 0.05% [62].

In our 10-year follow-up study of a total of 11,594 patients, 22 eyes (19 patients) developed an RRD after LASIK [63]. Patients underwent surgical correction of myopia from −1.50 to −10.00 D (mean −4.50D). RRD occurred between 1 month and 13 years (mean 31.6 months) after LASIK, with an increasing frequency and longer follow-up intervals. The frequency of RRD was 0.05% at 1 year and 0.15% at 5 years and increased to 0.19% at 10 years [63]. Patients were scheduled to be seen on the first postoperative day, at 3 months, at 12 months, and yearly thereafter. The clinical findings, frequency of RRD after LASIK, characteristics (evaluations of fundus drawings), and surgical outcomes of 22 eyes are presented. Preoperative examinations included a very thorough dilated fundoscopy with scleral depression and treatment of any retinal lesion predisposing to the development of an RRD.

Our 19 patients had an average age of 41.8 (22–70), and 12 (54.5%) were male. In our series, 1.5% required treatment of predisposing retinal lesion before LASIK, but no patients that developed an RRD after LASIK had previous prophylactic treatment of peripheral retinal lesions. No patient had a history of any other ocular surgery after LASIK. Retinal detachments were managed with vitrectomy, cryoretinopexy, scleral buckling, argon laser retinopexy, and pneumatic retinopexy. Vitreoretinal surgery to repair RRD after LASIK was performed at a mean of 34.8 days and 56 days (range, 7 days to 3 months) after the onset of visual symptoms. The mean follow-up after retinal surgery was 8.7 years (range, 1 month to 12 years).

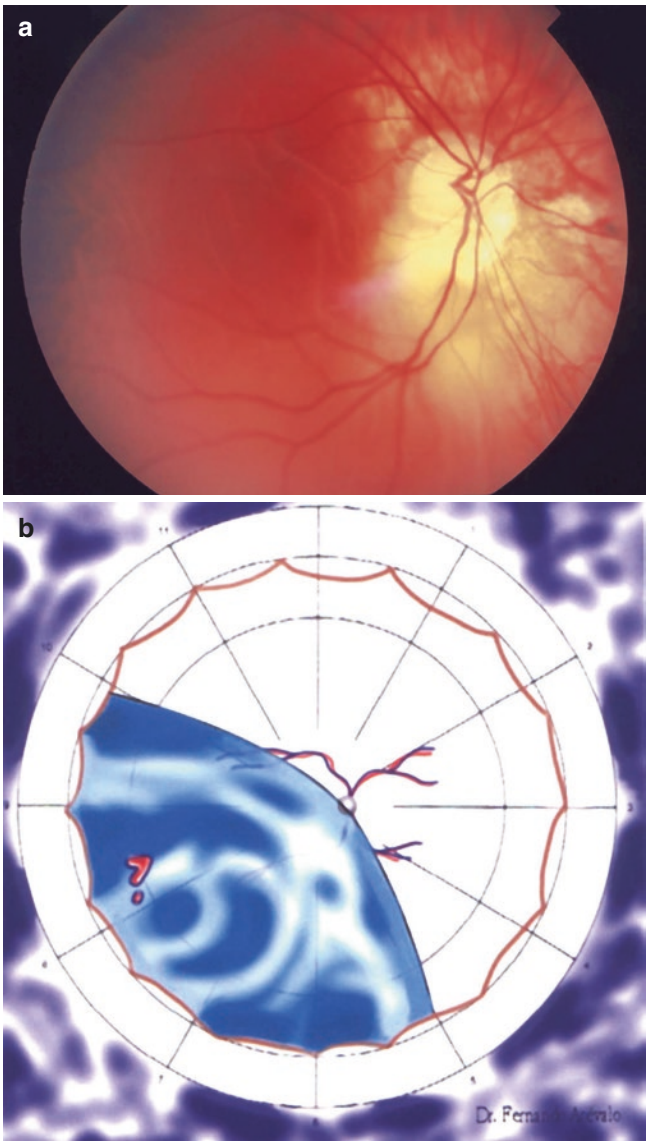

Fig. 24.2 (**a**) Fundus photograph of a subtotal inferotemporal retinal detachment (macula-off) after laser in situ keratomileusis. (**b**) Retinal drawing of the same case with partial posterior vitreous detachment, a horseshoe retinal tear at 8 o'clock, and a retinal hole at the same location

Final best-corrected visual acuity (BCVA) after surgery improved two or more lines in 57.1% of eyes. Poor VA (20/200 or worse) occurred in 31.8% of eyes. Reasons for poor VA included epiretinal membrane, myopic maculopathy, development of proliferative vitreoretinopathy, and optic atrophy. Anatomical success with one surgery was 100%.

Ruiz and Alio et al. studied the incidence of retinal disease observed in 9239 consecutive eyes (5099 patients) after

refractive surgery (including LASIK) [64]. Retinal detachment occurred at a mean of 24.6 ± 20.4 months after LASIK in 11 eyes (0.36%).

24.2.7 Retinal Detachment Characteristics and Retinal Breaks Distribution

Fundus drawings of the 22 eyes from our 10-year follow-up study were evaluated (Fig. 24.2b) [63]. Two detachments were total, and 20 were subtotal. Of the 20 subtotal RRD, 11 were macula-off RRD and 9 were macula-on RRD. Of the 20 subtotal RRD, 11 involved predominantly inferior quadrants and 9 were predominantly superior RRD. An RRD involved more than one quadrant in 15 out of 20 subtotal RRD. The inferotemporal quadrant was involved in 11 of the subtotal RRD, the inferonasal quadrant in 6, the superotemporal in 6, and the supero-nasal in 5. The mean number of retinal breaks per RRD was 3 (range, 1–9), including 43 holes, 22 horseshoe tears, and 1 retinal dialysis. Forty-eight (71.6%) retinal breaks were located temporally (31 inferotemporal), and nineteen (28.4%) were located nasally (10 inferonasal). Vitreous status was available from 11 of our cases: 7 (63.6%) had posterior vitreous detachment (PVD) and 4 (36.4%) had no PVD. Only two (9%) of our RRD cases had a retinal break associated with lattice degeneration. Four (18%) of our cases had proliferative vitreoretinopathy (PVR) grade C (Fig. 24.3). The distribution of retinal detachments and locations of retinal breaks are comparable to the data from the 24-month study [25].

The long interval between the onset of symptoms and RRD surgery may be responsible for some of the factors (including an 18% rate of PVR) that contributed to poor final VA in more than 30% of our cases. In some of our patients, there may have been some delay in the referral to the vitreoretinal specialist due to a belief that the visual symptoms were related to refractive or corneal problems after LASIK. In addition, other factors related to high myopia (including myopic degeneration and amblyopia) might also influence the final functional results regardless of our high anatomical success rate.

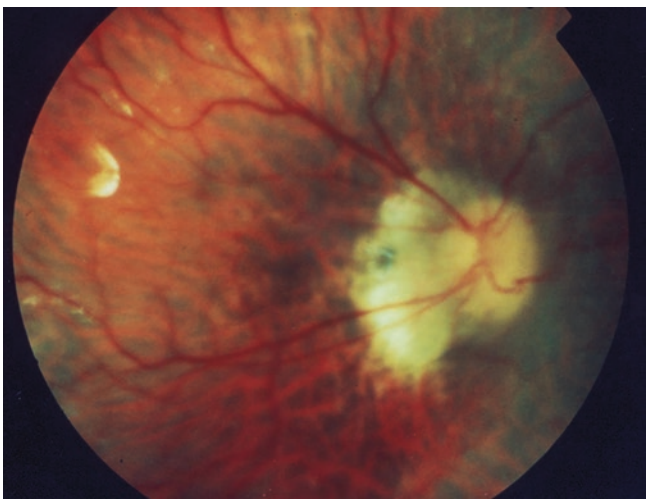

Fig. 24.3 Postoperative fundus photograph of a myopic eye that developed a rhegmatogenous retinal detachment with proliferative vitreoretinopathy (PVR) after laser in situ keratomileusis. Vitrectomy and silicone oil injection were successfully performed

Chan and coworkers [65] described the characteristics of a large number of eyes (60) with substantial myopia (mean myopia, −9.5 ± 5.8 D) with pre-LASIK retinal examinations and characteristics of post-LASIK retinal breaks and RRD. Fourteen eyes had documented lattice degeneration or small retinal breaks. Many of those eyes developed complex vitreoretinal complications (53.3% with 2 or more breaks, 26.7% eyes with 3 or more breaks, 30% with bilateral conditions, 8.3% with total RD, 8.3% with PVR, 6.7% with giant tears, and 5.0% with extensive retinal dialysis). Forty percent developed vitreoretinal complications within 6 months after LASIK. Distributions of retinal breaks in this study are comparable to those found in similar myopic eyes in young adults who have not had LASIK.

The authors concluded that in this study, retinal breaks, tears, and holes were distributed relatively evenly between the superior and inferior quadrants. The reason for this even distribution is unknown, but vitreoretinal stress induced at the posterior vitreous base during a posterior vitreous detachment will more likely lead to retinal breaks and RD in the temporal rather than in the nasal quadrants.

Several recent studies propose that the highest risk factor for the development of retinal detachment in myopic patients is the degree of myopia and earlier posterior vitreous detachment, not necessarily related to the refractive surgery procedure. A recent study from Kang and colleagues [66] compared retinal detachments in patients post-LASIK [57], patients post-laser-assisted subepithelial keratomileusis (LASEK, [67]), and myopic patients with no previous refractive surgery [64]. In particular, LASEK does not require the use of a suction ring. Comparison of characteristics between these eyes was not significantly different except that in eyes with RD after LASIK, and in those without a history of refractive surgery, there were more retinal holes per eye than in those with prior LASEK. In all groups, retinal holes and breaks were located predominantly temporally. A study from Singapore by Lee and coworkers [68] reported 10 cases of retinal detachment out of 12,760 eyes post-LASIK and photorefractive keratectomy. In their series, patients with retinal detachment were on average 11 years older than those with no retinal detachment and had a preoperative higher degree of myopia. The authors believe that RD is part of the natural history of myopia and that older high myopes intrinsically have a higher risk for PVD and subsequent RD.

24.2.8 Serous Macular Detachment

Singhvi et al. [27] reported a case of bilateral serous macular detachment after LASIK. They conclude that the possible mechanism of occurrence of central serous chorioretinopathy (CSCR) following LASIK includes the generation of shock waves due to the mechanical force of suction of the microkeratome ring, leading to alterations in the fragile submacular vessels or the RPE. Preexisting macular pathology, such as RPE atrophy, could be a contraindication to LASIK for hypermetropia with possible development of CSCR.

24.2.9 Macular Hemorrhage, Lacquer Cracks, and Choroidal Neovascular Membranes

Kim and Jung [69] reported one eye that lost greater than two lines of preoperative best-corrected vision due to macular hemorrhage. Luna et al. [70] have reported a case of bilateral macular hemorrhage after LASIK. One day after surgery, the patient's uncorrected visual acuity was in the 20/50 range, and by 17 days after surgery, his visual acuity had declined to the 20/200 range. Fundus examination showed multifocal subretinal macular and posterior pole hemorrhages. Fluorescein angiography showed some macular lesions compatible with lacquer cracks. Principe et al. [71] reported the first case of unilateral macular hemorrhage following uncomplicated, bilateral, simultaneous LASIK with femtosecond laser flap creation in a patient without macular pathology.

In conclusion, macular hemorrhage may occur after LASIK, even in the absence of previously identified risk factors, such as high myopia, preexisting CNV, lacquer cracks, and sudden changes in intraocular pressure associated with microkeratome-assisted flap creation.

To date, 28 eyes of 27 patients with choroidal neovascular membrane (CNV) following LASIK have been reported in the literature [72]. We were the first to describe the occurrence of CNV after LASIK [22]. A 48-year-old Hispanic hyperopic (+3.50 D OD and +4.00 D OS) man was seen at our institution because of visual loss OS 2 years after a LASIK procedure. On examination, visual acuity was 20/400, and biomicroscopy was unremarkable. Dilated fundoscopy and fluorescein angiography showed a juxtafoveal CNVM with subretinal fluid. A pars plana vitrectomy and a temporal retinotomy were performed to remove the CNVM from the subretinal space, and air was instilled into the vitreous cavity. Topical steroids and cycloplegics were prescribed. Eight months later, his visual acuity OS was counting fingers, and fundoscopy showed a juxtafoveal retinal pigment epithelium defect.

Ruiz and Alio et al. [73, 74] have reported an incidence of 0.1% CNV after LASIK and one case after photorefractive keratectomy (1/5936). Saeed et al. [75] reported one case of CNV after LASIK in a patient with low myopia. The incidence seems to be very low; however, the appearance and treatment of CNV were followed by a significant decrease of visual acuity.

Recently Maturi et al. [76] and others [77] have reported characteristics and potential mechanisms of a macular lacquer crack (one with subsequent development of subfoveal CNV) in myopic patients corrected by LASIK. Lacquer cracks often lead to poor visual outcomes because of CNV and macular atrophy in pathologic myopia. The risk of developing lacquer cracks in highly myopic patients corrected by LASIK, though uncommon, must be kept in mind.

Scupola et al. [78] and Arevalo et al. [79] have reported success in stabilizing or improving vision in patients with subfoveal CNV from pathologic myopia after LASIK with photodynamic therapy (PDT) with verteporfin. Scupola et al. [78] reported a case of CNV after LASIK following penetrating keratoplasty (PK). Photodynamic therapy was performed, and 1 year later, VA was stable at 20/200. Arevalo et al. [79] reported the management of subfoveal CNV in highly myopic eyes after LASIK with PDT. Five cases of CNV after LASIK for the correction of myopia (mean, 13.3 D; range, −8.00 D to −16.25 D) treated with single or multiple sessions of PDT with verteporfin were presented (Fig. 24.4). Two cases had improved visual acuity (VA) (2–5 lines) after PDT, two cases remained stable, and one case lost four lines of VA. Visual acuity improved or remained the same in 80% of cases (4/5 eyes). Photodynamic therapy with verteporfin seems to increase the chance of stabilizing or improving vision in patients with subfoveal CNV after LASIK in high myopes at least with a short period of follow-up (mean, 9.4 months; range, 3–13 months).

Recently, Neo et al. reported three cases of CNV post-LASIK for myopia which were treated with a combination of intravitreal anti-vascular endothelial growth factor (anti-VEGF) and PDT with verteporfin [72]. The time from LASIK to development of CNV varied from 1 to 18 weeks, and all three patients had classic CNV as documented on fluorescein angiography. One of the patients had laser photocoagulation for juxtafoveal CNV 10 years earlier and had a development of new extrafoveal CNV at the edge of the photocoagulation scar, whereas the other two did not have a history of CNV. Patients received one to three intravitreal injections of ranibizumab as well as one to two sessions of PDT until resolution of CNV. Final visual acuity ranged from 0 to 0.3 (equivalent to 20/20 to 20/40). Currently, anti-VEGF monotherapy would be the treatment of choice.

Choroidal neovascularization is related to myopia itself, and its incidence varies from 4 to 11% in patients with high myopia. In addition, lacquer cracks have been found to be associated to CNV in up to 82% of cases with myopia [77]. Theoretically, when a break in Bruch's membrane occurs, it allows the progression of the neovascular complex under the

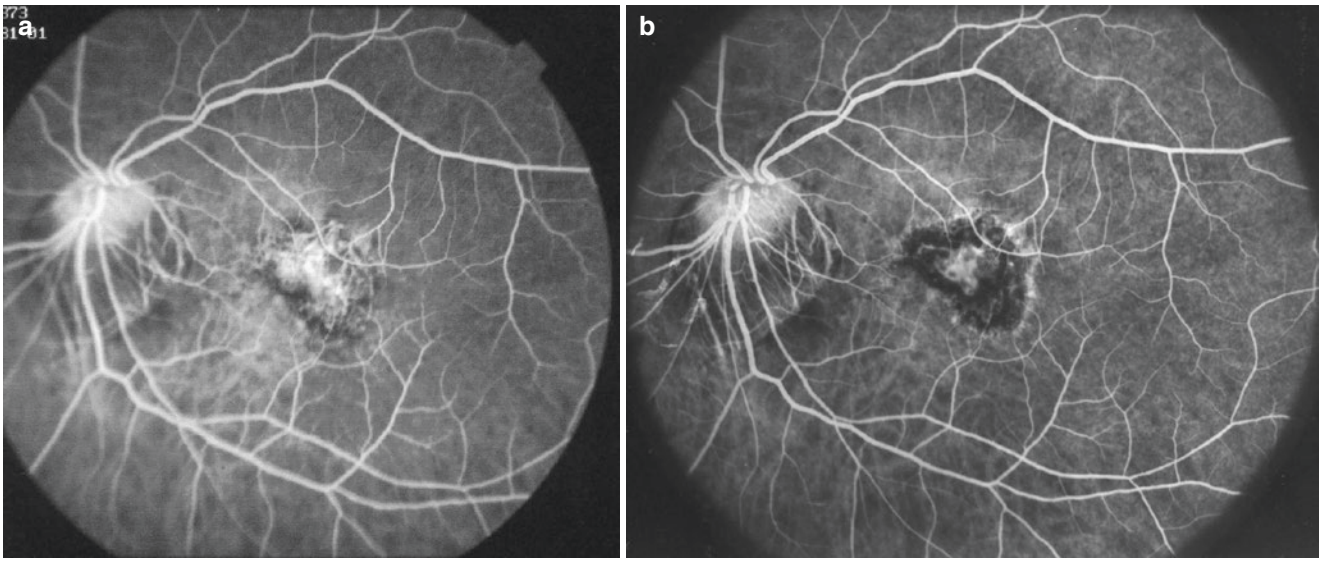

Fig. 24.4 (**a**) A subfoveal choroidal neovascular membrane (CNV) after laser-assisted in situ keratomileusis was diagnosed with fluorescein angiography (FA). (**b**) The CNV was treated with two sessions of photodynamic therapy (PDT) with verteporfin 6 months apart. After her last PDT treatment, the CNV was totally closed with a small central area of staining and no leakage on FA

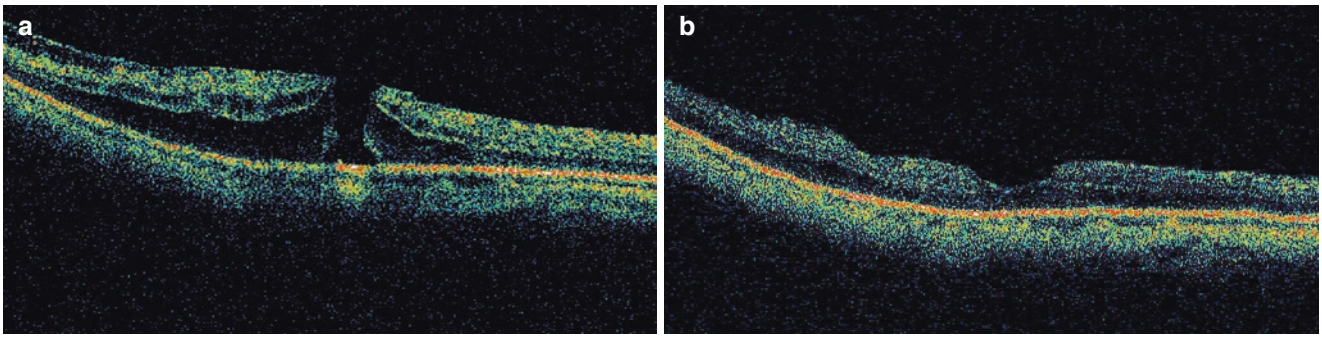

Fig. 24.5 (**a**) Optical coherence tomography (OCT) showed a full-thickness hole with significant surrounding retinal edema and cystic changes. The diameter of the hole measured directly from the OCT was 390 μ. (**b**) OCT after a vitrectomy performed 1 week after examination closed the macular hole

retina. The increase in intraocular pressure (IOP) to levels over 60 mmHg during suction with the microkeratome suction ring up to 4 mm posterior to the limbus may exert traction and compression posteriorly. In addition, we have to consider that the excimer laser generates a shock wave that is transmitted to the eye. These mechanisms may increase the gap in Bruch's membrane further if there is already a lacquer crack. We believe that in patients with high myopia and lacquer cracks, LASIK should be considered contraindicated and an alternative method of refractive surgery offered.

24.2.10 Macular Hole

Chan and Lawrence [26] have recently reported three eyes of three myopic patients that developed a macular hole in one eye after bilateral laser in situ keratomileusis or photorefractive keratectomy. The macular hole formed between 4 and 7 weeks after LASIK in case 1 (a 48-year-old woman) and within 2 months after LASIK in case 2 (a 36-year-old woman). In case 3 (a 45-year-old man), the macular hole was found 9 months after photorefractive keratectomy. A vitrectomy closed the macular hole of case 1 with final best-corrected visual acuity of 20/25 and case 2 with 20/30, whereas case 3 declined further surgery. The authors conclude that macular hole may develop in myopic eyes after laser in situ keratomileusis or photorefractive keratectomy and that vitreoretinal interface changes may play a role. Ruiz-Moreno et al. [80] and Bikbova et al. [67] each reported a case of macular hole formation after LASIK. Garcia-Fernandez reported a case of bilateral macular hole occurring 10 years after LASIK [81].

Our group [82] reported 20 eyes (19 patients) that developed a macular hole in one eye after bilateral LASIK for the correction of ametropia (Fig. 24.5). The macular hole formed

between 1 and 83 months after LASIK (mean, 12.1 months). Eighteen percent of patients were female, age range was 25–65, and all eyes were myopic. Posterior vitreous detachment was not present before and was documented after LASIK on 55% of eyes. A vitrectomy closed the macular hole in all 14 eyes that underwent surgical management. These 20 eyes reflect an incidence of 0.02% (20/83938) and represent the largest series of macular hole after LASIK to date.

How could the excimer laser, or the microkeratome, cause a macular hole? What is the pathophysiology? The suction ring induces a sustained increase in IOP, and then it is suddenly released. The anterior segment is rapidly drawn into a vacuum chamber associated with a rapid change in its shape. All structures posterior to the suction ring are also compressed and decompressed in sequence. This type of "trauma" is in some ways analogous to what happens in a closed eye injury. A mechanism for the development of peripheral retinal tears or macular disease could be anterior-posterior compression and expansion. The eye elongates along the anterior-posterior axis, and the diameter of the globe may increase. At the same time, because the eye is a closed system, the eye is constricted in the equatorial plane (Fig. 24.6a). As the anterior segment is drawn into a vacuum, the lens may be displaced forward along with the anterior hyaloid. This might accelerate vitreous detachment or cause traction at the vitreous base. When the suction is suddenly released, decompression leads to a dynamic overshoot with equatorial expansion and shortening in the anterior-posterior dimension (Fig. 24.6b). These events may cause acute vitreoretinal traction at the vitreous base and posterior pole.

In addition, when the excimer laser light ablates tissue, energy is released anteriorly as a plume of ablated tissue and is thrown into the air in front of the cornea. Certainly, such a powerful force may also be associated with backward force into the vitreous. Posteriorly, energy is transmitted in the form of a shock wave (Fig. 24.6c). The effect of shock waves and posteriorly radiated energy on the integrity of the vitreous is unknown.

24.2.11 Uveitis

Anterior uveitis after LASIK for the correction of ametropia is infrequent, with an incidence of 0.18% or an annual incidence of 0.06% (60 per 100,000 eyes) according to data reported by Suarez et al. [83]. This number is much higher than the annual incidence of anterior uveitis in the general population (0.008% or 8 cases per 100,000 population). The authors postulated that uveitis may be due to uveal trauma during surgery with disruption of normal anterior chamber-associated immune deviation, decreased anti-inflammatory cytokines, and increased proinflammatory cytokines.

Rarely, anterior uveitis post-LASIK can be severe, involving fibrinous exudates in the anterior chamber [84]. Treatment with intensive topical and oral steroids led to resolution of the inflammation within 2 weeks. A second case report described a patient known for ulcerative colitis and positive human leukocyte antigen (HLA)-B27, developing unilateral hypopyon uveitis 15 days after bilateral LASIK [85]. This patient's uveitis also resolved with aggressive topical and

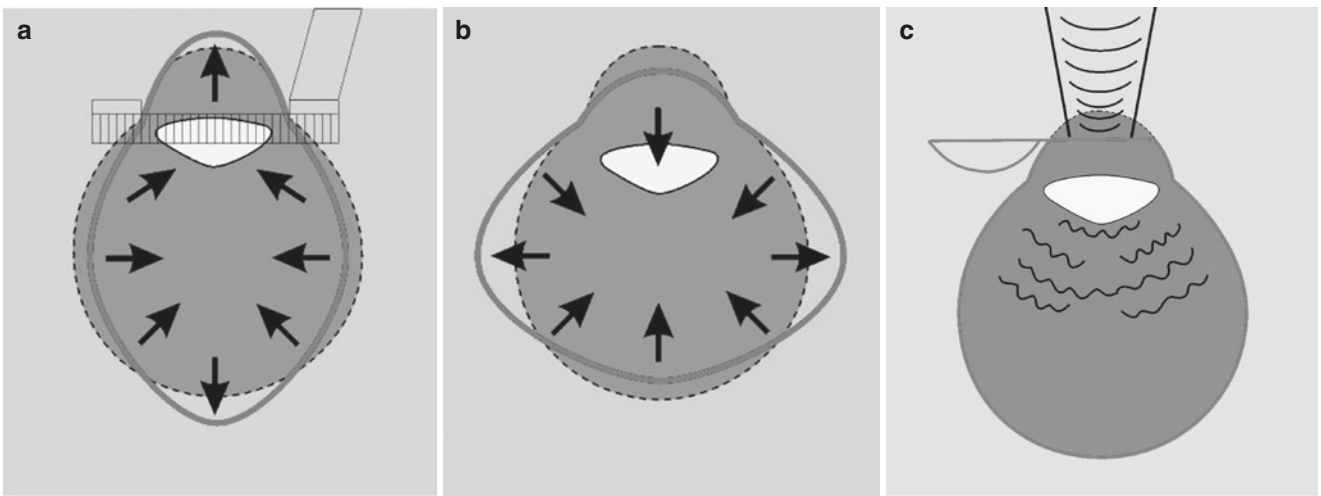

Fig. 24.6 The following changes may cause acute vitreoretinal traction at the vitreous base and posterior pole. (**a**) When the suction ring is in place, the eye deforms along the anterior-posterior axis, and the diameter of the globe may increase. At the same time, because the eye is a closed system, the eye must contract along the horizontal axis, and equatorial diameter may decrease. (**b**) When the suction stops and the suction ring is released, decompression leads to a dynamic overshoot with equatorial elongation and anterior-posterior contraction. (**c**) In addition, the excimer laser-induced shock wave may play a role in the development of posterior vitreous detachment (Reprinted from Arevalo et al. Rhegmatogenous retinal detachment in myopic eyes after laser in situ keratomileusis. Frequency, characteristics, and mechanism. J Cataract Refract Surg 2001;27:674–80, with permission from ASCRS & ESCRS)

oral steroid agents, with concomitant topical antibiotic coverage. Moshirfar and colleagues [86] assessed the incidence of acute anterior uveitis in 46 eyes (23 HLA-B27-positive patients) who had LASIK (0.200 per eye-year) vs. those who did not have LASIK (0.246 per eye-year), which was not statistically significant. A previous episode of uveitis did not appear to increase risk of uveitis after LASIK [86].

Lin and Tsai [24] reported a case of retinal phlebitis with cystoid macular edema in both eyes 8 weeks after LASIK. Their patient experienced blurred vision and demonstrated focal whitish patches in the parafoveal and juxtafoveal areas and lack of foveal reflex in both eyes. Visual acuity returned to normal, and the whitish fundus patches decreased in number and size in both eyes after the patient was treated with oral corticosteroids. They believed that the shock waves induced from LASIK may cause mechanical stress to the retina, resulting in structural damage and intraocular inflammation.

Barbara et al. [28] have reported a case of reactivation of ocular toxoplasmosis in a patient who underwent bilateral LASIK. The posterior segment examination revealed an old toxoplasmosis scar in the retinal periphery of the right eye. Uncorrected visual acuity improved postoperatively, and the patient was satisfied. However, 52 days after the procedure, he complained of loss of visual acuity in his right eye. Examination revealed signs of anterior uveitis, vitritis, and active chorioretinal lesion satellite of the old toxoplasmosis scar. The patient was treated with a multidrug regimen with resolution of the vitreous and lesion activity. The authors conclude that toxoplasmosis reactivation may develop after LASIK.

In eyes with uveitis, LASIK should be performed when the inflammation is quiescent to avoid severe postoperative inflammation. However, patients and clinicians should be aware of possible signs and symptoms of intraocular inflammation after LASIK [83].

24.2.12 LASIK After Retinal Detachment Surgery

Belda et al. [87], Sforza and Saffra [88], Sinha et al. [89], and Favardin et al. [90] have described a total of 23 patients with a previously placed encircling scleral buckle for a retinal detachment who had LASIK to correct myopia. In all patients, the uncorrected VA improved and the myopic spherical equivalent decreased after the procedure. However, scarred conjunctiva in some cases (8.7%, 2/23) may prevent generation of optimal suction for the microkeratome.

Holopainen et al. [91] followed ten patients with one or more surgeries for retinal detachment followed by PRK or LASIK for anisometropia post-scleral buckle for a mean of 67 months after refractive surgery. Adequate suction was obtained in all patients to create the LASIK flap, and 60% achieved refraction within 1D of the intended correction.

Barequet et al. [17] evaluated the safety and efficacy of LASIK for correction of myopia in nine eyes with previous retinal detachment surgery. LASIK was performed in 130 ± 123 months following retinal detachment surgery. The postoperative LASIK follow-up was 14.8 ± 12.5 months. No significant intraoperative, postoperative, or retinal complications were observed. The mean preoperative spherical equivalent refraction was −9.00 ± 3.00 D, uncorrected visual acuity (UCVA) was 0.06 ± 0.02, and best spectacle-corrected visual acuity (BSCVA) was 0.64 ± 0.16. At the end of follow-up, the mean spherical equivalent refraction was 0.65 ± 0.88 D, mean UCVA was 0.57 ± 0.14, and mean BSCVA was 0.72 ± 0.19. Therefore, LASIK was found to be a safe and efficient option for treating refractive errors in eyes with previous retinal detachment surgery.

24.2.13 Corneoscleral Perforations

In our series [25], two eyes suffered corneoscleral perforations with the surgical microkeratome when a corneal flap was being performed: one of them developed a vitreous hemorrhage and the other later developed a retinal detachment.

A 24-year-old Hispanic myopic (−5.00 D OD and −4.25 D OS) woman was seen at our institution because of visual loss OD immediately following a LASIK procedure. According to the refractive surgeon, he had omitted to place a spacing plate into the microkeratome when a corneal flap was being performed. An ocular perforation occurred with corneal and iris wounds, loss of the crystalline lens, vitreous loss, and the development of vitreous hemorrhage. A thorough anterior vitrectomy was performed with primary repair of the corneal wounds with 10-0 nylon. Oral and topical steroids were prescribed. Thirteen months later, her best-corrected visual acuity with a contact lens was 20/25-1.

In our second case, a 38-year-old Hispanic myopic (−20.00 D OD and −15.00 D OS) woman was seen at our institution because of visual loss OS following a LASIK procedure. According to the refractive surgeon, a corneal perforation had occurred with the microkeratome when a corneal flap was being performed. She had undergone crystalline lens remnants aspiration and an anterior vitrectomy 1 week later. On examination, a sutured (10-0 nylon) corneal wound with Descemet folds is seen on biomicroscopy. Dilated fundoscopy does not show details of the retina due to media opacities. Diagnostic B-scan ultrasound shows an inferior retinal detachment. A vitrectomy is performed with a 360° circumferential scleral band, endolaser, and SF_6. Topical steroids and cycloplegics were prescribed. Three months later, she developed a retinal tear in the fellow eye (also treated with LASIK), which was managed with an argon laser reti-

nopexy. Six months later, her visual acuity OS was hand motions due to corneal scarring and a recurrent inferior rhegmatogenous retinal detachment.

Some cases of laser in situ keratomileusis (LASIK)-induced corneal perforation have been treated by applying a therapeutic soft contact lens with topical antibiotics, oral carbonic anhydrase inhibitors, and eye patching. However, we believe that it is important to mention that LASIK-induced corneal perforations can be very severe and sutures may be necessary. In addition, severe cases may be associated to posterior segment damage as demonstrated in our report [25]. The incidence of vitreoretinal complications (vitreous hemorrhage and retinal detachment after corneoscleral perforations) during LASIK determined in our study is 0.006% (2/29,916).

We recommend that refractive surgeons be meticulous in properly assembling the microkeratome to create a corneal flap during LASIK. The use of currently available disposable microkeratomes may help to avoid this complication in the future.

24.2.14 Displacement of Corneal Cap During Vitrectomy

In one of our cases, a dislocated corneal flap occurred from corneal epithelial debridement during vitrectomy 69 months after LASIK. A similar case has been previously reported by Chaudhry and Smiddy [92], which underwent vitreous surgery only 4 months after LASIK. Tosi and colleagues report a case of flap displacement during vitrectomy 24 months after LASIK, which suggests that a minority of patients may be predisposed to this complication indefinitely [93]. More recently, traumatic flap dislocation has been reported 10 years after LASIK [94].

Displacement of a corneal flap after LASIK is a serious complication. Possibilities include losing the cap, epithelial ingrowth, interface particles, and striae in the flap, all of which may affect the final refractive outcome. Displacement of the corneal flap has been described after corneal epithelial debridement during a scleral buckling procedure and vitrectomy.

The recommendation for vitreoretinal surgeons when treating an eye with a retinal detachment is in identifying the history of LASIK or other refractive surgery procedures, including information such as hinge location. When possible, one should avoid debridement of the corneal epithelium. Lopez-Guajardo et al. describe a technique where a dry sponge applied to the edematous epithelium for several seconds followed by rinsing the surface with balanced salt solution may improve intraoperative visualization without need for epithelial debridement [95]. However, if it is necessary, debridement should be confined to the central part of the cap, sparing the peripheral fibrous adhesions [96]. Corneal debridement should be started at the hinge (nasally or superiorly) and advanced away from the hinge (temporally or inferiorly, respectively). In addition, we recommend the use of noncontact viewing systems when possible and avoid the use of a contact lens during vitrectomy. If a displaced corneal flap occurs, initial management includes repositioning of the flap using a blunt instrument such as a spatula [93]. Irrigation of the stromal bed is recommended to remove any residual debris. A wet sponge can be used to flatten the flap, and then the wound margin should be gently dried with a sponge for 5 min [93]. These maneuvers may be followed by patching and topical steroids. Refractory cases may require suture fixation. A bandage contact lens may be useful if striae develop. Persistent striae are an indication to elevate and reposition the flap. Ideally, a refractive or corneal surgeon should be accessible in order to manage flap complications.

24.2.15 Final Considerations

The incidence of vitreoretinal pathology after LASIK in our study ranged from 0.05% to 0.19% (annual incidence, 0.02%) [63]. This number is much lower than the incidence of RRD in myopes in general [6]. This finding may be explained by the fact that refractive surgery patients in the institutions involved underwent preoperative examinations including a very thorough dilated indirect fundoscopy with scleral depression and treatment of any peripheral retinal lesion predisposing for the development of an RRD before LASIK. In this study, extensive lattice degeneration, flap tears, atrophic holes, and retinal tufts were prophylactically treated regardless of symptoms. Such indication is justified by the fact that vitreoretinal surgery causes changes in corneal shape thus damaging the refractive surgeon's results. We suggest that cryopexy, argon laser retinopexy, pneumatic retinopexy, or vitrectomy without a scleral band be performed when appropriate because they tend not to change the shape or length of the globe. Another option in case of scleral buckling procedures is to remove the exoplants early, as suggested by Rodriguez and Camacho [8], after ensuring that all breaks have sealed and that no retinal detachment is present.

Lin and Tseng [22] have recently published a study to determine the efficacy and safety of prophylactic laser photocoagulation for retinal breaks in myopic patients undergoing LASIK. Retinal breaks were identified and treated in 39 eyes (2.02%) of 32 patients (3.2%). During a mean 19-month follow-up, none of the patients developed RRD except for one in a patient without retinal breaks who sustained ocular trauma 19 months after LASIK.

Chan et al. [97] suggested that pre-LASIK retinal examination might predict locations of certain post-LASIK retinal

lesions (breaks, retinal detachment) that may develop in highly myopic eyes with pre-LASIK vitreoretinal pathology (lattice, breaks), but prophylactic treatment of vitreoretinal pathology before LASIK does not guarantee the prevention of post-LASIK vitreoretinal complications.

Based on published data, we cannot determine whether prophylactic treatment is indicated. At the current time, it is not possible to scientifically determine whether peripheral retinal lesions should be treated differently from standard practice in a preoperative evaluation for LASIK. Most practitioners suggest that patients scheduled for LASIK be carefully examined with indirect ophthalmoscopy and scleral depression under pupillary dilatation to detect any myopic peripheral lesion that requires treatment before LASIK is performed. One could argue that this is prudent in myopes whether or not they undergo LASIK; given the potential of the procedure to exacerbate preexisting pathology, it might be wise to treat such pathology more aggressively.

Another important factor to take into consideration when we evaluate our state of knowledge in this area is duration of follow-up. In our 10-year follow-up study, the incidence of RRD increased with time, with an annual incidence of 0.02%. It is possible that LASIK-induced trauma might accelerate vitreous liquefaction and that over the years, these patients might have a higher incidence of retinal detachments and other vitreoretinal problems. It is equally likely that with the current practice patterns of shorter periods of follow-up, ophthalmologists may be unaware of this.

Macular diseases may be a relative contraindication to LASIK. Patients with high myopia and lacquer cracks in the macula are at high risk to develop macular hemorrhage or CNV after the intraocular pressure is raised with the suction ring during the procedure. Patients with angioid streaks and traumatic choroidal ruptures are in the same category of risk. Stage 1 macular holes may progress due to traction in the posterior pole during LASIK. In addition, eyes that are at risk of needing vitreoretinal surgery in the future have a relative contraindication to LASIK. On the other hand, in eyes with stable macular disease (scars), LASIK may be performed depending on the refractive surgeon criteria if the patient is aware and accepts his visual acuity limitations.

In summary, serious complications after LASIK are infrequent. It is very important to inform patients that LASIK only corrects the refractive aspect of myopia. Vitreoretinal complications in these eyes will occur, and only careful and large prospective studies in patients can determine if the procedure exacerbates myopic pathology. Such studies will need to be performed using careful prospective examinations including determination of risk factors, echography of the vitreous, indirect ophthalmoscopy and scleral depression, and possible photography and angiography of the macula region to determine whether the LASIK procedure itself can exacerbate pathologic changes in the myopic eye. In addition, our latest study shows that results may be not as good as expected after RRD surgery. Despite high anatomical success with one surgery, reasons for poor VA include the development of epiretinal membrane, proliferative vitreoretinopathy, myopic maculopathy, and optic atrophy. Final VA may be limited by myopic degeneration, amblyopia, or delayed referral to a vitreoretinal specialist.

Take-Home Pearls

- Because there is no real treatment for optic neuropathy after LASIK, it is extremely important to adopt preventive measures.
- Vitreoretinal stress induced at the posterior vitreous base during a posterior vitreous detachment after LASIK may lead to retinal breaks and RRD.
- Preexisting macular pathology in hyperopia, such as RPE atrophy, might be associated with the development of CSCR or subretinal fluid after LASIK.
- Macular diseases may be a relative contraindication to LASIK:
  - Patients with high myopia and lacquer cracks in the macula are at high risk to develop macular hemorrhage or CNV after the IOP is raised with the suction ring during the procedure.
  - Patients with angioid streaks and traumatic choroidal ruptures are in the same category of risk.
- Macular hole may develop in myopic eyes after LASIK or photorefractive keratectomy. Fortunately, vitrectomy is successful in closing the macular hole.
- In eyes with uveitis, LASIK should be performed when the inflammation is quiescent to avoid severe postoperative inflammation.
- LASIK was found to be a safe and efficient option for treating refractive errors in eyes with previous retinal detachment surgery. However, scarred conjunctiva in a few cases may prevent generation of optimal suction for the microkeratome.
- To avoid corneoscleral perforations, we recommend that refractive surgeons be meticulous in properly assembling the microkeratome to create a corneal flap during LASIK or use a disposable microkeratome.
- Vitreoretinal surgeons when treating an eye with a history of LASIK should avoid debridement of the corneal epithelium.
- Cryopexy, laser retinopexy, pneumatic retinopexy, or vitrectomy without a scleral band tends not to change the shape or length of the globe and should be preferred to repair RRD.
- Prophylactic treatment of vitreoretinal pathology before LASIK does not guarantee the prevention of post-LASIK vitreoretinal complications.

- At the current time, it is not possible to scientifically determine whether peripheral retinal lesions should be treated differently from standard practice in patients who will undergo LASIK; however, given the potential of the procedure to exacerbate preexisting pathology, it might be wise to treat such pathology more aggressively.
- It is very important to inform patients that LASIK only corrects the refractive aspect of myopia and that vitreoretinal complications after LASIK, although infrequent, may occur.
- Reasons for poor VA after surgery for RRD after LASIK include delayed referral to a vitreoretinal specialist.

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Effect of Refractive Surgery on Strabismus and Binocular Vision

25

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Core Messages

- The presence of diplopia or strabismus after refractive surgery is considered to be very low.
- This chapter discusses the causes, prevention, and treatment of strabismus and binocular vision following refractive surgery.

25.1 Background

In 1948, Jose Barraquer pioneered the field of altering corneal shape and curvature to correct refractive errors. He developed surgical techniques to remove portions of the cornea, freeze and reshape them, and then resuture them back to the cornea. His work was the driving force behind the development of modern-day refractive procedures. In the 1960s, Svyatoslav Fyodorov introduced radial keratotomy in Russia. However, the many complications associated with this procedure made it an unfavorable refractive procedure among ophthalmologists. The introduction of excimer laser technology in the 1970s revolutionized the world of ophthalmology. Patients who had been confined to spectacle or contact lens correction could now achieve "corrected" vision from their waking moments to the time they retired at night. Millions of patients benefited from a transformation in their vision and their quality of life. Ophthalmologists and patients alike embraced refractive surgery and all the advances in this field with open arms, as it allowed patients to gain independence from corrective lenses and significantly improved their quality of life. Due to the relative ease of the procedures and the improvement in the quality of life, refractive surgery has become one of the leading elective ophthalmic procedures since its introduction in the 1990s.

Refractive surgery, however, has some setbacks. The most well-known and well-published side effects of refractive procedures include glare, halos, and starbursting, especially in the early years after its introduction. Complications such as infections, dehisced flaps, epithelial ingrowth, and buttonholes are also well studied in the literature. One of the less commonly recognized effects of refractive surgery is decompensation of vision in patients who have latent or manifest strabismus. The prevalence of diplopia or strabismus after refractive surgery is considered to be very low; according to a study, this rate is 0.12%; however with a thorough exam, it could be even lower. Many of these patients presented with symptoms of binocular visual impairment, frank diplopia, or ocular misalignment following a refractive procedure. This chapter discusses the cause, prevention, and treatment of this postrefractive complication.

25.2 Causes of Strabismus and Binocular Vision Impairment in Refractive Patients

In many of the early studies, patients who had preoperative strabismus were noted to have orthophoria after undergoing refractive surgery. However, as more time elapsed after their procedure, strabismus-related problems started surfacing in these patients. Another subset of patients had well-controlled strabismus preoperatively with spectacle correction but suffered either from ocular misalignment or diplopia immediately postoperatively. Finally, there was a subset of patients who had "de novo" strabismus or binocular vision impairment after refractive surgery. Initially, these patients presented an enigma to ophthalmologists. What caused this decompensation? We now know that several factors attributed to these symptoms. One of these factors is disruption of binocular vision after refractive surgery, which can lead to decompensation of a phoria to a

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tropia. This interruption is longer with surface ablation procedure (compared with LASIK), uniocular surgery, or monovision procedure; therefore, these patients are more likely to experience a decompensation. It is very important to communicate with the patients about these risks after surgery.

25.3 Patients with Delayed Decompensation of Strabismus After Refractive Surgery

In the early postoperative period, many patients with preoperative strabismus had orthophoric outcomes. However, as more time elapsed after their procedure, decompensation of their strabismus occurred. What causes this delayed decompensation? A major factor in these cases is regression toward the preoperative refractive error. High myopes and hyperopes are especially susceptible to regression after refractive procedures. In most patients without strabismus, this does not pose any significant problems except blurry vision. However, in patients with preexisting strabismus, even a minimal regression is adequate to affect their binocular vision. Their decompensation, thus, is a function of the sensorimotor alteration following their refractive procedure.

25.4 Patients with Spectacle-Corrected Preoperative Strabismus

Another scenario included patients with preoperative strabismus that was adequately controlled with glasses. These patients were noted to have strabismus after their refractive procedure. What induced ocular misalignment in these patients who were previously well controlled with spectacle correction? While refractive surgery does not cause ocular misalignment, in some cases, it allows the manifestation of the ocular misalignment that was previously present.

Glasses have a prismatic effect on both eyes. Patients who are accustomed to wearing glasses are used to this prismatic effect. Refractive surgery eliminates the prismatic effect in these patients and induces a "reverse prismatic effect" after their procedure. This offsets their retinal correspondence and falsely gives the illusion of an abnormal retinal correspondence (ARC). This causes nonphysiologic diplopia in these patients. This problem is usually associated with patients with high myopia, hyperopia, or anisometropia. These patients would have a similar effect with contact lenses as the contact lens removes the prismatic effect of spectacles.

25.5 Patients with Preoperative Latent or Manifest Strabismus

Many patients were noted to have strabismus "de novo" following refractive surgery. However, further research and review of their previous exams revealed that these patients had preexisting *eso* or *exo* phoria.

In another scenario, patients with preoperative latent or manifest strabismus had frank diplopia or strabismus after their refractive procedure. One of the attributing factors in such cases is inaccuracy in their refractive correction. An undercorrection or overcorrection in these cases, no matter how minimal, is often adequate to cause strabismus-related problems. Patients with latent or manifest strabismus have fragile binocular fusion reserve. Thus, disturbing their refractive balance offsets this reserve and causes decompensation of their preexisting strabismus. Furthermore, over- or under-correction changes their nodal point, which also impairs their functional binocular vision.

Decentration of the flap and/or treatment is an intraoperative cause of postoperative deviations, especially vertical deviations. Furthermore, this intraoperative complication may cause night glare, ghosting of images, tilting or distortion of images, and acquired regular and irregular astigmatism with reduction of best-corrected vision. When the treatment in one eye is in the visual axis and the treatment in another eye is decentered, the eye with the eccentric treatment will deviate in the direction of the best treatment zone. For example, if the flap or the treatment in the eye is decentered temporally, especially in someone with a preexisting exophoria or exotropia, then the patient will have an exotropia after the refractive procedure. If the flap and/or treatment is decentered superiorly or inferiorly, then the patient will have a vertical deviation. This situation may occur when patients are looking up or down during the procedure, in the presence of vertical angle kappa or due to a dilated pupil; thus, there is a lack of orientation by the surgeon. Patients with a preexisting horizontal phoria or tropia often develop a V- or A-pattern deviation if their treatment is decentered vertically. Furthermore, patients with a congenital superior oblique palsy may manifest their deviation and present with diplopia following a decentered flap/treatment.

While refractive surgery can lead to manifestation of strabismus in some patients, in patients with refractive accommodative esotropia and amblyopia, refractive surgery can be used to treat underlying hyperopic refractive error and improve the alignment, uncorrected visual acuity, and stereopsis. Both accommodative and nonaccommodative strabismus can attain orthophoria or microtropia following refractive surgery. Refractive surgery can also be utilized in children with strabismus and amblyopia who fail treatment with contact lenses and spectacles.

25.6 Monovision and Strabismus

Patients with preoperative strabismus who opt for monovision require special evaluation. In these patients, binocular fusion is very fragile. They require both of their eyes aligned and require their vision similar in both eyes to maintain fusion. Therefore, disrupting this fusion by creating partial or complete monovision places them at high risk for binocular vision impairment after surgery. This is especially the case when the dominant eye is corrected for near vision and nondominant eye is corrected for distance. The diplopia is more likely to occur when they fixate with the nondominant eye. However, some patients who have a mild degree of phoria or tropia might be able to tolerate partial monovision. Therefore, a trial with contact lenses or monovision trial frames is imperative in such circumstances to determine if the patient is a good candidate for monovision. If diplopia occurs, the patient has a very high risk for postoperative double vision. Otherwise, the absence of diplopia does not exclude postoperative diplopia since sometimes it presents several years after monovision surgery. Therefore, it is essential for the patient to be informed about this possibility.

If you perform monovision in these patients, a difference greater than 1.25 D between the two eyes is not recommended. This anisometropia offers patients comfortable stereo vision at both distance and near fixation. Studies have reported that a major difference can lead to suppression of the defocused eye, reducing binocular function as fusion is unable to be achieved at a difference greater than that.

25.7 Prevention of Strabismus and Binocular Vision Impairment in Refractive Patients

The degree of strabismus may be a determining force in whether a patient will develop strabismus-related problems postoperatively. The most important intervention to prevent strabismus and binocular vision impairment in patients undergoing refractive surgery is a thorough preoperative evaluation. Patients should be asked extensively about their ocular history. Have they had previous muscle surgery? Have they suffered from double vision at the end of the day or when tired? Has anyone in the family noticed a "wandering eye," especially when the patient is tired? Have they had difficulties with binocular vision with contact lenses? This is especially important in someone considering monovision.

Equally important is a thorough exam, including a cover–uncover test, an alternate cover test, cycloplegic and manifest refraction, and sometimes even a Maddox rod evaluation.

An important study describes the importance of stratifying patients into low, medium, and high risk. Myopia, anisometropia of less than four diopters, no prior history of strabismus or diplopia, no prism in glasses, and at most a minimal phoria on alternate cover/uncover testing and prism test, and current spectacles, manifest refraction, and cycloplegic refraction all within 0.5 D of each other is considered as low risk. These patients can develop diplopia in case of technical problems, such as scarring or unfavorable optical outcomes.

Moderate risk is considered when patients do not meet these criteria, necessitating further testing—fusional convergence and divergences amplitudes, trial of monovision prior to correction, trial with neutralizing prisms, and measurements of monocular and binocular astigmatic axes. When the patient fails these additional tests, he/she is considered to be at high-risk for postoperative diplopia. Moderate or high risk of diplopia is not always an absolute contraindication for refractive surgery; however, these patients should be studied by a strabismologist before undergoing surgery and should be explained the risks thoroughly.

In patients who have established strabismus, it may be wise to try them in contact lenses to evaluate the role of prismatic effect from their glasses. In strabismic patients considering monovision, it is almost essential to try them with monovision contact lenses to simulate the effects of refractive surgery.

Finally, intraoperative care should be taken to ensure that the flaps and the treatment are not decentered. In addition, under- or overcorrection may throw the patient's binocular vision off and cause decompensation of a phoria into a tropia or cause a persistent tropia or vertical deviation.

Ultimately, it is critical to recognize that patients with a preoperative history of latent or manifest strabismus have fragile binocular fusion. They are at risk of disruption of ocular alignment and fusion with minimal alteration in their refractive balance. This should be discussed extensively with the patients preoperatively.

25.8 Treatment of Decompensated Strabismus

The treatment in cases where refractive surgery has induced a decompensation of strabismus depends on the underlying cause, but usually, most patients can be corrected with prism (64%) or strabismus surgery (19%) if their sensory status is adequate. If the decompensation is determined to be secondary to an undercorrection or regression, then an enhancement may be a suitable option. In cases of overcorrection, spectacle correction might be useful. In these cases, the hope would be for the patient to regress eventu-

ally to emmetropia. If the decompensation is secondary to a decentered treatment, then the management is more challenging. Some experts recommend determining the postoperative refractive error and treating the refractive error with centration in the central visual axis. Often times, however, these patients require spectacle correction. In cases of vertical deviations, patients often require prisms to maintain fusion. There is a small group of patients that will have persistent diplopia; in these cases, occlusion therapy will be required.

Take-Home Pearls

- Careful selection of patients for refractive surgery is especially important in avoiding strabismus-related complications after refractive surgery.
- A thorough preoperative evaluation of phorias and latent strabismus can reduce the rates of manifest strabismus postrefractive procedures.
- Pre-existing strabismus is the most common cause of binocular diplopia after refractive surgery.
- An accurate manifest and cycloplegic refraction are essential in preventing strabismus associated with under- or overcorrection.
- Centration of flaps and treatment is an important intraoperative measure of reducing strabismus following refractive procedures.
- Monovision should be approached with care in patients with latent or manifest strabismus.
- Patients with a preoperative strabismus have fragile binocular fusion and are at risk of disruption of ocular alignment and fusion with minimal alteration in their refractive balance.
- Treatment for strabismus or a residual diplopia is diverse (spectacles or refractive re-intervention, prescribing prisms, botulinum toxin injection, or strabismus surgery), but definitely, the best strategy is prevention.

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Small Incision Lenticule Extraction (SMILE) Complications

26

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Core Messages

- SMILE is a new refractive surgical procedure for low, mild, and high myopia with or without astigmatism.
- This chapter discusses the intraoperative and postoperative complications related to SMILE.

26.1 Introduction

Surgeries in every specialty are always challenging. Refractive surgeons aim for:

1. Minimal invasiveness
2. Fast recovery with less collateral damage

LASIK has become the most popular corneal surgery in the last two decades with approximately 1 million procedures per year in the United States [1]. It represents the gold standard, because of it's safety, efficacy, and predictability. Although a high satisfaction rate is reported, creating a flap may still lead to complications and dry eye. Additionally, the biomechanics of the cornea is compromised, and in susceptible eyes, this may lead to ectasia.

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Since the inclusion of femtosecond laser technology for corneal surgery, a number of technological advances, such as short pulse time, high instantaneous power, high repetition rate, low monopulse energy, and small thermal effect, have increased its efficacy [2].

In 1996 the first procedure to correct a refractive problem using a picosecond and not an excimer laser was described in order to achieve a refractive lenticule extraction (ReLEx) [3, 4]. Despite this novel approach, significant manual dissection was required, thus generating an irregular surface. However, the use of the femtosecond laser for corneal procedures [5] has shown improved efficacy, predictability, and safety [2].

Following the introduction of the VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany) in 2007, the intrastromal lenticule method was reintroduced in a procedure called femtosecond lenticule extraction (FLEx) [6, 7]. FLEx procedure was followed by small incision lenticule extraction (SMILE) technique, which is not the objective of this chapter to describe, but it is important for the reader to know that it is considered the third generation of refractive procedures (after PRK and LASIK). SMILE technique is a new technique for low, mild, and high myopia with or without astigmatism, offering efficacy, safety, and predictability as published in several studies [7–19].

SMILE technique is becoming the new direction in refractive surgery, and the ocular surface changes after SMILE are attracting more attention.

Few articles have been published about complications. Here, the reader will find a review of the most common complications and how to manage them.

For a better understanding, we have divided the complications in two sections:

Intraoperative complications
Postoperative complications

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26.2 Intraoperative Complications

1. *Contact glass of the femtosecond laser, suction application, and correct centration*

In this stage of the surgery, the suction ports are activated to keep the patient's eye fixated in the correct position while the lenticule is created. For obvious reasons, the eye must be fixed, and if sudden anxiety produces ocular movement during the operation, the complication will defer depending on the moment of the surgery. In case it occurs in the *incision creation stage*, a radial tear can occur from the incision, and if it is long enough, it may divide the cap in two as described in the literature [20]. The surgery can be finished with the removal of the lenticule, and a contact lens must be inserted. If ocular movement occurs in the *lenticule creation*, an uneven lenticule cut will be obtained with an obvious descentration, and the procedure must be aborted.

In the docking process with the contact glass, no water droplets and/or debris may exist between the coupling device and the ocular surface, as this can be a cause of *black spots* (Fig. 26.1). This black spot will not allow the correct laser-tissue interaction that may imply more difficulty in the dissection of the lenticule and cap. The creation of a black spot is a complication associated with docking, as reported in the literature [21] and is an avoidable complication.

The *loss of suction* [20–22] is also a complication that the surgeon must be alert in case it occurs. Published data report a 0.8 [20]–11% [21] incidence of loss of suction during surgery, leading to abortion of the laser procedure (Fig. 26.2).

In cases in which the bottom and side cut of the lenticule is performed before suction is lost, re-treatment may be attempted. Otherwise, another refractive procedure may be considered such as PRK or LASIK. Studies demonstrate that this complication is the most uncommon to occur.

Decentration of the optical zone, the difference between the pupil center and corneal vertex normal, may be a cause of visual compromise in the outcomes following SMILE for the treatment of myopia and myopic astigmatism. One study demonstrated that better refractive outcomes will be achieved when the lenticule center is closer to the normal corneal vertex [22].

2. *Incision and lenticule dissection, lenticule extraction, and energy laser settings*

Minor epithelial abrasions and tears of the incisions are the most frequent complications [20, 21], and it is a mild problem solved in 1 or 2 days with the use of artificial tears with no effect on visual acuity (Fig. 26.3). Mostly the excessive management of the incision due to the lack of experience of the surgeon and the incorrect election of the spatula dissection in terms of thickness may cause these abrasions and tears.

Difficulty in removing the lenticule (Fig. 26.4) is also a common intraoperative complication. Lack of identification of the posterior and anterior plane, incorrect management of the laser energy, and excessive use of topical anesthetics are causes of difficulty for lenticule extraction. The surgeon must have the total certainty that the full lenticule has been extracted, positioning it over the anterior surface of the cornea in order to

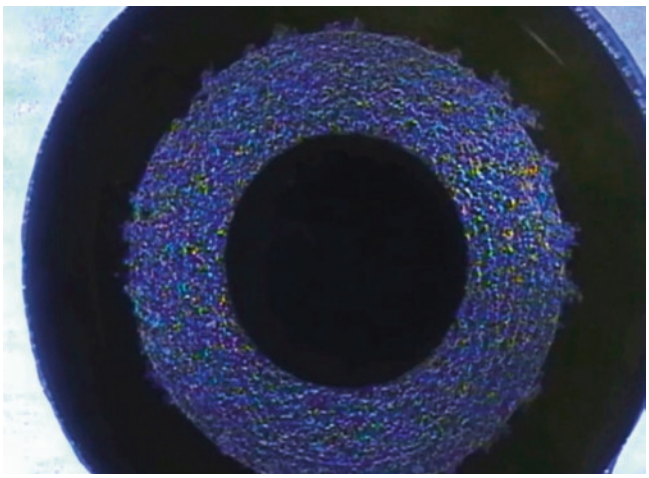


Fig. 26.2 Suction loss during posterior lenticule surface creation

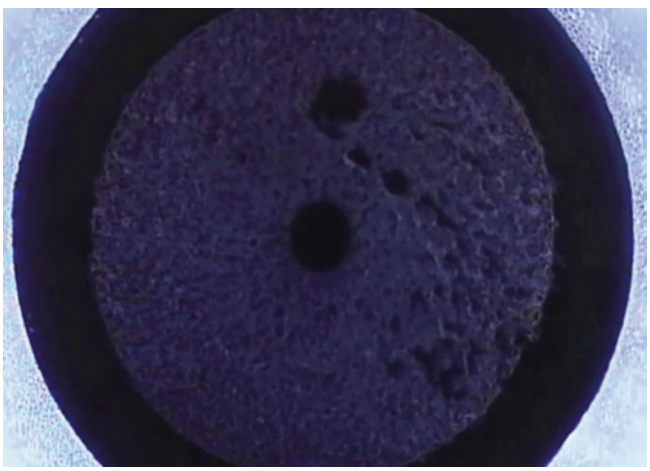


Fig. 26.1 *Black spot* after and during the docking process

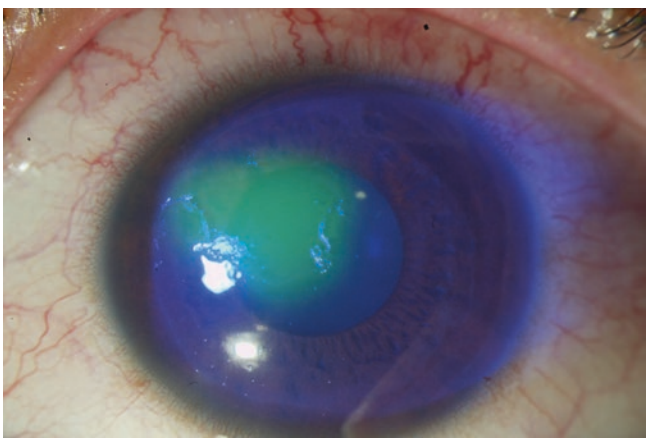


Fig. 26.3 Epithelial defect in a patient at postoperative day 1 after SMILE surgery

appreciate the full lenticule. The lenticule extraction difficulties didn't show any significant differences in preoperative characteristics from those of the average patient [21].

The difficulty of a lenticule extraction may lead to a *cap perforation* (Fig. 26.5a) or to a *rupture of the cap edge* (Fig. 26.5b). In these cases, the recommendation is to insert a contact lens after the surgery for 1 day, and depending on the dimension of the perforation, it will result in minor or major scars. In another study, three months after the surgery only minor scars were observed, and no significant loss of corrected distance visual acuity (CDVA) was noted, and none of the patients had visual symptoms when a cap perforation occurred [21].

A rare complication can be presented when the *conjunctiva is trapped under the contact glass during suction*, leading to an incomplete creation of the anterior lenticular surface.

Cavitation gas bubbles (known as opaque bubble layer (OBL)) have also been reported as a complication [21–23]. The exact origin of these bubbles is unknown, and extreme OBL can result in intracameral bubbles as well. Some theories have suggested that they originate from stray laser pulses into the aqueous humor [24] or that they migrate in a retrograde way through the Schlemm's canal into the anterior chamber. Generally, this OBL tends to disappear within minutes.

As published in one study [21], in 16.2% of the complicated cases, an OBL blocked the laser treatment, and the small incision could not be performed. In order to solve this surgical complication, the authors described the use of a crescent blade or a graduated keratome to accomplish the small incision manually.

Our recommendations for a *correct laser energy setting* for SMILE technique are frequency of 500 kHz, cut energy index of 170 nJ femtosecond laser pulse, and 4.5 mm spot spacing. These settings don't significantly affect the optical quality including the intraocular scattering of the eyes.

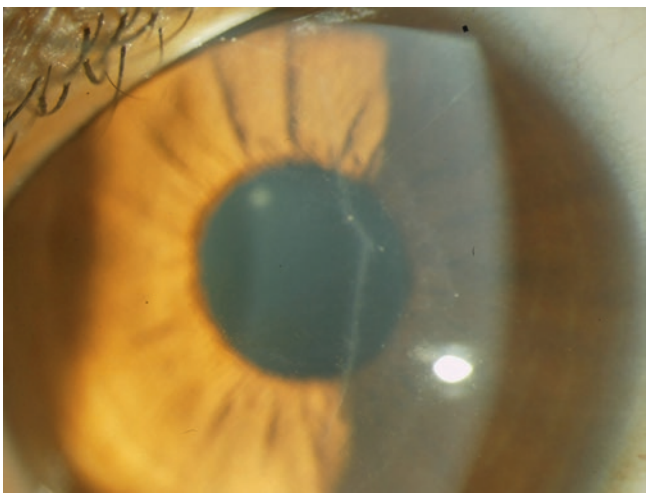


Fig. 26.4 Difficult lenticule extraction leading to incomplete removal

26.3 Postoperative Complications

The most frequent complications were *haze* (54%) and *dryness of the corneal surface* (32%) and were not associated with later visual symptoms [20].

Corneal haze (Fig. 26.6) was noted in eyes where tears in the incision or when difficult lenticule extraction occured, this has direct relation with the energy settings and the experience of the surgeon. Patients in our study responded to topical steroids treatment, including late haze formation after 3 months postoperative presented in only one patient that had 2-line loss in CDVA. However, by 1 year, CDVA had fully recovered [21].

Patients in our study responded for *dry eye* symptoms within the first 3 months after SMILE. One study reports that none of them needed further treatment after 3 months or

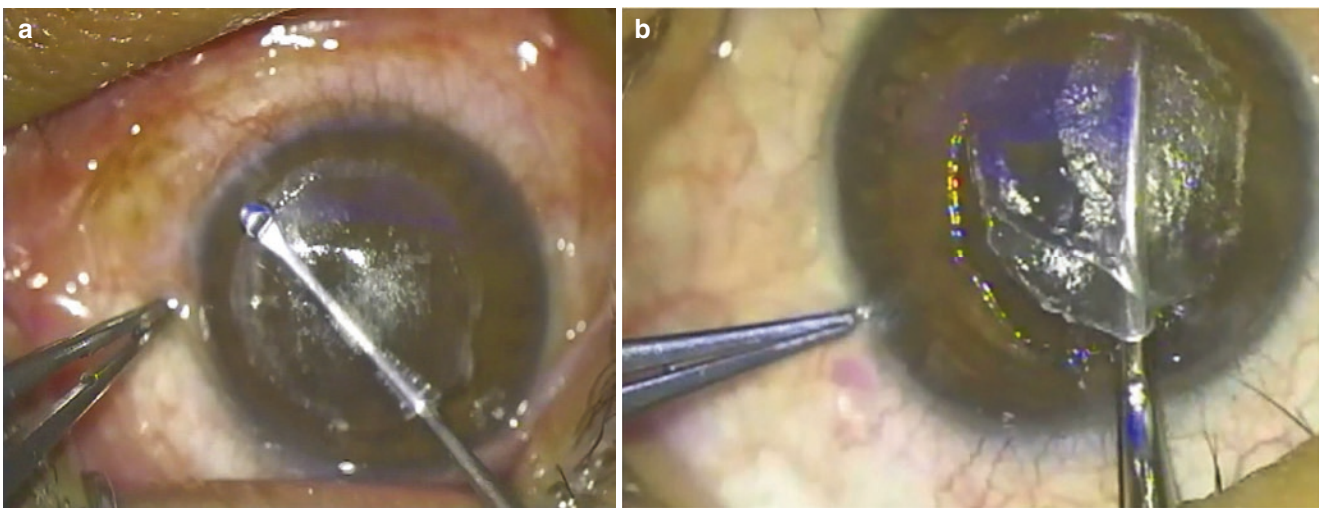


Fig. 26.5 (**a**) Perforation during lenticule dissection and extraction. (**b**) Rupture of cap edge

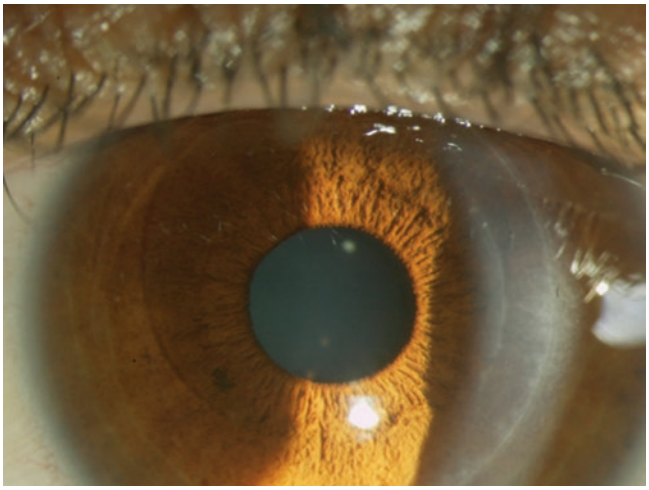


Fig. 26.6 Corneal haze at the edge of lenticule

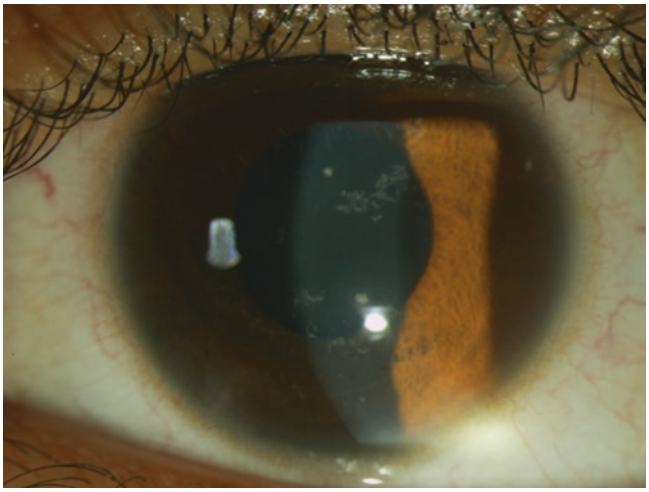


Fig. 26.7 Epithelial cells trapped in the interface

reported any associated side effects up to a 5-year follow-up [17].

In a comparison of signs and symptoms of dry eye and corneal sensitivity between SMILE and femtosecond LASIK (FS-LASIK) for myopia, SMILE resulted in a short-term increase in dry eye symptoms, tear film instability, and loss of corneal sensitivity. However, SMILE surgeries have superiority over FS-LASIK in lower risk of postoperative corneal staining and less reduction of corneal sensation [25]. The incidence of postoperative dry eye syndrome was found to be less problematic in SMILE than in FS-LASIK [26, 27].

The same results in normal eyes are shown in the previous study. A review of ocular surface diseases and corneal refractive surgery patients, identified as having an increased risk for postoperative dry eye, may benefit from surgical techniques such as SMILE and FS-LASIK [28].

In comparative outcomes of SMILE versus LASIK, a high incidence of mild to moderate dry eye disease was observed in both groups, 1 month postoperatively, which remained significantly higher in the LASIK group than in the SMILE group 6 months after surgery. The SMILE procedure has a less pronounced impact on the ocular surface and corneal innervation compared with LASIK, further reducing the incidence of dry eye disease and subsequent degradation in quality of life after refractive surgery. Clinical evaluation was measured by Ocular Surface Disease Index [OSDI]), tear breakup time [TBUT], Schirmer I test, corneal staining, and tear osmolarity. Function and morphology of the corneal innervation were evaluated by corneal esthesiometry and sub-basal nerve imaging using in vivo confocal microscopy (IVCM).

Small fibers have been described to appear in the first days after the surgery [21] in the interface, and irrigation of the interface can be necessary in these cases.

Islands of epithelial cells [20, 21] (Fig. 26.7) can be found near the incision. In reported cases, no progression was observed, and a spontaneous resolution in all patients occurred. In some of them, resolution took up to 1-year follow-up.

Some patients may experience *monocular ghost images* after surgery [21], with no improvement during the first 3 months. In these rare cases, Pentacam HR examination showed irregular topography, probably by some of the complications named above that can cause these irregularities. It seems that late compensatory mechanisms, which may include corneal or epithelial remodeling and abnormal tear film, may help to cause this situation.

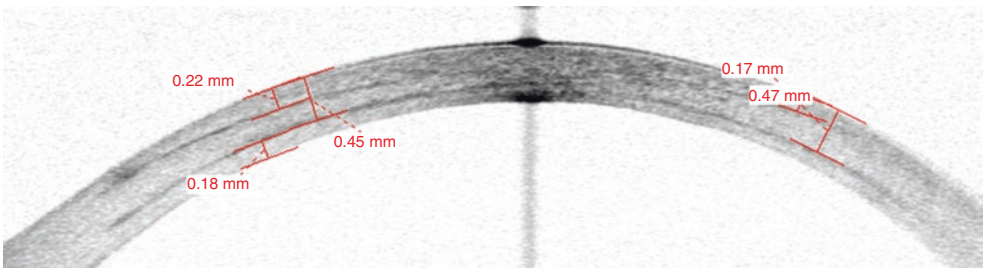
No aberration where induced after SMILE in comparison to other refractive techniques. In this current comparative study [29], it was found that total higher-order aberrations (HOAs) and spherical aberrations were significantly lower in the SMILE group compared to the FS-LASIK group at 1 and 3 months. Similar findings were reported in another study [30] where SMILE showed good safety, efficacy, and stability in correcting moderate to high myopia, and patients were highly satisfied. HOAs increased after SMILE, mainly due to the increase of coma, whereas retinal image quality and intraocular scattering barely changed. A greater preservation of corneal biomechanical strength and corneal nerves was observed in SMILE when compared with LASIK or PRK [31]. All these findings are interesting, because it proves that the cornea biomechanically is more stable and allows, as reported by Graue et al. [32], the combination of small incision lenticule extraction and cross-linking which may be a promising treatment option in patients for whom conventional laser refractive surgery is contraindicated.

First corneal ectasia reported following SMILE suggests that patients showing preoperative forme fruste keratoconus or early keratoconus may develop significant progression of corneal ectasia after the SMILE procedure showing that the procedure can affect the corneal biomechanics [33]. Another case reported [34] involves a 19-year-old patient with forme

fruste keratoconus. SMILE was performed, and 6.5 months later, corneal ectasia was diagnosed based on anterior and posterior surface keratometry. This report documents corneal ectasia as a complication of SMILE and highlights the importance of preoperative evaluation and the need for long-term follow-up. Studies show that maximum changes in biomechanical parameters following femtosecond lenticule extraction and SMILE occurred within the first week [35], followed by subsequent corneal stability. Deeper stromal corrections may be possible in this technique without additional risk for postoperative ectasia [36]. Preoperative screening for patient selection in SMILE should be as stringent as that for LASIK correction.

Diffuse lamellar keratitis (DLK) in SMILE has also been reported in the literature [37]. One study enrolled 1112 eyes (590 patients); 18 eyes (1.6%) (11 patients) developed DLK. These patients presented 1–3 days postoperatively with mild to moderate inflammation. DLK is a potential complication after SMILE, although it has a low incidence. The risk factors for DLK must be further elucidated. It is well known that DLK is a white blood cell infiltrate that coalesces in the interface [38]. This nonspecific interface inflammation is certainly associated with intraoperative epithelial defects [39]. All cases were treated successfully with topical corticosteroids and responded in a maximum period of 3 months.

False intrastromal dissection plane: During the early learning curve, if a very low energy is used, the anterior and posterior planes may be difficult to find. In this scenario, if a false plane is created, the stromal disc won't come out as this new plane will not be connected with the femtosecond laser side cut. The procedure should be suspended and the case ended with either a PRK or a phakic IOL 1 month later.



Take-Home Pearls

Despite the efficacy, predictability, and safety of SMILE technique, like any other surgical procedure, the balance between risks and benefits must be taken into account. The risk and management of complications must be understood for the new refractive surgeon to be fully equipped in optimally selecting and performing SMILE.

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Complications Related to Femtosecond Laser-Assisted LASIK

27

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Core Messages

- Femtosecond lasers have several advantages in flap accuracy, safety, and predictability over the microkeratome.
- This chapter describes the (intraoperative and postoperative) complications related to the use of femtosecond laser technology and their management.

27.1 Introduction

Mechanical microkeratomes and femtosecond lasers have been the two methods used for LASIK flap creation. With either technique, LASIK has been shown to be a well-tolerated procedure, with equivalent visual outcomes and low complication rates. Studies have shown that compared with mechanical microkeratomes, femtosecond lasers provide safer and more predictable flap dimensions [1–12]. However, the femtosecond laser can produce unique complications, which are not seen with the use of mechanical microkeratomes [7–11]. Complications can occur intraoperatively or postoperatively (Table 27.1).

Table 27.1 Intraoperative and postoperative complications related to femtosecond laser-assisted LASIK flap creation

Intraoperative	Postoperative
Suction loss	Flap slippage
Difficult lifts	Flap striae
Flap tears	Flap edema
Vertical (epithelial) gas breakthrough[a]	Diffuse lamellar keratitis
Epithelial defects/loose epithelium	Pressure-induced stromal keratitis
Anterior chamber gas bubbles[a]	Central toxic keratopathy
Bleeding	Epithelial ingrowth
Opaque bubble layer[a]	Interface haze
Decentered flap	Dry eye/LASIK-induced neurotrophic epitheliopathy
Interface debris	Transient light-sensitivity syndrome[a]
Vitreoretinal complications	Rainbow glare[a] Infectious keratitis Postoperative corneal ectasia Need for enhancement

[a]Complication specific to femtosecond laser

In this chapter, we describe complications related to the use of femtosecond laser technology and their management. We provide a comprehensive review of the most recent studies concerning complications with newer-generation femtosecond lasers. We also summarize the studies comparing femtosecond laser and mechanical microkeratomes; and we present results from a 2006 review of 19,852 cases (13,721 microkeratome cases and 6131 femtosecond laser cases) highlighting postoperative complications in a refractive surgical practice from one of the authors (Karl G. Stonecipher), when the use of the microkeratome was more prevalent and the comparison between the two techniques was a focus.

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27.2 Intraoperative Complications

27.2.1 Suction Loss

Although rare, loss of suction may occur during flap creation. Factors that may contribute to loss of suction and consequently an incomplete flap include improper technique in applying the suction ring, flat corneas with mean curvature less than 42.0 diopters, narrow palpebral fissures, deep-set eyes, patient movement, eye rotation, and head tilt [7–10]. The first sign of suction loss is often the appearance of a peripheral asymmetric and incomplete meniscus. Once detected, it is important to discontinue the laser treatment immediately (Fig. 27.1).

Suction loss with the mechanical microkeratome are also uncommon, but may result in more severe flap complications. In our series of 13,721 mechanical microkeratome-performed flaps, partial flaps occurred with an overall incidence of 0.11%, which did not allow the procedure to be completed (Karl G. Stonecipher). The management of these microkeratome-related complications was to reposition the flap, wait on average 6 months, and retreat the patient with either surface photorefractive keratectomy (PRK) or cutting a new flap at a deeper depth.

On the other hand, our reviewed series of 6131 cases contained no partial flaps with the femtosecond laser. That is because loss of suction with the femtosecond laser is resolved by replacing the suction ring and re-docking the same applanation cone (unless a manufacturing defect is noted) to subsequently repeat the treatment at the same depth [2, 7, 8].

In the event of suction loss with the femtosecond laser, the vertical limbal pocket, typically created to absorb the cavitation bubbles, can be deactivated if it was already created in the first pass. If the loss of suction occurs during the side cut, the surgeon must ensure that the subsequent side cut is created within the lamellar cut used to fashion the flap by decreasing the subsequent side cut by 0.5 mm in diameter [7, 8].

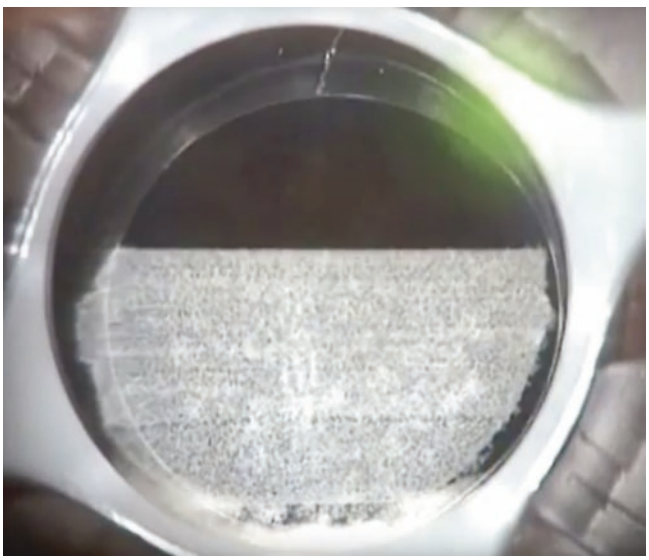

Fig. 27.1 Loss of suction during femtosecond laser-assisted flap creation. Note the peripheral asymmetric meniscus and irregular raster pattern

Shah and Melki [7] reported that multiple raster passes do not result in an irregular stromal bed or intersecting flaps. Surface ablation with mitomycin C (MMC) can be considered over the incomplete flap after repeated suction attempts prove unsuccessful. In this case, it is prudent to wait at least 2 months to perform the surface ablation over the incomplete flap so that an excessive healing response resulting from the simultaneous lamellar cut and surface ablation does not lead to stromal haze [8].

27.2.2 Difficult Lifts and Flap Tears

Femtosecond laser-created flaps are often more difficult to lift compared to microkeratome-created flaps, and the risk of a tear is even higher because the flaps tend to be thinner [13]. Difficulty on lifting the flap is related to residual flap adhesions to the underlying stroma, not fully separated by the femtosecond laser original raster pattern. Platforms that use lower energy pulses with higher frequency produce flaps that are usually easier to lift due to less bridges between the cavitation spots. Minor adhesions can be carefully broken with a blunt dissecting instrument, but attempts to break larger or more coalescent adhesions may result in flap tears [7–9].

If the flap tear is small and peripheral, stromal ablation can still be performed in the same procedure in some cases. If a significant tear occurs at the hinge, it can result in a *free cap*. If a torn flap compromises the pupillary axis, it is prudent to reposition the flap and abort the procedure. Surface ablation with photorefractive keratectomy (PRK) or phototherapeutic keratectomy (PTK) can be done at another time (preferably several months later) to complete the treatment and remove the resulting scar [7, 8].

27.2.3 Vertical (Epithelial) Gas Breakthrough

Cavitation bubbles created by the femtosecond laser can dissect upward toward the epithelium and may either stay below Bowman's membrane or break through the epithelium (buttonhole). This complication appears to be most commonly seen in the creation of thin flaps (programmed at 90 μm) and also in eyes with previous RK surgery, corneal scars, and microscopic breaks in the Bowman's membrane [7, 8].

If a significant vertical gas breakthrough is seen between the glass cone and the epithelium, then the surgeon must stop the procedure and not wait for the side cut to finish. A true buttonholed flap should not be lifted because it can lead to scarring or epithelial ingrowth [8]. If the side cut is completed, then it is recommended not to lift the flap, and the surgeon should treat the patient several months later either

with PRK with MMC or perform a new cut at least 40 μm deeper than the original flap's intended depth. It will also be prudent to save the cone which was used and return to the manufacturer as well as have the femtosecond laser system serviced to check the z-calibration. This comprises a complete investigation of the probable cause of the incident.

In our reviewed series of 6131 femtosecond laser-assisted cases, there was only one case of this complication, but it occurred peripherally related to a previous scar; the flap was lifted and the patient treated without complication in the same procedure (Fig. 27.2).

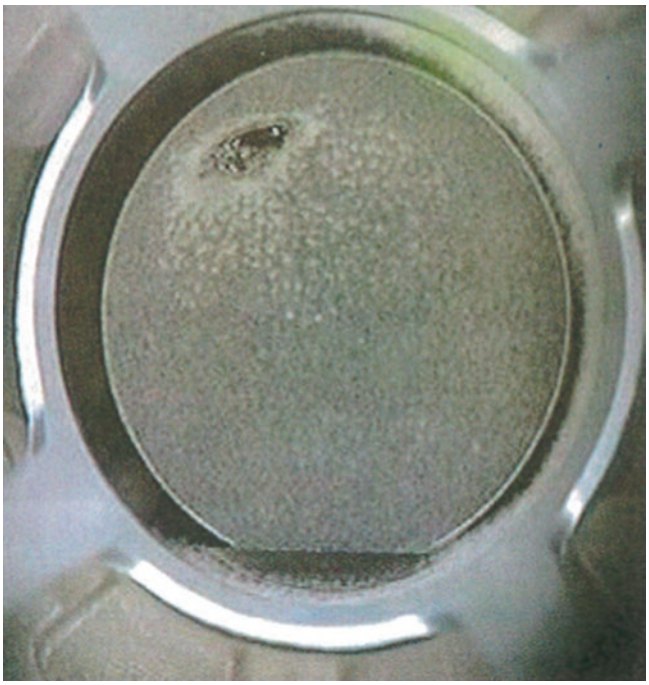

Fig. 27.2 In the peripheral edge of the flap at the 10–11 o'clock position, we see evidence of gas trapped between the docking cone and the surface epithelium, indicating a vertical gas breakthrough (buttonhole)

27.2.4 Epithelial Defects or Loose Epithelium

Epithelial defects or loose epithelium is a complication more commonly seen with the mechanical keratome versus the femtosecond laser [4, 7–10]. In a large study comparing the IntraLase and the mechanical keratome, the incidence of epithelial defects was 8.65% and 0, respectively [4]. Epithelial integrity is a major factor related to healing, since injuries to the epithelium are related to postoperative complications such as DLK, epithelial ingrowth, and need for enhancements [6–8]. When severely injured, the epithelium produces high amounts of cytokines, such as interleukin-1 alpha, that stimulate keratocytes to produce chemokines that attract inflammatory cells, leading to DLK [14] (Fig. 27.3**).** Preoperative risk factors for large epithelial defects include elderly patients, anterior basement membrane dystrophy, history of recurrent erosion syndrome, use of larger flap diameters, and application of excessive topical anesthetic [4, 7, 8].

The main advantage of the femtosecond laser is the absence of the microkeratome rotational movement, which can lead to tearing or shearing of the epithelium [4]. Nonetheless, trauma to the epithelium can still occur with femtosecond laser-assisted LASIK when the laser makes the pocket and shock waves traumatize the overlying epithelium or when surgeons have difficulty in inserting the dissecting spatula under the flap edge [7, 8]. In this series, epithelial slides were reported in 0.45% of mechanical keratectomies and only 0.16% with the femtosecond laser.

Management of peroperative epithelium-related complications include (1) stopping the procedure when severe epithelial injury is present, (2) bandage contact lens application, (3) prophylactic topical antibiotic, and (4) management of the associated risks such as epithelial ingrowth and DLK (topical steroids every 2 h for the first 24–48 h followed by weekly tapering).

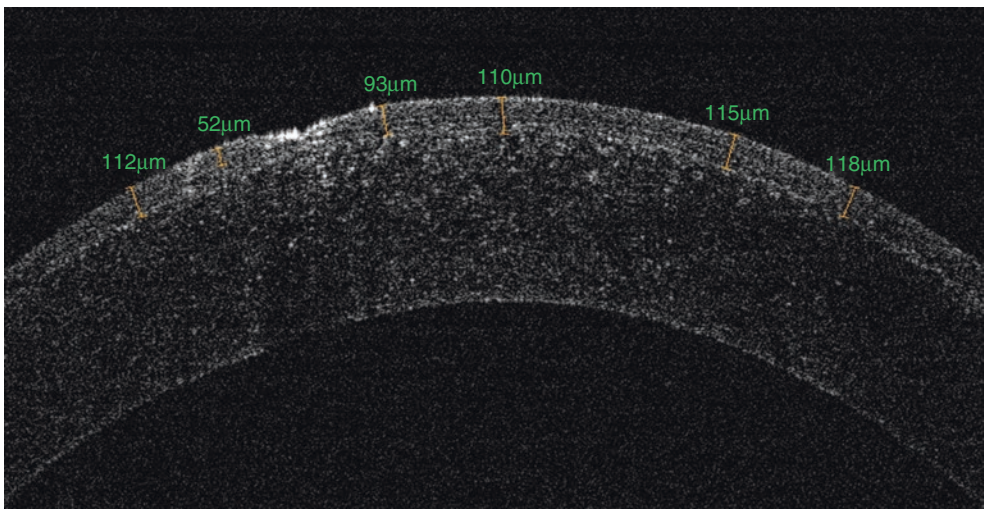

Fig. 27.3 AS-OCT showing a femtosecond laser-created flap with epithelial defect and underlying focal DLK, as well as variable thickness along the flap diameter

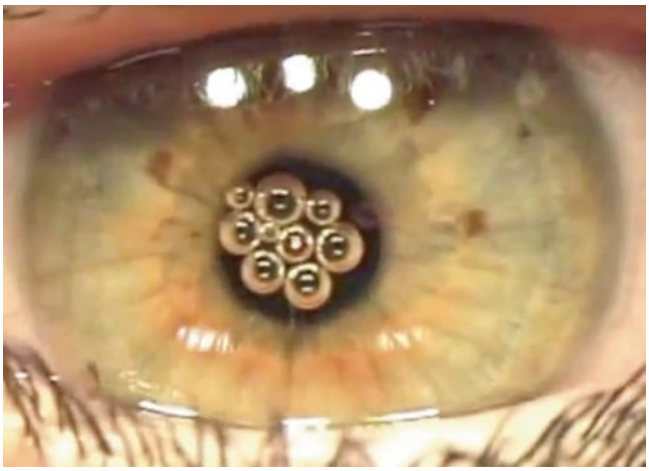

Fig. 27.4 Presence of gas bubbles in the anterior chamber immediately after femtosecond laser-assisted flap creation

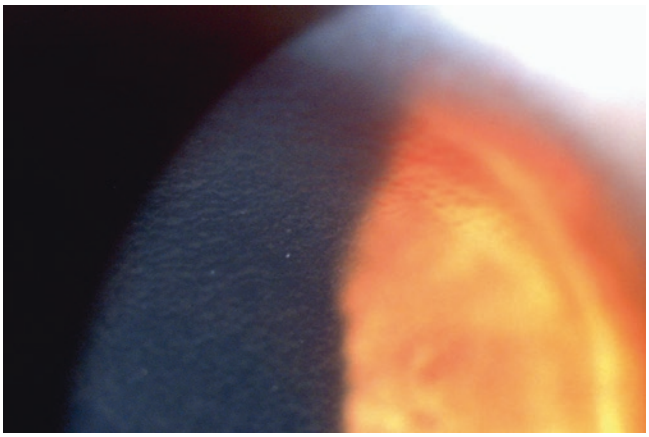

Fig. 27.5 Presence of blood traits in the peripheral interface associated with stage 2 DLK

27.2.5 Anterior Chamber Bubbles

Presence of gas bubbles in the anterior chamber is another complication specific to the femtosecond laser, with an incidence of 0.2% (Fig. 27.4); however, to date, it has not resulted in an interruption of treatment of any patient in our prospective series of 6131 cases. Gas bubbles in the anterior chamber seem to correlate with femtosecond laser dissections that are close to the limbus.

Cavitation bubbles dissecting across a lamellar plane in proximity to Schwalbe's line may, in certain circumstances, gain retrograde access to the anterior chamber through the trabecular meshwork via Schlemm's canal [15–17]. It has been reported to interfere with certain eye trackers on different excimer laser platforms, but treatment has only been interrupted by 1 day, allowing for bubble reabsorption and resolution with routine intervention, with no consequences to postoperative refractive outcomes and no further complications during or after the LASIK procedure [15–17].

One approach is to test the excimer laser eye tracker prior to lifting the flap and then wait for the bubbles to reabsorb if interference is noted while reassuring the patient of the transient and benign nature of this event, thus avoiding unnecessary anxiety and discomfort [8, 15].

27.2.6 Bleeding

Subconjunctival hemorrhages can occur during suction, especially when multiple suction applications are needed due to suction loss or decentration [7–9]. One study reported mild subconjunctival hemorrhage in 68.9% of eyes that had LASIK with the IntraLase compared to no eyes with the VisuMax platform [18]. This difference could be attributed to differences in the docking mechanisms between the two lasers: suction is applied to the conjunctiva/sclera with the IntraLase laser but is applied to the cornea with the VisuMax laser. Slow and controlled application of suction and release prevents subconjunctival bleeding [7]. Subconjunctival hemorrhages clear over 1–2 weeks and do not affect the surgery outcomes, but it is important to inform patients so they are not alarmed.

Bleeding at the flap edge can occur in the presence of peripheral corneal neovascularization (associated with rosacea, atopy, prominent limbal vascularization, or chronic contact lens use), as well as with decentered or large diameter flaps [18]. This bleeding can easily be controlled with a cellulose sponge or a ring-like Chayet sponge during the excimer laser ablation and after the flap is replaced. If the bleeding enters the ablated zone during excimer laser treatment, it can cause irregular astigmatism by causing surface irregularity. Also, the surgeon must irrigate the interface during flap repositioning to eliminate any blood traits in the interface, which is a high risk factor for DLK (Fig. 27.5). Therefore, in patients with peripheral corneal neovascularization, the surgeon must use a smaller flap diameter to avoid transecting peripheral blood vessels and cause bleeding [7, 8].

27.2.7 Opaque Bubble Layer

Opaque bubble layer (OBL) is a well-known intraoperative finding, specific to this technology. Cavitation bubbles formed during flap creation can enter interlamellar spaces in the stroma and expand into a cleavage plan. OBL is a term used to describe the collection of gas bubbles in the interlamellar space above and below the planar flap. It is hypothesized that when the laser energy is too high (causing excessive bubbles) or too low (resulting in an inadequate pocket to vent the bubbles), microplasma bubbles can travel in errant directions, push apart collagen fibrils around them, and expand into space between the bubbles [7]. Interference with the

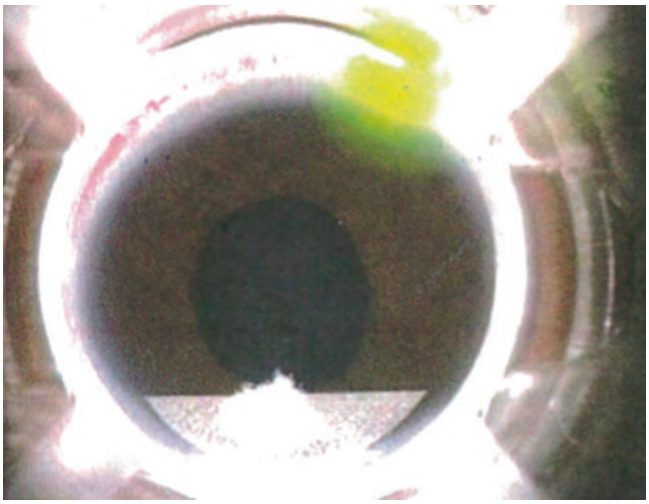

Fig. 27.6 Early or hard OBL is seen at the initial flap creation and appears in advance and opaque in comparison to the normal raster pattern

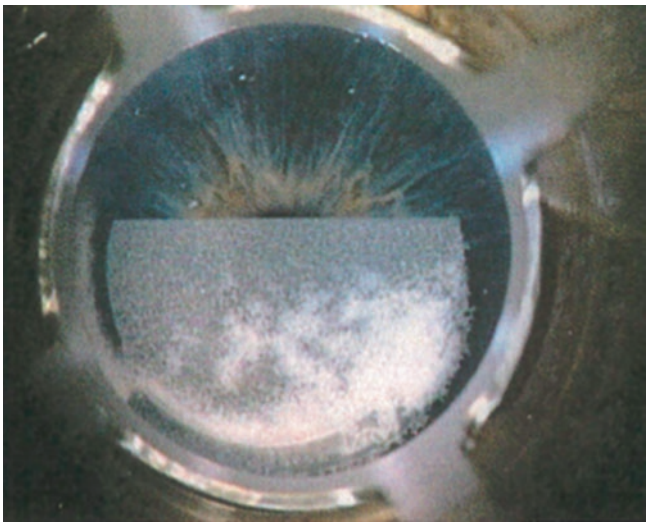

Fig. 27.7 Late OBL has a notably diffuse pattern and appears later in the stage of flap creation

laser eye tracker or iris registration has been noted in some cases, and management involves waiting to allow for resolution as the bubbles dissipate.

27.2.7.1 Early or Hard Opaque Bubble Layer

This occurs when the pulses initially placed in the cornea have no space available and the water vapor and carbon dioxide produced have nowhere to go, creating an OBL that appears before and in a more advanced position in relation to the front line of the raster plane. Early or hard OBL can block subsequent pulses and lead to uncut or poorly cut tissue, making flap lifts more difficult and increasing the risk for flap tears. Appropriate management includes changing laser settings to reduce OBL (Fig. 27.6).

27.2.7.2 Late Opaque Bubble Layer

The produced gases can also travel into the intralamellar spaces after their placement. The main cause of this type of OBL is the result of poor separation of the corneal tissue, and it appears more transparent and patchy. Again, lifts can be more difficult with late OBL. Management includes changing laser settings to reduce OBL (Fig. 27.7).

27.2.8 Decentered Flap

In the reported series of 19,582 cases, no significant decentered flaps were seen that did not allow excimer laser ablations either with the mechanical keratome or the femtosecond laser. However, it can occur if the suction ring is not placed properly. If this happens, the flap must not be lifted, or it must be repositioned, and the surgery is postponed until refractive stabilization and healing have been achieved, usually 3–6 months after the first procedure.

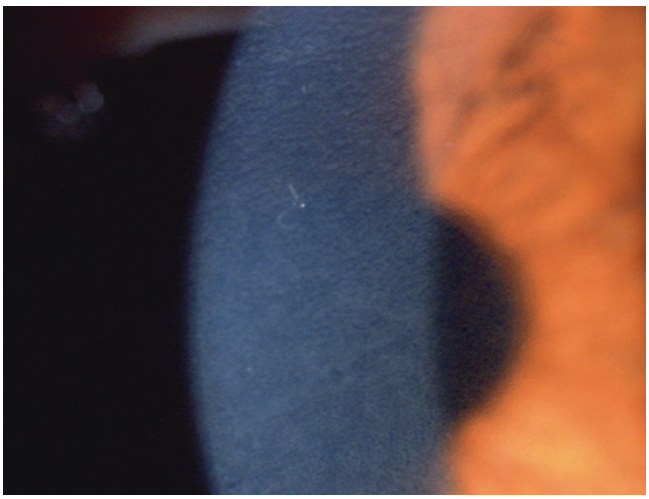

Fig. 27.8 Interface debris (fiber) associated with DLK in the visual axis

27.2.9 Interface Debris

Debris in the interface is a common finding after both femtosecond laser and microkeratome-assisted LASIK. Debris usually consist of meibomian gland secretions, fibers from sponges and eyelashes, or talc from gloves. It is important to distinguish debris from inflammatory or infectious conditions as debris are usually inert and can simply be observed in the absence of inflammation or associated visual symptoms [7]. However, when located over the pupil area, debris can cause visual symptoms or loss in CDVA, in which case they must be removed by lifting the flap and performing copious irrigation of the interface (Fig. 27.8).

27.2.10 Vitreoretinal Complications

Vitreoretinal complications (such as posterior vitreous detachment, retinal breaks and retinal detachment), although extremely rare, have been reported after LASIK [19]. The application of the suction ring in highly myopic eyes could be a contributing factor, but this association is highly controversial and could not be proved from previous studies. There were no vitreoretinal complications in this series treated with the femtosecond laser. There is only one reported case of macular hemorrhage in over 1,000,000 cases treated with the femtosecond laser [20].

27.3 Postoperative Complications

27.3.1 Flap Slippage

The definition of a slipped flap is one that has moved significantly enough to affect postoperative best-corrected visual acuity (BCVA). Most of these are related to traumatic dislocations, but other etiologies include medication-related and postoperative dry eye-related flap slippage. It most commonly presents in the first 12–24 h following the procedure, when the flap is less adherent, so that minor insults such as rubbing the eye or eyelid squeezing can dislocate the flap [21] (Fig. 27.9). Dislocated flaps can occur any time after surgery secondary to mechanical trauma to the flap, most commonly causing acute pain and decreased vision.

Studies have shown a significant lower incidence of flap displacements in LASIK flaps created with femtosecond lasers when compared to mechanical microkeratome, probably due to better flap stability associated with the angulation of the side cut, resulting in increased flap adhesion [7, 8, 22].

The reported incidence of flap slippage with the mechanical keratome has been reported to be as high as 1.1–2.0% [19, 23]. In our reviewed series, the use of the femtosecond laser reduced the incidence of slipped flaps by 50% compared with that of the mechanical keratome.

In a study comprising 81,238 eyes, with 23,997 treated with Moria One microkeratome and 57,241 treated with 60-kHz IntraLase femtosecond laser, Clare et al. [21] found eight eyes (0.033%) with flap displacement occurring within 48 h of the procedure in the microkeratome group and two eyes (0.003%) in the femtosecond group. The authors also found the highest incidence of flap displacements after surgery for hyperopia and the lowest rates after surgery for mixed astigmatism and myopia with femtosecond lasers.

A dislocated flap should be repositioned immediately. The underside of the flap and the stromal bed may need to be scraped to remove epithelial ingrowth. Any folds should be treated with flap elevation, hydration, and repeated massage with a spatula. Epithelial debridement may be needed to flatten recalcitrant flap folds. Rarely, suturing of the flap is necessary. Use of contact lenses, placing a shield over the eyes while sleeping, use of lubricants every 1–2 h in the first days and/or temporary punctal plugs, advise patients not to squint, and encouraging patients to blink softly in the immediate postoperative period are some protective measures used to avoid this complication.

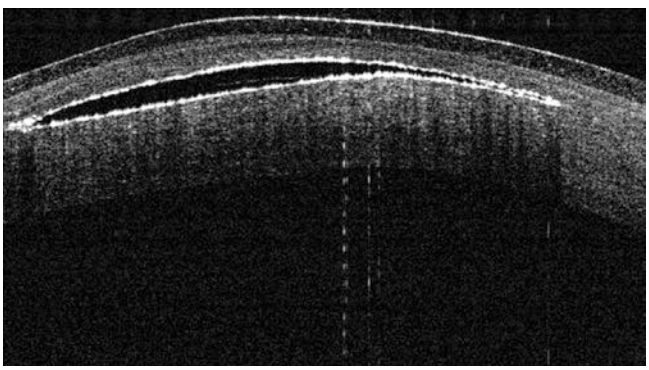

Fig. 27.9 AS-OCT showing collection of gas in the interface leading to flap displacement in the immediate postoperative examination

27.3.2 Flap Striae

Striae and folds on the flap are common postoperative flap complications that can lead to symptoms such as halos, diplopia, glare, and starbursts. Flap striae can be divided into two subcategories: visually significant and visually insignificant.

Visually significant striae or *folds*, defined as those that affect postoperative BCVA, result from a true flap movement or slippage and usually involve the visual axis, inducing irregular astigmatism. The earlier striae are noticed, the easier is their management, since fixed folds can form when epithelial hyperplasia takes place in the crevices between folds. Management consists of simple lifting and refloating of the flap and hydrating and stretching the flap radially with systematic sweeps using moist surgical sponge directed from the hinge out in a single parallel or center-to-periphery radial fashion. Instruments such as Pineda or Caro LASIK flap irons can also be used. Recalcitrant folds may need placement of antitorque sutures to stretch the flap in position, which can cause astigmatism [7]. Swelling the flap with hypotonic solutions may facilitate flattening when the flap is dehydrated. In cases of flap striae that are resistant to multiple treatments, surface ablation [24] and PTK with masking agent smoothing can be considered.

Visually insignificant striae or *microstriae* (VIMS) are defined as striae that are observed objectively by the examiner (better visible under retroillumination) but do not inter-

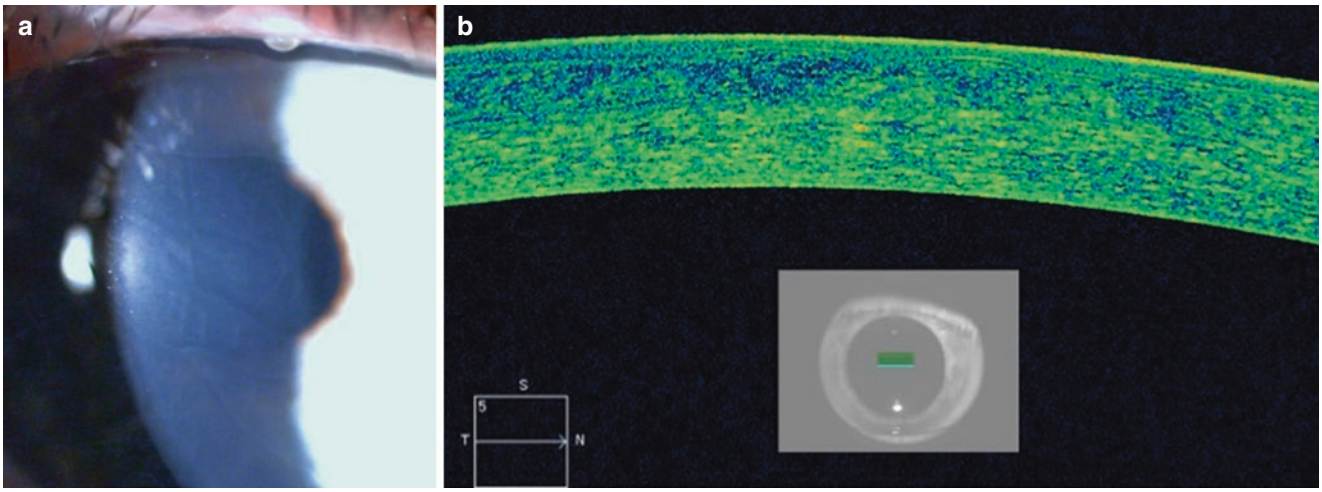

Fig. 27.10 (**a**) Visually significant striae (folds) affecting the visual axis; (**b**) AS-OCT showing flap folds

fere with *BCVA*. They result from the poor adaptation of the posterior surface of the flap to the laser-modified curvature of the underlying ablated stroma. For this reason, VIMS are more common in eyes that underwent higher amounts of myopic LASIK correction. Monitoring of VIMS is the treatment of choice, but thorough examination to determine if the quality of vision is affected by this finding is imperative. Patient's subjective complaints may warrant intervention similar to that of visually significant striae (*folds*).

Femtosecond laser flaps have stronger adhesion than microkeratome flaps, contributing to a lower incidence of striae or folds (Fig. 27.10) [10, 25].

27.3.3 Flap Edema

Flap edema is a localized swelling of the flap related to the surgical insult itself. It can be considered normal when limited to 24–72 h postoperatively and when management is usual topical steroids and antibiotic prophylaxis. However, should flap edema persist, then toxic etiologies should be ruled out and managed appropriately. This should be differentiated from interface flap edema syndrome or pressure-induced stromal keratitis (discussed later in this chapter).

27.3.4 Diffuse Lamellar Keratitis

Diffuse lamellar keratitis (DLK) is an uncommon, nonspecific sterile inflammatory response, typically seen within the first week after LASIK and occurs in the interface of the flap and underlying stroma. Patients can be asymptomatic or present with decreased vision and pain. DLK has been reported following either mechanical or femtosecond-related keratectomies [26], being more prevalent with femtosecond laser. The etiology appears to be multifactorial in published papers reviewing the syndrome [19, 26–30]. The first paper reporting this syndrome was by Smith and Maloney in 1998 [31].

The most commonly used classification system grades DLK in four stages [26] (Fig. 27.11):

- **Stage 1:** white granular cells in the periphery of the flap, sparing the visual axis. Usually seen on day 1 postoperatively
- **Stage 2:** progression of white granular cells onto the visual axis. Typically seen on days 1–3
- **Stage 3:** condensation of denser clumping of granular cells in the central visual axis, with haze and reduced vision, and relative clearing in the periphery
- **Stage 4:** severe lamellar keratitis with stromal melting and scarring, often leading to secondary hyperopia and irregular astigmatism

DLK related to laser-treated flaps has been mostly seen to start in the periphery and has been reported to occur 1–7 days after flap creation. The cause is unknown; however, it has been thought to be related to excessive manipulation of the flap edge and high side-cut energy settings. Earlier models of femtosecond laser microkeratomes were associated with higher incidence of stages I and II of DLK within the first week of the procedure compared with microkeratome [9, 33–35].

The design of the 60-, 150-, or 200-kHz femtosecond laser models allowed for much lower energy delivery to cut the flap and, therefore, a substantial reduction in keratocyte necrosis to the point that the overall inflammatory response is not significantly different from that noted with mechanical microkeratomes [13, 32].

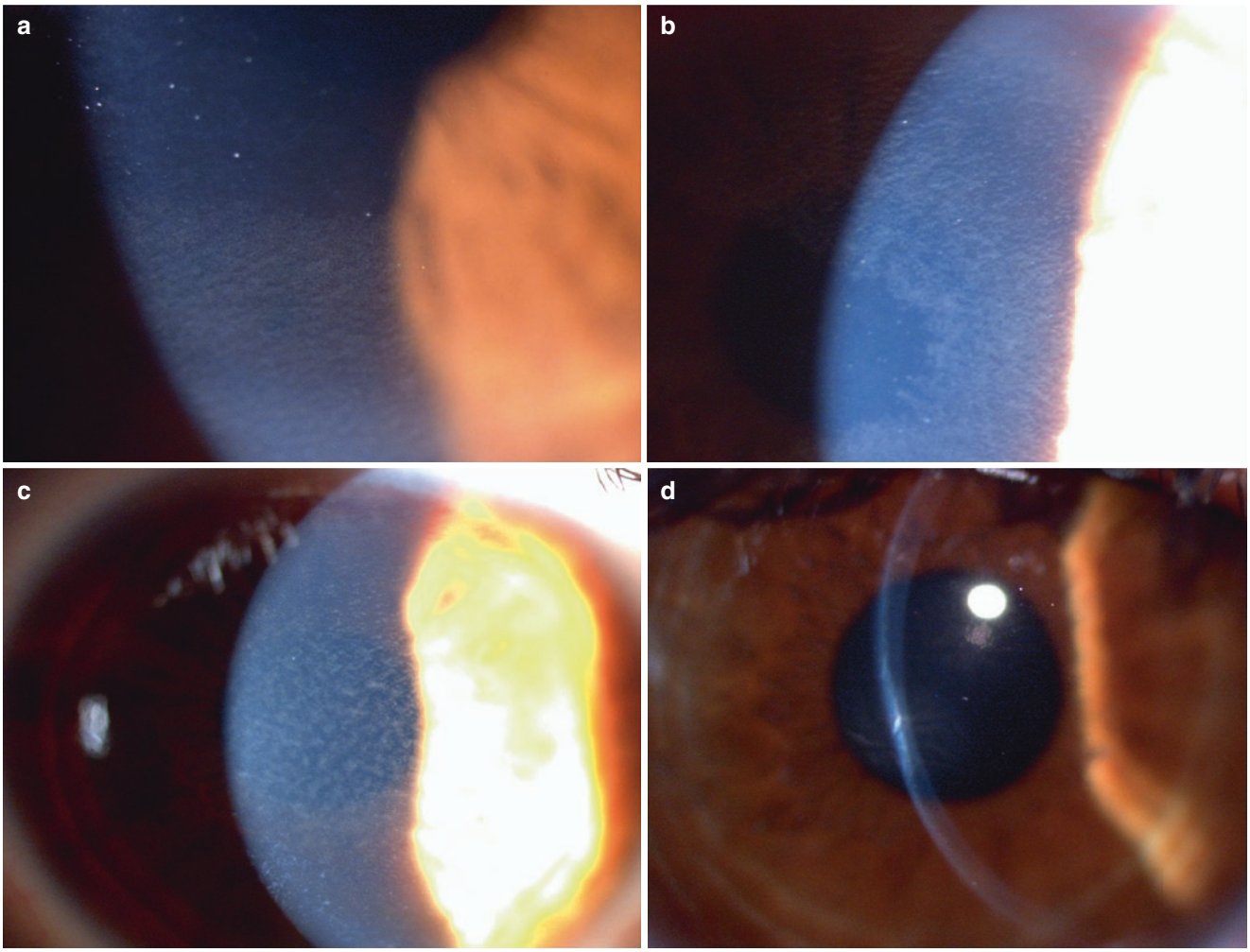

Fig. 27.11 (**a**) Stage 1 DLK; (**b**) stage 2 DLK; (**c**) stage 3 DLK; (**d**) stromal scar resulting from stage 4 DLK with stromal melting

Causes of DLK are multifactorial. The importance of identifying causal relationships and prevention is key to the management of this complication. Two factors commonly associated with DLK are flap epithelial defects and blood retained in the interface. Bacterial endotoxin or exotoxin from sterilizers, meibomian secretions, and infectious keratitis can also cause DLK [1, 33]. It is important to exclude infection by culture analysis if the condition is sufficiently severe that the flap should be lifted [8].

In a review of 6131 femtosecond LASIK cases, DLK stages 1–2 were present in 0.08% of cases. To date, no cases of stages 3 or 4 have been seen in this series. Pretreatment with topical antibiotics and corticosteroids has reduced the incidence of DLK in this series of 6131 cases from 0.08 to 0.04%. Pretreatment may reduce the inflammatory components of the tear film thereby reducing the reactionary patterns associated with DLK. All cases were managed with aggressive therapy with topical corticosteroids, and no postoperative complications were observed. Increased frequency of topical corticosteroids is needed to prevent DLK in the first 48 h after surgery when either of these occur after LASIK. Lifting the flap and irrigating underneath will be necessary for management of stages 3 or 4 DLK in addition to aggressive postoperative corticosteroids and possible systemic oral corticosteroids.

27.3.5 Pressure-Induced Stromal Keratitis

Pressure-induced stromal keratitis is caused by acute corticosteroid responsiveness, leading to increased intraocular pressure and subsequent presence of fluid in the interface [34–36]. It is often misdiagnosed as DLK or flap edema. Presence of fluid in the interface can falsely underestimate the IOP and can delay diagnosis and treatment. Management is directed at lowering intraocular pressure and cessation of corticosteroids.

27.3.6 Central Toxic Keratopathy

Central toxic keratopathy (CTK) is an acute-onset, rare, self-limited, noninflammatory process that results in a central or paracentral dense focal opacification of the corneal stroma, usually starting in 3-9 days after laser keratorefractive surgery. It is typically associated with loss of overlying tissue, stromal thinning, and a "lacquer" or "mud crack" appearance. The scarring process typically leads to hyperopic changes [37, 38]. The incidence in our series of 6131 femtosecond laser-assisted LASIK cases is 0.016%. Close monitoring and regular follow-up remains as the primary management strategy since the central stomal haze in CTK usually resolves spontaneously within 18 months. Central toxic keratopathy mimics stage 4 DLK, but it occurs early in the postoperative period and is noninflammatory. Furthermore, DLK tends to be diffuse, starting in the periphery and then advancing to the central optical zone [8, 34].

27.3.7 Epithelial Ingrowth

Epithelial ingrowth is typically diagnosed during slit lamp examination within the first 2–3 months after LASIK as islands of cells in the flap-stromal bed interface associated or not with a fibrotic demarcation line. Although usually asymptomatic on early stages, these cells may lead to decreased vision due to irregular corneal astigmatism, cell migration onto the visual axis, or melting of the overlying flap [1, 39–42] (Fig. 27.12). Occasionally, patients will complain of dryness or foreign body sensation and increased light sensitivity.

Multiple mechanisms have been proposed to explain the access of epithelial cells into the interface: invasion of cells through a buttonhole or a focal irregularity on the flap edge (with poor adhesive or apposed flap edge), direct implantation by the microkeratome blade or dissecting instrument (Fig. 27.13), and backflow of fluid carrying cells during irrigation of the interface. Risk factors include any factor that contributes to an epithelial defect preoperatively (epithelial basement membrane dystrophy, history of recurrent erosions, increased patient age, diabetes mellitus, previous corneal surgeries such as LASIK, transplants, or radial keratotomy) or perioperatively (intraoperative epithelial defect, ablation extending past the flap diameter, irregular flaps, thinner flaps, buttonholes, free cap, postoperative lamellar keratitis, flap relift, enhancement procedure, flap edema, flap misalignment or shift). A bandage contact lens should be strongly considered in the event of an intraoperative epithelial defect [39–42].

Because femtosecond laser creates more regular and adherent flaps, better apposed flap edges with angulated/vertical side cuts and causes less epithelial defects or traumas to the flap, the incidence of epithelium ingrowth after LASIK is lower with femtosecond laser flaps compared to mechanical microkeratomes. Kamburoglu et al. reported a rate of epithelial ingrowth of 0.03 and 1.8% following primary and enhancement procedure using a femtosecond IntraLase platform among 6415 eyes examined [40].

Epithelial ingrowth can be classified by the Probst/Machat epithelial ingrowth classification [41]:

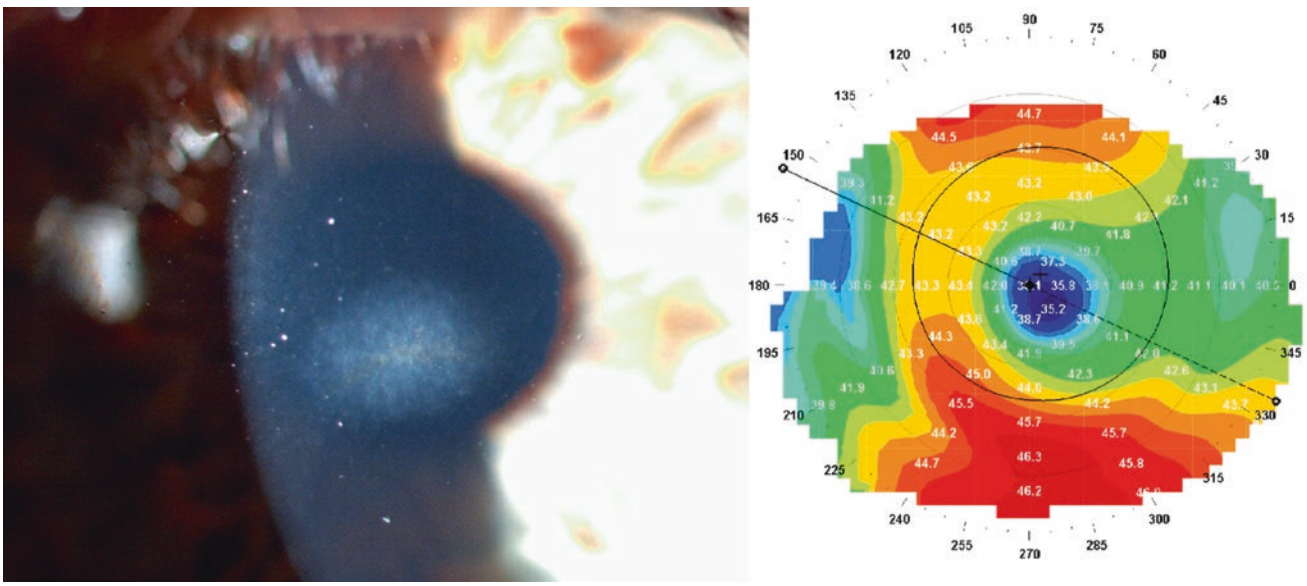

Fig. 27.12 CTK showing central dense focal corneal opacity and correspondent flattening of the anterior curvature

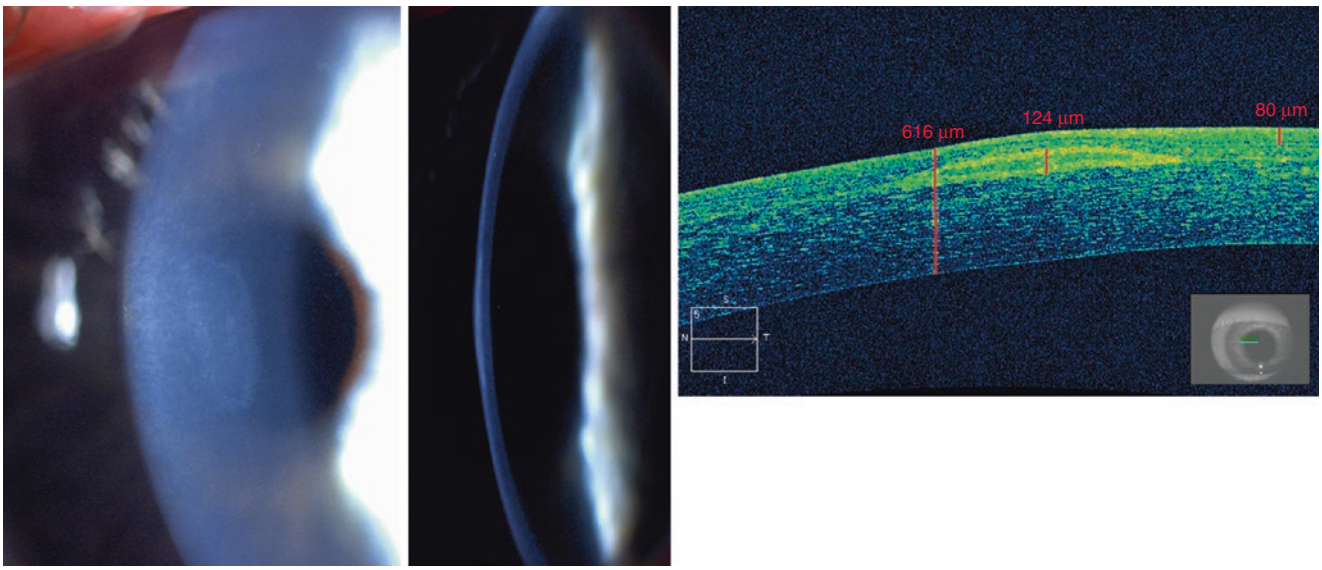

Fig. 27.13 6th day postoperative of femtosecond laser-assisted LASIK. Nest of epithelial cells in the central interface with no communication with the surface epithelium by the flap edge or buttonhole, suggesting that epithelial cells were directly implanted in the interface by the dissecting spatula or backflow of fluid

- **Grade 1:** thin ingrowth, 1–2 cells thick, limited to within 2 mm of flap edge, transparent, difficult to detect, well-delineated white line along advancing edge, no associated flap changes, and nonprogressive (no treatment required) (Fig. 27.14a).
- **Grade 2:** thicker ingrowth, discrete cells evident within nest, at least 2 mm from flap edge, individual cells translucent, easily seen on slit lamp, no demarcation line along nest, corneal flap edge rolled or gray, no flap edge melting or erosion, and usually progressive (requires non-urgent treatment within 2–3 weeks) (Fig. 27.14b).
- **Grade 3:** pronounced ingrowth, several cells thick, greater than 2 mm from flap edge, ingrowth areas appear opaque, obvious on slit lamp, white geographic areas of necrotic epithelial cells without a demarcation line, and corneal flap margins rolled with thickened white-grayish appearance. Progression results in large areas of flap melting from collagenase release from necrotic epithelium. Confluent haze develops peripheral to the flap edge as flap pulls away, leaving exposed stromal bed in contact with surface epithelium (urgent treatment required with close follow-up due to frequent recurrences) (Fig. 27.14c, d).

Treatment involves removing the invading epithelial cells from the interface by lifting the flap and scraping the epithelial cells from the stromal bed and undersurface of the flap with a scalpel blade; copious irrigation of the interface, pushing any tongues of epithelium back from the flap edge; and placement of a bandage contact lens to achieve closure of the flap edge, preventing recurrent invasion of epithelium into the flap stromal interface space. Adjuvant treatments such as ethanol, mitomycin, phototherapeutic keratectomy (PTK), or Nd:YAG laser have been described for recurrent epithelial ingrowth; however, these measures may cause adverse effects and are rarely necessary. Suturing the flap or the use of fibrin glue to seal the interface can be considered in recurrent cases [39–44].

27.3.8 Interface Haze

The incidence of interface haze is significantly less after LASIK compared to surface ablation treatment such as PRK, due to maintenance of the central corneal epithelial basement membrane with LASIK [1, 7, 45]. Post-LASIK corneal haze was significantly associated with younger age and thinner flaps, as flap cleavage plane might be closer to Bowman's membrane and epithelial basement membrane [46, 47]. Any damage to the epithelial basement membrane, such as with a buttonhole flap, may lead to activation of keratocytes into myofibroblasts and consequent localized haze [45, 49].

In the reported series of 19,852 LASIK cases, no interface haze has been noted in either the mechanical microkeratome or femtosecond laser group. Rarely, in both groups, the authors have seen a reticulated haze that was visually insignificant and that occurred at 2–3 months, without major subjective complaints or objective findings. In these rare isolated cases, a 2- to 3-week course of topical corticosteroids has resulted in resolution.

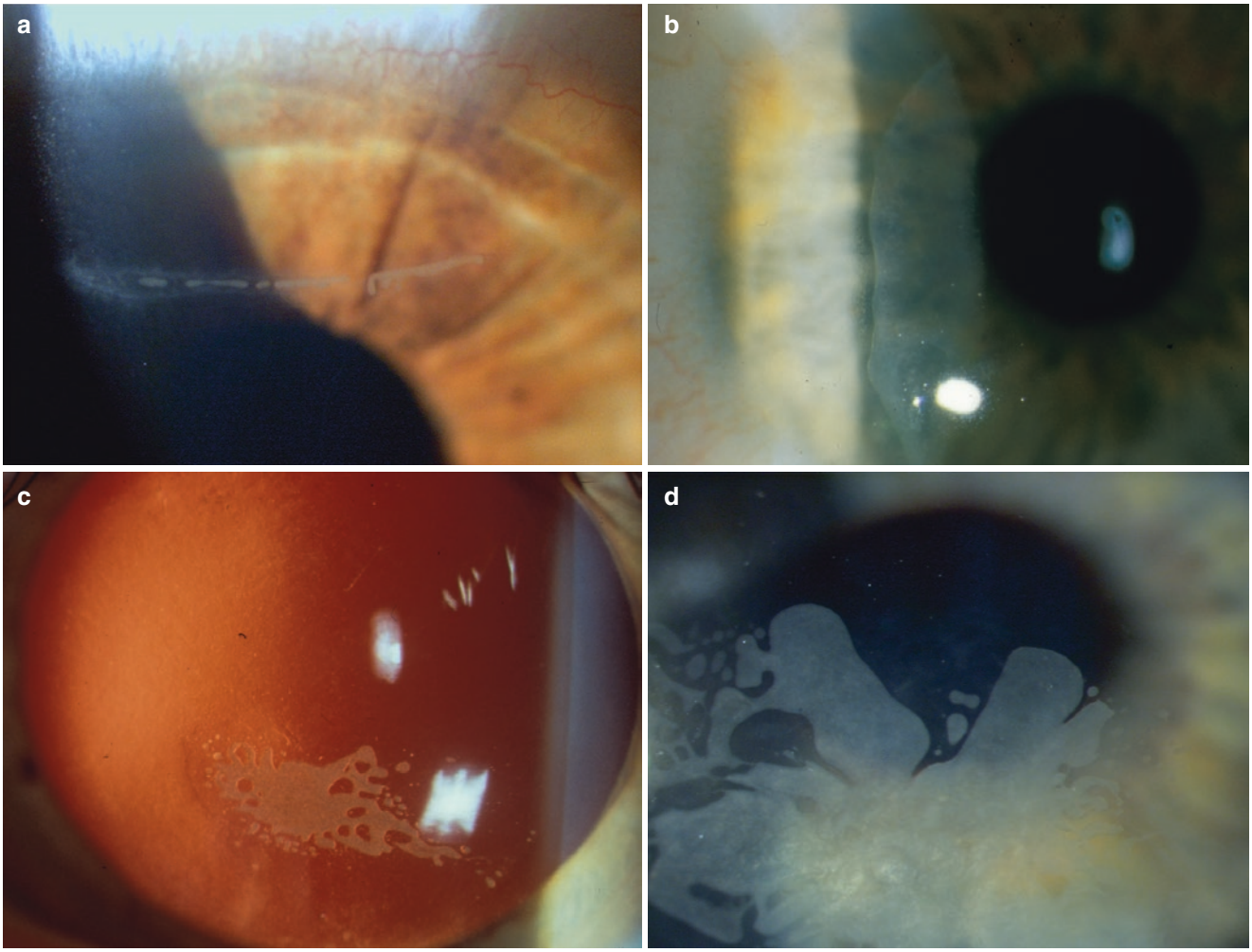

Fig. 27.14 (**a**) Grade 1 epithelial ingrowth adjacent to the hinge. (**b**) Grade 2 epithelial ingrowth. (**c**, **d**) Grade 3 epithelial ingrowth

27.3.9 Dry Eye and LASIK-Induced Neurotrophic Epitheliopathy

Dry eye or LASIK-induced neurotrophic epitheliopathy is the most common complication after LASIK. Multiple mechanisms may be involved: destruction of the corneal nerve endings, leading to decreased blinking rate, tear production, and tear film stability and distribution; increased evaporation of the tears; and loss of limbal goblet cells [7, 25, 48, 50].

Salomao et al. [50] postulated that eyes with femtosecond flaps, when compared to microkeratome, had a lower incidence of LASIK-associated dry eye (8% vs 46%, respectively, $P < 0.0001$) and required less treatment for the disorder. According to them, in addition to neurotrophic effects from corneal nerve cutting, other factors may be important because no correlation was found between flap thickness (or ablation depth) and the incidence of LASIK-induced dry eye. Conversely, Golas and Manche [51] found no statistically significant difference in dry eye symptoms between femtosecond and microkeratome-based flaps in a prospective study with 51 patients who underwent each technique in each fellow eye. Huang et al. [52] found that position of the flap hinge had no significant effect on corneal sensation or dry eye parameters in patients undergoing femtosecond laser-assisted LASIK.

Most cases of post-LASIK dry eye are well treated with preservative-free lubricants until corneal nerves regenerate at 6–8 months postoperatively. In more severe cases, topical cyclosporine A should be considered to treat the underlying inflammatory dry eye condition [50, 53]. Temporary collagen plugs or longer-lasting silicone punctal plugs, along with the short-term use of corticosteroids, have been used to control dry eye symptoms [7, 8, 53, 54]. The use of hemoderivatives such as autologous serum or platelet-rich plasma (PRP) eye drops is recommended in chronic cases which not respond to other treatments.

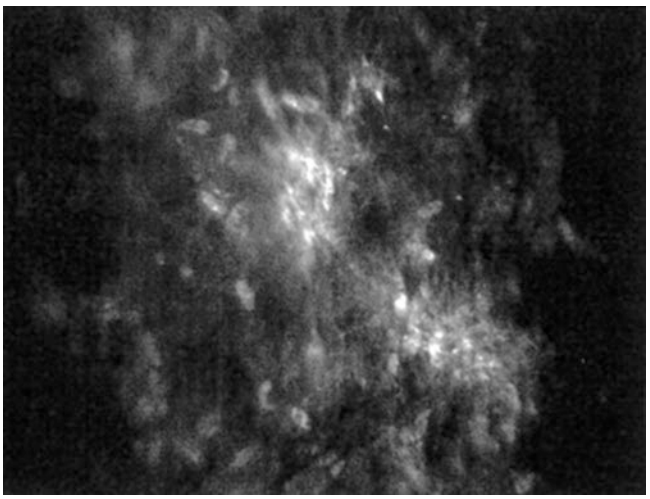

Fig. 27.15 Confocal microscopy of a patient with active TLSS illustrates the underlying activated keratocytes

27.3.10 Transient Light-Sensitivity Syndrome

Transient light-sensitivity syndrome (TLSS) is described as an intense light sensitivity with normal visual acuity and unremarkable slit lamp examination following routine femtosecond laser-assisted LASIK [55]. TLSS presents in patients within 2–6 weeks after femtosecond laser-assisted LASIK, although it can rarely occur several months after surgery. TLSS is a rare complication specific to the femtosecond laser technology and was most commonly seen when higher energies were used in earlier femtosecond laser platforms, such as with the 6- and 15-kHz IntraLase models, but has been noticed rarely with 30- and 60-kHz or even later models [55]. The incidence of TLSS has been reported as 0.17 and 0.4% in two separate series [6, 55]. The incidence significantly decreased after the introduction of lower raster bed and side-cut energies.

Although the etiology remains unknown and specific objective findings are absent, confocal microscopy analysis of affected patients' corneas has shown increased keratocyte activity (Fig. 27.15). It is thought that the laser energy may affect keratocytes or corneal nerve endings [7]. It has also been proposed that expelled gases traumatize the ciliary body and trigger localized inflammation [55]. As the name implies, it is transient and resolves with aggressive corticosteroid therapy over a short course of 2–3 weeks.

27.3.11 Rainbow Glare

Rainbow glare is a rare optical side effect of femtosecond laser-assisted LASIK that was first described in 2008 by Krueger et al. [56]. Patients have described seeing a spectrum

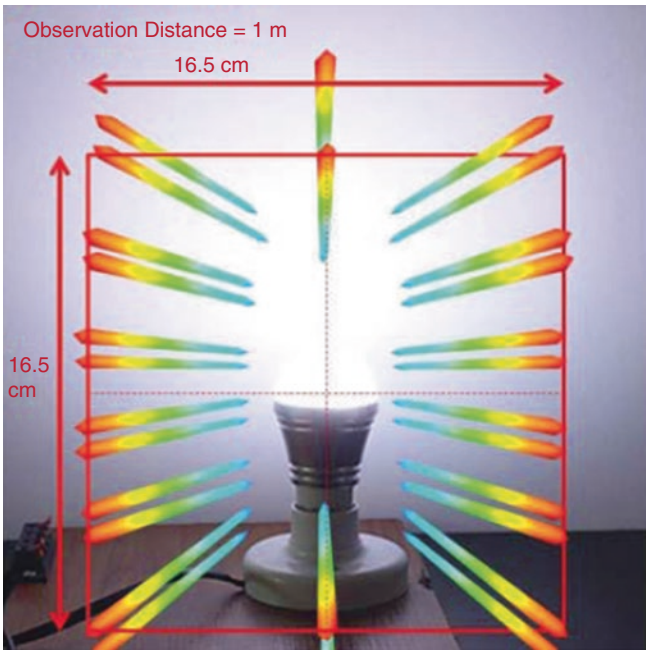

Fig. 27.16 Illustration offered by a patient reporting symptoms of rainbow glare. Six bands of color are seen around each side of a white light source (Image courtesy of Damien Gatinel, MD)

of 4–12 coloured spoke-like bands radiating from a white light source, most prominent in a dark environment, as in a nighttime setting or dark room [56–59] (Fig. 27.16). The cause of the rainbow glare is thought to be the diffraction of light from the grating pattern created on the back surface of a femtosecond laser-created LASIK flap [56]. To date, this complication has been reported at an incidence of 5.8% with the IntraLase FS60 (Abbott Medical Optics, Inc., Santa Ana, CA) and one case with the WaveLight FS200 (Alcon Laboratories, Inc., Fort Worth, TX) femtosecond laser platforms [57, 58].

Initial management consists of observation and monitoring these patients since the symptom eventually resolves with time. In eyes presenting with persistent and visually impairing rainbow glare symptoms, phototherapeutic keratectomy on the stromal side of the LASIK flap can eliminate the condition [59].

27.3.12 Infectious Keratitis

Although rare, infectious keratitis is the most dreaded postoperative complication of LASIK. Symptoms include redness, decrease in vision, photophobia, and pain with acute or gradual presentation within days or weeks. Bacterial keratitis tends to present earlier, within 3 to 5 days, whereas atypical mycobacteria or fungus presents a few weeks later [7].

In our review of 6131 cases, we have not seen a postoperative infection with femtosecond laser-assisted in situ ker-

atomileusis (LASIK). Additionally, in a report by Binder et al., in 1000 cases followed prospectively, no infections were noted [60].

Peripheral infectious infiltrates can be treated with broad-spectrum topical antibiotics, while those in the flap interface require more aggressive management, including lifting the flap, culture, irrigation, and replacing the flap. If the flap becomes necrotic, flap amputation may be necessary. Lid hygiene and optimization of the ocular surface prior to LASIK, aseptic surgical technique, and use of prophylactic broad-spectrum antibiotics in the first two weeks postoperatively are important preventive measures [7].

27.3.13 Postoperative Corneal Ectasia

Iatrogenic corneal ectasia is a rare complication of LASIK that usually occurs in eyes with predisposing factors such as forme fruste keratoconus. It is hypothesized that thinner and more predictable flaps obtained using the femtosecond laser lead to better biomechanical stability of the cornea and a lower risk of ectasia [10, 61, 62]. A new metric to evaluate ectasia risk factor after LASIK was recently introduced: Percentage of tissue altered (PTA) determines the integrated relationship between central corneal thickness (CCT), flap thickness (FT), ablation depth (AD), and the residual stromal bed. It is calculated by the formula PTA = (FT + AD)/CCT, and recent studies have shown that a PTA of 40% or more is significantly associated with ectasia in eyes with normal preoperative topography. Femtosecond laser and modern mechanical MK perform LASIK flaps as thin as 90 μm, therefore permitting lower values of PTA [61, 62].

27.3.14 Need for Enhancement

Enhancements are routinely performed after refractive stability, which usually occurs after 3–6 months postoperatively. Most surgeons prefer to lift the previously made flap and treat the residual stromal bed as long as enough tissue remains. While increased adhesion of femtosecond laser-created flaps is an advantage in preventing flap displacements and other complications, increased flap edge healing can be difficult or even impede re-lifting of the flap for LASIK enhancement, especially in flaps created more than a year before [10]. In this cases, enhancements may have to be performed with PRK with MMC, or a new side cut using femtosecond laser (within the old flap margin and intersecting with the previously created interface) can be created to enable flap re-lift [64–66]. Increased healing responses and subsequent difficult re-lifts are less common with newer femtosecond laser models. In cases in which residual stromal bed thickness is in question, many surgeons proceed with surface photorefractive keratectomy with administration of topical MMC and oral vitamin C to reduce the risk of postoperative haze or scarring.

In our series of 13,721 microkeratome cases versus 6131 femtosecond laser cases with the same surgeon, enhancement rates after at least 1-year follow-up were 4.2 and 1.6%, respectively. Enhancements rates have been dropping over the course of time due to excimer laser technological advancements.

Conclusion Since the introduction of the femtosecond laser for patient use in 2002, several technological advances have reduced flap creation time and allowed for reduced energy levels. Femtosecond LASIK flaps have shown advantages over mechanical microkeratome flaps regarding more regular and predictable morphology of the flaps, better flap adhesion with subsequent less risk of dislocation or epithelial ingrowth, and lower risk of epithelial damage or serious complications such as free caps. On the other hand, femtosecond laser is related to complications derived from a more intense inflammatory response, such as DLK and TLSS, as well as unique complications related to its mechanism such as OBL, anterior chamber bubbles, vertical gas breakthrough leading to buttonholes, rainbow glare, and hard-to-lift thin flaps leading to flap tears.

Newer femtosecond models allow for much lower energy delivery to cut the flap, to the point the overall inflammatory response is not significantly different from the microkeratome [10]. Many of the complications reported have been eliminated or reduced to lower levels with technological advances of newer models. Fortunately, with femtosecond technology, most of these complications are not sight threatening.

Take-Home Pearls

- Femtosecond LASIK flaps are more accurate, reproducible and uniform than those created by mechanical microkeratome.
- Femtosecond LASIK flaps present better adhesion to the stromal bed and better apposed edges, with less risk of dislocation, epithelial ingrowth, or serious flap-related complications such as free caps.
- Complications associated with the femtosecond laser technology — such as DLK, OBL, TLSS, anterior chamber bubbles, vertical gas breakthrough and raibow glare — are less common in the latest platforms that use lower energy and higher frequency of pulses.
- Femtosecond laser-related complications are usually non-sight threatening if managed appropriately.

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Part VII

Surface Ablation: Complications

Complications of Laser Epithelial Keratomileusis (LASEK)

28

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Core Messages

- Whilst laser epithelial keratomileusis (LASEK) offers excellent visual and refractive outcomes, with comparative studies demonstrating similar outcomes to laser in situ keratomileusis (LASIK), sight-threatening and non-sight-threatening complications may be associated with this procedure, albeit rarely.
- Such complications may occur perioperatively as well as hours, days, months and even years after surgery.
- Careful preoperative screening is mandatory to exclude eyes unsuitable for laser refractive surgery such as those with pre-existing corneal ectasia.
- Symptoms of recurrent corneal erosion syndrome are common in the first few months after LASEK and other surface ablation procedures. Such symptoms usually respond to lubricant therapy, but further outpatient surgical intervention may be necessary to address them in 1 in 200 cases.
- Patients need to be thoroughly counselled preoperatively as to the frequency and nature of possible complications of LASEK as part of any informed consent process.

28.1 Introduction

It has been over a decade since the technique of LASEK was described separately by Camellin [1], Azar [2] and Shah [3]. Unlike PRK, where the central epithelium is wholly debrided by blades or brushes, in the classically described LASEK technique, an epithelial flap with a superior hinge is created by means of a perioperative application of a dilute solution of alcohol, which creates a cleavage plane between the lamina lucida and the lamina densa of the epithelial basement membrane [4]. Following excimer laser treatment, the intact epithelial sheet is typically repositioned over the ablated corneal stroma, and to keep it in place, a bandage contact lens is applied during the first few days post-operatively. The reported purpose of replacing the epithelial sheet is to reduce post-operative pain, speed visual recovery and decrease the risk of iatrogenic haze occasionally seen after PRK by diminishing the early epithelial-stromal wound-healing interactions [1–3]. Such epithelial flaps, unlike the deeper partial-thickness stromal flaps created in LASIK, are not associated with intra-lamellar flap complications such as diffuse lamellar keratitis, permanent wrinkling, flap melt, epithelial ingrowth, etc., which can, albeit rarely, severely limit visual performance following LASIK [5].

Whilst LASIK offers clear advantages in terms of rapidity of post-operative recovery, multiple comparative studies using modern laser platforms have demonstrated similar medium- and long-term visual and refractive outcomes between LASEK and LASIK for low hyperopic and low, moderate and even high myopic corrections [6–15]. Indeed, a recent study by Kirwan and O'Keefe demonstrated less induction of higher-order aberrations in LASEK compared to LASIK-treated eyes [14]. A finding has also been reported in two recent published prospective studies by Wallau and Campos and Moshirfar et al. comparing PRK and LASIK, with less induction of higher-order aberrations in PRK-treated eyes [16, 17]. In a recent meta-analysis, Zhao et al. identified 12 controlled trials comparing LASEK (780 eyes) to LASIK (915 eyes) and noted no significant differences in visual and refractive outcomes between the two surgeries for low to moderate myopia. However, the incidence of loss of ≥1 line of corrected visual acuity was significantly higher for high myopia treated by LASEK than LASIK in the mid-term and long-term follow-up, due to the increased incidence of stromal haze with LASEK [18]. It is of note, however, that mitomycin C (MMC) was not used as an adjunctive treatment with LASEK in high myopic eyes in any of these studies [18].

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Comparative studies of LASEK and PRK have demonstrated no consistent significant differences in clinical outcomes. In terms of early post-operative recovery, whilst Leccisotti et al. [19] demonstrated no differences, Autrata and Rehurek [20] and Lee et al. [21] in prospective bilateral studies found less pain and faster visual recovery after LASEK. In contrast, Litwak et al. [22] found more pain and slower epithelial healing after LASEK, although they exposed the epithelium to 20% alcohol for 45 s, which would result in the death of virtually all cells in the flap [23]. In the only reported comparative study of hyperopic corrections, Autrata and Rehurek [24] reported less pain, faster visual recovery and quicker refractive stability with LASEK compared with PRK. A more recent randomized, bilateral clinical study by Einollahi et al. utilizing confocal microscopy comparing mechanical versus alcohol-assisted epithelial debridement with PRK reported retarded epithelial healing time and decreased retro-ablation stromal keratocyte density with mechanical debridement [25].

In terms of visual and refractive outcomes, recently published meta-analyses by Zhao et al. and Cui et al. of clinical outcomes of LASEK and PRK in myopia, while demonstrating less sub-epithelial haze at 1 and 3 months after surgery with LASEK, failed to demonstrate any differences in primary outcome (UCVA, manifest refractive spherical equivalent) or secondary outcome (epithelial healing, pain, haze) measures after these time points [26, 27]. Similarly, Ghoreishi et al. in a randomized controlled trial comparing alcohol-assisted versus mechanical epithelium removal in PRK in 1250 eyes found entirely comparable results between the two techniques [28].

With regard to other methods of surface excimer laser ablation, whilst Teus et al. in a randomized prospective trial comparing LASEK and Epi-LASEK demonstrated faster visual rehabilitation and better safety and efficacy after LASEK for low to moderate myopic corrections [29], Hondur et al. in a prospective, bilateral study of Epi-LASIK and LASEK for myopia found comparable results between the two methods at 1 year [30], and Reilly in a retrospective chart review reported less pain and a trend towards less haze with Epi-LASIK [31]. Similarly, whilst Aslanides et al. in a randomized, bilateral prospective study comparing trans-epithelial to alcohol-assisted PRK reported lower pain scores, faster epithelial healing and less haze at 6 months with the all laser techniques [32], Luger et al. in a randomized, bilateral study demonstrated no differences in efficacy or safety between the two techniques [33].

Published outcomes of LASEK procedures over the past decade are very encouraging [6–34]. In a review article by Teneri et al., the cumulative reported safety index of 11 peer-reviewed papers was 1.0, with only a single eye of nearly 1500 studied, losing two or more lines of BSCVA due to a macular cyst unrelated to the LASEK procedure [34]. Reported predictability was excellent with 83% of eyes within +0.50 D of the intended correction at 6 months, with an efficacy index of 0.947 [34]. Similarly, the author's own experience with this technique has been very positive with excellent efficacy and safety not only for low and moderate myopia but also for high myopia (−6.00 to −12.00 dioptres) and hyperopic corrections [35, 36].

Such results are the product of two decades of increasing knowledge of laser-tissue interactions and corneal wound-healing responses, the development and access to advanced technologies and meticulous attention to detail with regard to preoperative patient education and counselling, preoperative evaluation, operative procedures and post-operative care. A detailed knowledge of possible complications both sight threatening and non-sight threatening, their avoidance and management is absolutely essential in order to minimize adverse events post-operatively and optimize visual and refractive outcomes and patient satisfaction. This is especially important taking into consideration the elective nature of keratorefractive procedures and the associated high patient expectations.

28.2 Intraoperative Complications

28.2.1 Alcohol Escape and Perioperative Pain

The LASEK procedure is relatively easy to perform and takes only a few minutes to undertake. It is normally painless. However, if alcohol escapes from underneath the LASEK well onto the bulbar conjunctival surface, then significant ocular pain and discomfort can result. Alcohol escape should be avoided not only to facilitate a painless surgical procedure but also as it might cause limbal epithelial stem cell damage, which may delay epithelial healing, and conjunctival epithelial damage, which will increase post-operative discomfort and inflammation. To avoid this complication, patients should receive adequate topical anaesthesia with 2–3 drops of topical tetracaine 1% (which also helps facilitate the alcohol epithelial removal). They should be fully informed of the need to stay still during alcohol application and told that they will experience a pressure sensation when the well is placed on the globe and loss of visual clarity as it is filled with alcohol. Firm, but not excessive, pressure should be used when holding the LASEK well on the ocular surface. Should alcohol escape occur, the ocular surface should be immediately irrigated with balanced saline solution, the conjunctival and corneal surface dried and the well reapplied for the remainder of the application time.

28.2.2 Poor Epithelial Flap

With application of 15–20% alcohol for 25–40 s, the fashioning of an intact epithelial flap with an adequate superior hinge is usually straightforward [1–3, 23, 24, 34–37]. However, in a few cases, the epithelium may be especially adherent. In the author's experience, this tends to occur in individuals who have undertaken excessive long-term contact lens wear. This has been similarly noted by Claringbold, who also identified young men and postmenopausal women as having more adherent epithelium [36]. In such eyes the author increases alcohol exposure time to 30 s instead of 25. Camellin, in his series, reported difficulty in obtaining an intact epithelial flap in 12% of eyes [1, 38]. The author reported adherent and incomplete epithelial flaps in 4% of high myopic [35] and 6% of hyperopic eyes [36].

If adherence is encountered, replacing the flap and applying alcohol for 10 more seconds usually facilitate improved flap creation. However, if it is not possible to obtain a complete epithelial flap, then the procedure can be simply converted to a PRK technique by mechanically debriding the epithelium with the knowledge that although the patient may [21, 24, 25] or may not [22] experience more post-operative pain and a slightly slower visual recovery, the long-term clinical outcomes are the same [26–28].

28.2.3 Free Flap

It is the author's observation that the corneal epithelium is often less adherent superiorly than inferiorly, which helps facilitate superior hinge formation. However, it may be occasionally difficult to fashion an adequate epithelial hinge, and a free epithelial flap can occasionally occur. This tends to be more common in the treatment of hyperopic eyes where much larger (9.00–10.00 millimetre (mm)) flaps need to be fashioned. In such cases the flap can still be repositioned over the ablated stromal surface, although care should be taken to ensure the flap is placed basal epithelial-side down. Following replacement of a free flap, a few minutes drying time should be allowed, and a bandage contact lens can then be carefully inserted in the usual manner to keep the epithelium in place. Post-operative care can then continue in the usual manner. It should be noted, however, that for many surgeons, it is their usual practice to discard the epithelial flap before contact lens placement. Liu et al. reported less post-operative pain and faster visual recovery with a flap removal technique in a series of 582 patients [39], whilst Taneri et al. in a comparative case series demonstrated no difference in terms of pain, epithelial closure time and haze development in eyes treated with flap retention or removal [40]. Similarly, Kalyvainaki et al. in a double-masked, bilateral randomized study of epi-LASIK found no differences with discarding or keeping the epithelium [41]. It is therefore not unreasonable to simply discard the epithelium in cases of free or poor flaps as the ultimate refractive and visual outcome should still be very satisfactory.

28.3 Early Post-operative Complications (Hours/Days)

28.3.1 Pain

Whilst some comparative studies have shown no differences [19], others have reported less post-operative pain after LASEK compared with PRK [20, 21]. Camellin reported that over 60% of his patients experienced little/no pain following LASEK [38]. However, it is the author's experience [35, 36] that the majority of individuals do experience pain/discomfort during the first 1–24 h after LASEK and a number of individuals may report considerable pain.

Most surgeons prescribe oral analgesics for 2–3 days after the procedure, both opiate and non-opiate. Topical non-steroidal anti-inflammatory agents have been shown to be efficacious in reducing pain following LASEK and other ocular surface ablation procedures [42–44]. A number of different agents have been utilized with efficacy being demonstrated with topical indomethacin 0.1%, diclofenac 0.5%, nepafenac 0.1% and ketorolac 0.4% [42–44]. Care must be exercised, however, with administration of these agents as corneal melting has been reported very rarely with their usage [45–47]. They should only be used for a few days following surgery, in limited dosage, and patients must be carefully counselled regarding their correct usage and dosage.

Considerable pain relief without any detrimental effects on visual and refractive recovery has also been demonstrated by Verma et al. with the use of limited and supervised topical anaesthetic administration after PRK [48, 49]. In the author's practice, great benefit has been found, with no detrimental effects, with the use of topical preservative-free anaesthetic drops (benoxinate 0.4%) in a limited dosage, with a maximum of one drop every 2 h for the first 18 h following surgery (maximum of ten drops in total) for acute pain control after LASEK [35, 36]. Patients, however, must be very carefully counselled as to the importance regarding the correct dosage of such agents as keratopathy after LASEK with their excessive use has been reported [50].

28.3.2 Delayed Epithelial Healing

In the author's experience, epithelial closure is usually present in myopic LASEK corrections within 3–4 days [35] and hyperopic corrections, which have larger overall ablation

diameters, within 3–7 days following surgery [36]. Kornilovsky reported epithelial closure at 4 days [51], Camellin et al. 4–5 days [1, 38] and Lee et al. 3.68 + 0.69 days [21] in myopic LASEK corrections. Taneri et al. in a review article reported a closure rate of 78% at 3 days and 99% at 1 week [34]. Most surgeons remove bandage contact lenses between 3 and 5 days or when epithelial closure is complete. Late epithelial closure beyond 5–7 days is unusual. Such patients need to be carefully examined and monitored because of the risks of underlying stromal melt, the ongoing risk of infection and the possible development of late corneal haze and scarring. Any signs of stromal infiltration should alert the practitioner to the possibility of potential sight-threatening complications such as an infection or melt. Conditions predisposing to delayed epithelial closure include dry eye problems, preservative toxicity, drug allergy (topical antibiotics), topical drug abuse and overusage (non-steroidal anti-inflammatory and anaesthetic drops) and limbal stem cell anomalies.

Prior to surgery, it is vital to eliminate patients with dry eye problems, as this may exacerbate epithelial healing problems following surgery. Patients with overt dry eye problems do not make good candidates for laser refractive surgery and are contraindicated. Those with mild dry eye symptoms and signs can be treated prior to surgery with ocular lubricants, punctal plugs, aggressive treatment of concurrent lid disease and omega-3 oral supplementation [52, 53]. If satisfactory resolution occurs, then keratorefractive surgery may be possible provided there is no associated manifest connective tissue problem. Whilst surface laser ablation is generally associated with less induction of post-operative dry eye problems [54], if delayed epithelial healing occurs in the presence of dry eye, ocular lubricants, punctal plugging and omega-3 supplementation should be implemented immediately [52, 53].

Toxicity of preservatives and drug allergy should be suspected in cases of retarded epithelial healing and in the presence of a history of previous intolerance to contact lens solutions, continuing conjunctival injection and punctate epithelial erosions. In eyes where epithelial closure is delayed beyond 4–5 days, the use of preservative-free medications is advisable.

Patients with conjunctival cicatrizing conditions and limbal stem cell deficiencies are not candidates for keratorefractive surgery and should be excluded preoperatively by careful slit-lamp biomicroscopic examination.

28.3.3 Slow Visual Recovery

Immediately after LASEK, provided an intact epithelial flap has been created and successfully replaced, patients typically notice an immediate improvement in unaided post-operative visual performance. It is not uncommon for patients to then experience a reduction in visual acuity after the first 12–24 h, as epithelial cells within the flap damaged by alcohol swell and die [23] or occasionally if the flap sloughs off. Patients should be warned before surgery that although ocular pain, redness and swelling improve after 12–24 h, early visual impairment is not unusual and will not influence the ultimate final outcome. Vision begins to improve after a few days following epithelial closure, and even in high myopic corrections (greater than −6.0 D), 90% of eyes have an UCVA of 20/40 or better and 70% of 20/30 or better by 1 week [35]. For low myopic corrections and in younger patients, visual recovery is much faster. With hyperopic LASEK corrections, visual recovery is typically more protracted [36]. Less than 50% of such patients achieve an UCVA of 20/40 or better by 1 week, as epithelial regeneration is slower in the presence of larger flap diameters and in older patients, and myopic overcorrection during the first few weeks and months after surgery is usual [36]. Hyperopic LASEK patients need to be counselled preoperatively that although functional unaided near vision may be achieved during the first few weeks, satisfactory levels of unaided distance visual acuity may take several weeks and even months [36].

Protracted visual recovery in the early post-operative period, beyond that considered above, is typically the result of delayed or irregular epithelial healing. As discussed above, predisposing causes include dry eye, preservative toxicity, drop allergy, anaesthetic and non-steroidal eye drop abuse, infection and pre-existing ocular surface anomalies. Prevention is always better than cure, and it is obligatory that all patients have a complete preoperative ophthalmic consultation and examination by a suitably experienced practitioner with a thorough knowledge of anterior segment disease so that pre-existing conditions are adequately treated prior to surgery and unsuitable patients with untreatable and/or extensive ocular surface disorders are excluded. In the presence of delayed epithelial healing, infectious and non-infectious keratitis must be excluded, investigated and appropriately managed, the tear film optimized [52, 53] and correct compliance with topical medication ensured [45–47, 50].

28.3.4 Sterile Infiltrates

Punctate sterile epithelial infiltrates without stromal infiltration may develop during the first few weeks after LASEK. They may occasionally be the result of dry eye and/or preservative toxicity/drug allergy. They can be treated by optimizing the pre-corneal tear film and frequent preservative-free topical corticosteroid administration.

Occasionally, anterior stromal infiltration may occur. In these cases infectious keratitis needs to be excluded, and eyes with an associated overlying epithelial defect must be assumed infected and investigated and treated appropriately. Where the overlying epithelium is closed and the anterior chamber quiet, such eyes may be treated by increasing the

frequency of topical corticosteroid medication whilst maintaining antibiotic cover until the infiltrates have resolved [55]. However, the patient must be kept under very careful observation and a high degree of suspicion for infective keratitis be maintained, and if in any doubt, appropriate microbiological specimens must be taken.

28.3.5 Early Infectious Keratitis

Infectious keratitis is a very rare event after LASEK and other surface laser ablation procedures with a reported incidence in one multicentre study of 18,651 eyes of 0.2% [56]. It has been postulated that as the infectious process commences at the epithelial level in LASEK/PRK and not intrastromally as in LASIK, it might be easier to manage in terms of the taking of microbiological specimens and antimicrobial penetration [57]. Because of its serious sight-threatening potential, surgeons need to maintain a high level of suspicion with regard to its occurrence. In suspected cases immediate and aggressive management is imperative, with the taking of appropriate microbiological specimens and targeted intensive topical antimicrobial therapy. With such management, good visual acuity is usually restored [56, 58, 59]. In de Rojas's multicentre study of surface ablation procedures including LASEK, 72% of cases were presented within 7 days, cultures were positive in about 50%, *Staphylococcus* was the most frequently isolated organism and over 90% retained a corrected distance acuity of 20/40 or better [56].

In order to minimize the potential occurrence of infective keratitis, patients must be examined preoperatively for signs of active lid margin disease, which must be treated appropriately with lid hygiene and, if indicated, systemic tetracyclines before considering laser refractive procedures. Following laser refractive surgery, practitioners typically advocate the use of a broad-spectrum prophylactic topical antibiotic regimen until epithelial closure is complete. Common therapies include the use of an aminoglycoside, such as tobramycin, which covers gram-negative organisms including *Pseudomonas*, and/or a fluoroquinolone, which covers both gram-positive and gram-negative species. Preferred agents include ofloxacin and fourth-generation fluoroquinolones such as gatifloxacin and moxifloxacin.

28.4 Early Post-operative Complications (Days/Weeks)

28.4.1 Slow Visual Recovery

At 1 month over 80% of myopic eyes after LASEK achieve an UCVA of 20/20 or better [6–9, 11–15, 19–22, 24, 26, 27, 29–40]. Occasionally, however, visual recovery may take longer, up to 3–4 months. As well as residual refractive error, this can be due to epithelial irregularity because of delayed epithelial healing (as discussed above). Such patients need to be carefully examined to exclude the presence of sight-threatening complications such as late infective keratitis, non-infective keratitis/melt and steroid-induced raised intraocular pressure.

In hyperopic LASEK corrections, visual recovery is generally slower, with less than 40% of eyes achieving an UCVA of 20/20 or better at 1 month due to myopic overcorrection that may take several months to settle, especially in high-order corrections greater than +3.00 D [36].

28.4.2 Intraocular Steroid Pressure Response

Although randomized clinical studies have indicated little benefit from topical corticosteroid administration following surface excimer laser procedures [60], the vast majority of surgeons still prescribe topical steroids during the first few weeks after LASEK/PRK to minimize the development of corneal haze. Fluorometholone 0.1% (FML) is often the preferred agent, as its reduced ocular penetration reduces the risk of associated intraocular complications such as increased intraocular pressure, enhanced risk of infective keratitis and cataract formation [60–62]. When prescribing such medications, it is essential to monitor patients for an intraocular pressure (IOP) response if they are used for longer than 10 days. Ideally patients should have intraocular pressure measurements every 2 weeks whilst they are administering such medications [63]. With FML usage, steroid-induced ocular hypertension has been reported in up to 3% of cases [61]. Should an elevated intraocular response occur, the steroid medication should, if possible, be terminated. Topical antiglaucomatous medications, in the first instance preservative-free Timoptol 0.25% twice daily (unless contraindicated), may be prescribed. Preservative-free apraclonidine 1% three times a day is useful if the pressure is greater than 30 mmHg. Systemic acetazolamide is rarely required. The intraocular pressure usually returns to normal levels at 1–2 weeks after stopping the steroid drops. The use of new steroid agents, designed to produce less intraocular pressure problems, such as loteprednol etabonate 0.5% in laser refractive surgery has been encouraging [64]. Thanathanee et al. in a recent randomized prospective clinical trial comparing a loteprednol etabonate 0.5% with dexamethasone 0.1% found no differences in post-operative vision and haze but less occurrence of elevations of IOP with loteprednol etabonate [64].

28.4.3 Recurrent Corneal Erosion Syndrome

Fifteen to 20% of patients undergoing LASEK and PRK report "dryness" and discomfort on first opening their eyes when waking in the morning or in the middle of the night

[65]. Such symptoms are indicative of mild recurrent corneal erosion syndrome. They occur during the first few months post-operatively and then typically resolve. In persistent cases or when symptoms become frequent and problematic, the use of topical lubricant ointments such as Lacri-Lube and Simple at night for 8–10 weeks is often successful in alleviating and resolving such problems. In cases with pre-existing lid disease, systemic tetracyclines are a useful adjunctive treatment, possibly due to inhibition of metalloproteinase-9 [66]. Optimization of the tear film with ocular lubricants, punctal plugging and omega-3 supplementation is often beneficial [52, 53].

After 9–12 months, in persistent cases that have not responded to medical therapy, it may be necessary to perform a peripheral anterior stromal puncture procedure. This can be performed as a quick outpatient procedure under topical anaesthesia with a 25G needle. The stromal punctures are directed to the 360°, 3.0 mm paracentral/peripheral corneal area outside the central optical zone, both to avoid scar formation across the visual axis and as the epithelium overlying the area of ablation is typically firmly adherent to the underlying stroma (Fig. 28.1). In the author's experience of 12 years of performing LASEK, anterior stromal puncture has been necessary in ten eyes of six patients (<0.5%) when symptoms have persisted after 9 months. In all cases, it has resulted in improvement/resolution of symptoms, with only one case requiring a repeat procedure.

Symptoms of recurrent erosion syndrome are more common after surface ablation procedures than LASIK [65]. In the author's experience, it is more common with low-order myopic corrections (typically less than −4.00 D) and in myopic rather than hyperopic corrections due to the width of the stromal ablation. Patients should be counselled and warned preoperatively about the occurrence of such symptoms as they can have a significantly adverse effect on patient satisfaction [65]. Prior to alcohol administration, it can be useful to test the adherence of the epithelium with a LASIK sponge. If the epithelium moves and wrinkles, it is likely that there is an underlying epithelial basement membrane dystrophy, and then the procedure can be performed without alcohol administration and early medical therapy, with topical lubricants before sleeping, instigated immediately post-operatively. In eyes with signs of epithelial basement membrane dystrophy preoperatively (epithelial cysts and whorls seen on slit-lamp examination), it is the author's practice not only to warn the patient prior to surgery of the increased risks of recurrent erosion syndrome but also to combine the LASEK procedure with a peripheral anterior stromal puncture technique (Fig. 28.1).

28.4.4 Corneal Melt

Corneal melting after LASEK/PRK is an extremely rare occurrence. Cases have been reported in the presence of collagen vascular diseases such as systemic lupus erythematosus (SLE) [67]. It is important to exclude such patients preoperatively. Some practitioners regard collagen vascular diseases as only a relative contraindication to refractive laser surgery with surgery being considered possible in cases of completely controlled systemic disease with no ocular manifestations and no clinical signs or history of dry eye symptoms [68]. However, the presence of active systemic disease with past ocular involvement and dry eye is an absolute contraindication.

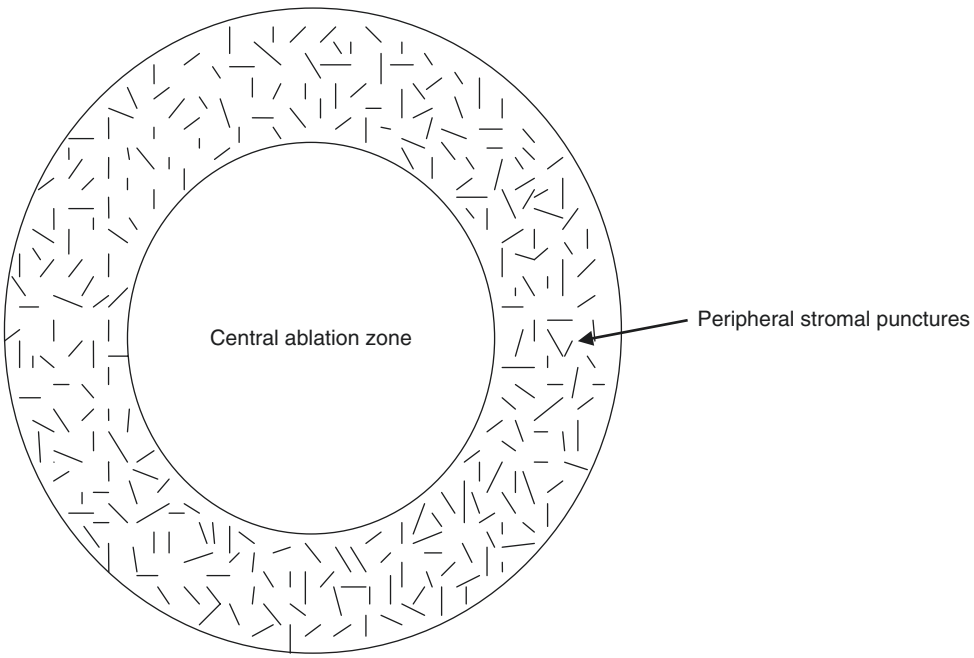

Fig. 28.1 The stromal punctures are directed to the 360°, 3.0 mm paracentral/peripheral corneal area outside the central optical zone

As well as collagen vascular diseases, other predisposing causes for corneal melting after LASEK include dry eye, anaesthetic [49] and non-steroidal eye drop abuse [45–47], infection and pre-existing ocular surface anomalies. It has been particularly associated with the use of non-steroidal drops, which have been shown to induce the production of collagenases and matrix metalloproteinases [45–47]. It is for this reason that the author prefers not to prescribe these medications after keratorefractive surgery and prefers limited topical anaesthesia application for the first 18 h after surgery.

If corneal melting should occur, then associated dry eye problems must be immediately and aggressively treated and infectious keratitis excluded. If being administered, topical anaesthetic and non-steroidal drops should be stopped. Expert subspecialist ophthalmic medical management is required with intensive topical preservative-free corticosteroid and systemic immunosuppressive therapy. Further surgical interventions such as amniotic membrane grafting and keratoplasty may be necessary [45–47, 50, 68].

28.4.5 Herpes Simplex Keratitis

Patients with recurrent herpes simplex keratitis are not candidates for routine keratorefractive surgery. Phototherapeutic keratectomy (PTK) can be useful in selected cases, but reactivation may occur [69], and such eyes require prophylactic systemic antivirals (acyclovir 400 mg bd starting for 2 weeks prior to surgery and for 6 months following surgery). Any eye with an unexplained corneal scar preoperatively must be regarded as suspicious, and a full history must be taken. In patients that develop labial herpes simplex during the early/medium post-operative period, it is recommended that they are prescribed systemic prophylactic acyclovir.

28.4.6 Late Infectious Keratitis

Late infectious keratitis is a rare event after LASEK. As discussed above the incidence of infectious keratitis after surface laser ablation procedures is 0.2% with the majority of cases occurring within the first week after surgery [56]. Infection presenting after the first week in similarity to those cases after LASIK tends to occur in the presence of atypical organisms such as mycobacterium species [70] and fungi [71, 72].

Surgeons must be aware of the occurrence of such late infections so they can be adequately managed. Patients should be informed that they must return promptly with any symptoms of pain, redness and sudden visual loss occurring in the first couple of months after surgery. In such patients especially where there are signs of corneal infiltration/melting, there should be a high suspicion of late infectious keratitis. Microbiological specimens should be taken, particularly for atypical organisms, and appropriate antimicrobial therapy instigated. In the presence of worsening signs and symptoms and negative cultures, corneal biopsy and even therapeutic keratoplasty may be required. The role of corneal cross-linking in such cases is as yet undetermined and requires further evaluation but may perhaps be of benefit [73].

28.5 Medium-Term Post-operative Complications (Weeks/Months)

28.5.1 Overcorrection/Undercorrection

For corrections between +4.00 and −8.00 D and up to −5.00 DC, published studies of LASEK indicate that 80–90% of eyes achieve refractive outcomes within +0.50 D of that intended [6–9, 11–15, 19–22, 24, 26, 27, 29–40], with refractive stability being achieved by 1–3 months in myopic [35] and 3–6 months in hyperopic corrections [36]. Uncommonly, over- and undercorrection may occur especially in high-order corrections [18, 35, 36]. Reported retreatment rates vary between 0% and 7% [6–9, 11–15, 19–22, 24, 26, 27, 29–40]. In cases of early regression, especially in the presence of sub-epithelial haze, some practitioners advocate the use of topical corticosteroids [62, 74] although not all such cases respond and retreatment may be necessary.

The optimum timing of retreatment is as yet undetermined. It should not be undertaken before at least two stable refractive measurements have been obtained at least 3 months apart. It is advisable not to consider retreatment in cases of myopic surface excimer laser ablation before 6–9 months, and for hyperopic cases before 12 months, due to the risk of precipitating an aggressive healing response. In such eyes which have undergone previous corneal surgery, the use of intraoperative mitomycin C (MMC) is advisable to reduce post-operative haze formation [75]. Careful preoperative evaluation with corneal topography and tomography is essential to ensure that any regression, especially in myopic cases and where there has been an increase in cylindrical refractive error, is not due to an ectatic process.

28.5.2 Haze

As excimer laser refractive surgery is undertaken on healthy eyes, any deterioration in post-operative corneal transparency and hence visual performance is of great concern. In PRK, sub-epithelial haze can arise within the ablated area 3–4 weeks following surgery, with maximal disturbances at 3–6 months. Haze development is associated with increasing depths of stromal ablation and small optical zone treatments [76–79]. In LASEK, it has been postulated that the formation

of an intact epithelial layer to cover the laser-ablated area might reduce epithelial-stromal cytokine crosstalk during the initial phases of post-operative wound healing and induce less haze [1–3]. With regard to haze, prospective bilateral comparative studies of LASEK versus PRK have demonstrated contradictory results. Hashemi et al. reported no differences [80], whilst Autrata and Rehurek [20] and Lee et al. [21] found less haze in eyes undergoing LASEK. In the author's own published series, with modern laser platforms and large optical zone diameters of 6.50 mm or greater, visually significant haze formation is an infrequent event even in high myopic and hyperopic corrections, with 90% of corneas being completely clear or showing only the merest trace of haze at 6–12 months post-operatively [35, 36]. Because of the increased risks of visually significant haze development with high corrections, small ablation diameters and increasing depths of stromal ablation, it is the author's protocol to only treat eyes with LASEK (without adjunctive MMC) for corrections between +2 mm and −6.00 D and up to −2.5 DC, to only use optical zones of 6.5 mm for myopia and 7.0 mm for hyperopia and to limit the maximum depth of stromal ablation to less than 100 μm.

For surface ablation procedures including LASEK and especially for high-order corrections, many surgeons advocate the adjunctive use of MMC. MMC is a DNA alkylating agent, derived from *Streptomyces caespitosus*. It inhibits DNA/RNA replication especially in rapidly dividing cells such as fibroblasts, and thereby suppresses wound healing. Its use as an adjunctive medication applied intraoperatively immediately after laser ablation in PRK was first suggested by Talamo over two decades ago [81]. Re-interest in surface ablation over the past decade led to resurgence in its usage and now routine implementation, especially in high corrections and eyes at risk for the development of haze, such as those which have undergone previous corneal surgery. Leccisotti in a prospective, randomized, double-masked, paired eye study of PRK corrections between −6.5 and −10 dioptres (D) reported statistically less haze in eyes treated with MMC 0.2 mg/ml for 45 s albeit with a reported overcorrection of 6% [82]. Similarly, Wallau and Campos, as well as demonstrating better outcomes for PRK with MMC compared to LASIK, reported no haze after PRK with the use of MMC [16]. A recent meta-analysis of clinical outcomes comparing surface ablation with and without 0.02% MMC showed that it indeed reduces haze in PRK, although the results of MMC in conjunction with LASEK were less certain [75].

There is, however, some controversy concerning the use of MMC in keratorefractive surgery. Corneal and sclera melting both early (within months) and late (after many years) has been reported following its perioperative application in pterygium surgery [83]. Certainly there are concerns regarding its potential unknown long-term complications after laser refractive surgery, with reported delays in epithelial wound healing [83], although other investigators have not found such changes [84]. In relation to possible endothelial damage, in a recently published review article, Roh and Funderburgh identified five clinical studies in the peer-reviewed literature, three of which reported no change in corneal endothelial density, whilst two found statistically significant cell loss following MMC application after surface ablation [85]. A more recent prospective study with 0.02% MMC applied for 40 s showed no change in central endothelial counts at 6 months after surgery [86]. Similarly, Gambato et al. in a randomized bilateral study using in vivo confocal microscopy with 5-year follow-up, found no changes in endothelial cell counts, epithelial thickness, keratocyte density, number of corneal nerve fibres, nerve beadings, nerve branching and tortuosity with the intraoperative use of MMC 0.02% [87, 88].

Whilst these studies afford support for the use of perioperative MMC, large series, longer follow-up studies are required to determine the precise influence many decades after LASEK/PRK of intraoperative MMC on the health and functioning of the cornea and its endothelium. In the meantime, preoperatively, patients should be informed and consented concerning the possibility of rare and as yet undetermined possible long-term complications associated with MMC usage. It is the author's personal preference to reserve the adjunctive use of MMC in LASEK to eyes undergoing myopic corrections >−6.0 D, hyperopic corrections >+2 D and astigmatic corrections >2.5 DC and in eyes with previous corneal surgery such as keratoplasty, radial keratotomy (RK) and previous surface ablations.

Although there is evidence to suggest that topical corticosteroids merely delay rather than prevent haze formation [60], in eyes where haze greater than grade I (easily visible with the slit lamp) develops during the first 3 months, it is recommended that topical corticosteroids are prescribed (preservative-free dexamethasone 0.1%) possibly in conjunction with preservative-free topical Timoptol 0.25% twice daily (providing there is no contraindication to its usage) to negate steroid intraocular pressure responses [62]. The topical steroid medication should be tapered over a 6–12-week period, with careful biweekly monitoring of the intraocular pressure. It is important to note that with or without the use of topical steroids, long-term studies indicate that with time haze, however dense, will clear in the vast majority of eyes with return of any associated loss of BSCVA [89, 90].

In eyes with persistent and significant haze (>grade 2 beyond 9–12 months post-surgery), steroid medication will only have a limited effect [61]. Although haze does very gradually clear with time [89, 90], further surgical intervention may be necessary depending on any associated loss of BSCVA, regression of correction and patient preference. A number of surgical options for persistent post-PRK/post-

LASEK haze are available. Vigo et al. reported a series of 35 eyes of 30 patients with severe haze and regression after PRK that underwent epithelial debridement and scraping of the stromal surface with topical application of MMC 0.02% applied for 30–45 s 6–12 months after surgery. All eyes had significant improvements in corneal transparency and refractive error, and only two required a further debridement treatment [91]. Porges et al. presented a series of eight eyes of seven patients with severe haze following PRK who were treated with phototherapeutic keratectomy (PTK) to remove the haze layer augmented with intraoperative MMC 0.02% [92]. All eyes had an improvement in visual performance [92]. It is the author's preferred practice to use a corneal wavefront topography-assisted excimer laser ablation augmented with intraoperative MMC 0.02% to treat such eyes [93]. This is best performed when the refractive status and corneal appearance have been stable for at least 6 months and should not ideally be performed until 12 months after the original procedure. A trans-epithelial approach is most beneficial with the laser being used to remove the epithelium, as epithelial hyperplasia/hypoplasia smooths much of the underlying irregularities caused by the haze formation, and the epithelium is typically very adherent, overlying areas of aggressive haze. When using MMC, it is necessary to undercorrect the spherical and cylindrical component of the intended refractive correction by about 10%. Very rarely, cases of severe haze cannot be managed with excimer laser retreatment and may require deep anterior lamellar corneal grafting procedures.

28.5.3 Night Vision Disturbances/Halos

In the early days of excimer laser keratorefractive procedures, night vision disturbances and halo phenomena in mesopic and scotopic conditions were not infrequent with the use of small (4–6 mm) diameter optical zone treatments [76, 79, 94]. This was due to this mismatch between the optical zone size and mesopic/scotopic pupil diameter and the spherical profile of the corrections. Such phenomena were associated with considerable patient dissatisfaction and in some cases have persisted with over 12 years of reported follow-up [90, 94]. With a greater understanding of the need to evaluate the preoperative pupil diameter, the use of larger optical zone treatments (>6 mm), the advent of wavefront technology and the development of aspheric ablation profiles to reduce the induction of fourth-order spherical aberration post-operatively, the incidence of such problems have reduced dramatically [35, 95].

Patients, especially professional drivers, must be counselled preoperatively as to the rare occurrence of night vision disturbances that may preclude driving on unlit roads such as motorways [96]. Careful preoperative evaluation of mesopic/scotopic pupil diameter is mandatory [96]. Matching the optical zone to the pupil diameter should be attempted, and the use of aspheric ablation profiles (wavefront-optimized or total wavefront) is mandatory in modern keratorefractive surgery, especially with myopic corrections and in patients with mesopic/scotopic pupil diameters greater than 6.5 mm [94, 96].

If night vision disturbances should occur, some benefit may be derived from the use of brimonidine tartrate 0.2% or pilocarpine 1% eye drops to induce miosis, taken half an hour before driving on unlit roads [96, 97]. Wavefront-guided retreatments with optical zone enlargements may be useful in problematic cases [96].

28.5.4 Recurrent Erosion

Continuing symptoms 9–12 months after LASEK may be treated with a 360° peripheral anterior stromal puncture procedure, as described above (Fig. 28.1). In the author's experience of ten cases over the past 12 years, this has resulted in improvement/resolution of symptoms, with only one case requiring a repeat procedure. If, however, anterior stromal puncture does not alleviate the problem, then it may be necessary to perform an epithelial debridement and 15–20 μm ablation depth and 10 mm diameter PTK procedure, which has been shown to be efficacious for the management of recurrent corneal erosion syndrome [98]. It is the author's preference to combine this "limited" PTK with a peripheral anterior stromal puncture procedure.

28.6 Late Post-operative Complications (Months/Years)

28.6.1 Overcorrection/Undercorrection

See above.

28.6.2 Haze

Late haze occurring 17 months after LASEK, requiring a manual debridement procedure with PTK and MMC, is a rare event that has been reported as a single isolated case report [99]. After PRK, late-onset corneal scar triggered by trauma [100] and vitreoretinal surgery with silicone oil tamponade but no epithelial debridement [101] has been reported. Following surface ablation procedures, it is prudent to warn patients of the rare occurrence of late haze when undergoing such vitreoretinal procedures and in cases of ocular trauma in patients who have previously undergone surface laser ablation topical corticosteroid therapy, and careful patient monitoring is indicated.

28.6.3 Recurrent Corneal Erosion Syndrome

See above.

28.6.4 Ectasia

Whilst ectasia occurs less often after PRK/LASEK than after LASIK [102], because of the greater degradation of corneal biomechanics in LASIK due to its inherent flap creation [103], ectasia has been reported after PRK even with low myopic corrections [102, 104]. Such cases typically occur in eyes with abnormal topography indicative of forme fruste or early keratoconus [102, 104], and whilst there are case series of successful and stable outcomes of PRK in eyes with mild keratoconus [105, 106], surface ablation is controversial and based on current evidence not recommended in such eyes because of the risk of post-operative ectasia.

Careful preoperative corneal topographic, wavefront and tomographic evaluation is necessary in all eyes to identify abnormal patterns, and most devices now have statistical packages that identify high-risk cases, which should not be treated. Preoperative corneal pachymetric measurements are essential prior to surface ablative procedures, and any eyes with central pachymetric measurements of less than 500 µm, although in many cases suitable for surgery [107], should be regarded with some suspicion. It is the author's recommendation to leave all eyes with a residual minimal central corneal thickness of 400 µm as a precaution against problems with long-term corneal biomechanical instability and to perform corneal collagen cross-linking if it becomes necessary, should ectasia develop.

Eyes with ectasia after keratorefractive surgery typically present with myopic and especially oblique/against the rule astigmatic regression/induction. They show features of irregular astigmatism and usually inferior steepening on corneal topography and anterior and posterior protrusion on corneal tomography. Should ectasia occur, topical anti-glaucomatous medications may slow/reverse progression, and treatment should be initiated [108]. Riboflavin (vitamin B2)/UV-A (370nn) light corneal collagen cross-linkage CXL appears to halt the progression of ectasia and should certainly be considered in eyes with central corneal thicknesses of at least 400 µm or greater [109, 110]. In terms of visual rehabilitation, rigid contact lens fitting is the mainstay of treatment. Intra-stromal corneal ring (Intacs) insertion has been shown to be of benefit in mild-to-moderate cases, improving UCVA, BSCVA and contact lens fitting [111], and in such cases, it is the author's preference to generally use single inferior Intacs insertion [111] (Fig. 28.2). In eyes with advanced ectasia intolerant to contact lenses, deep anterior lamellar keratoplasty may be the only option.

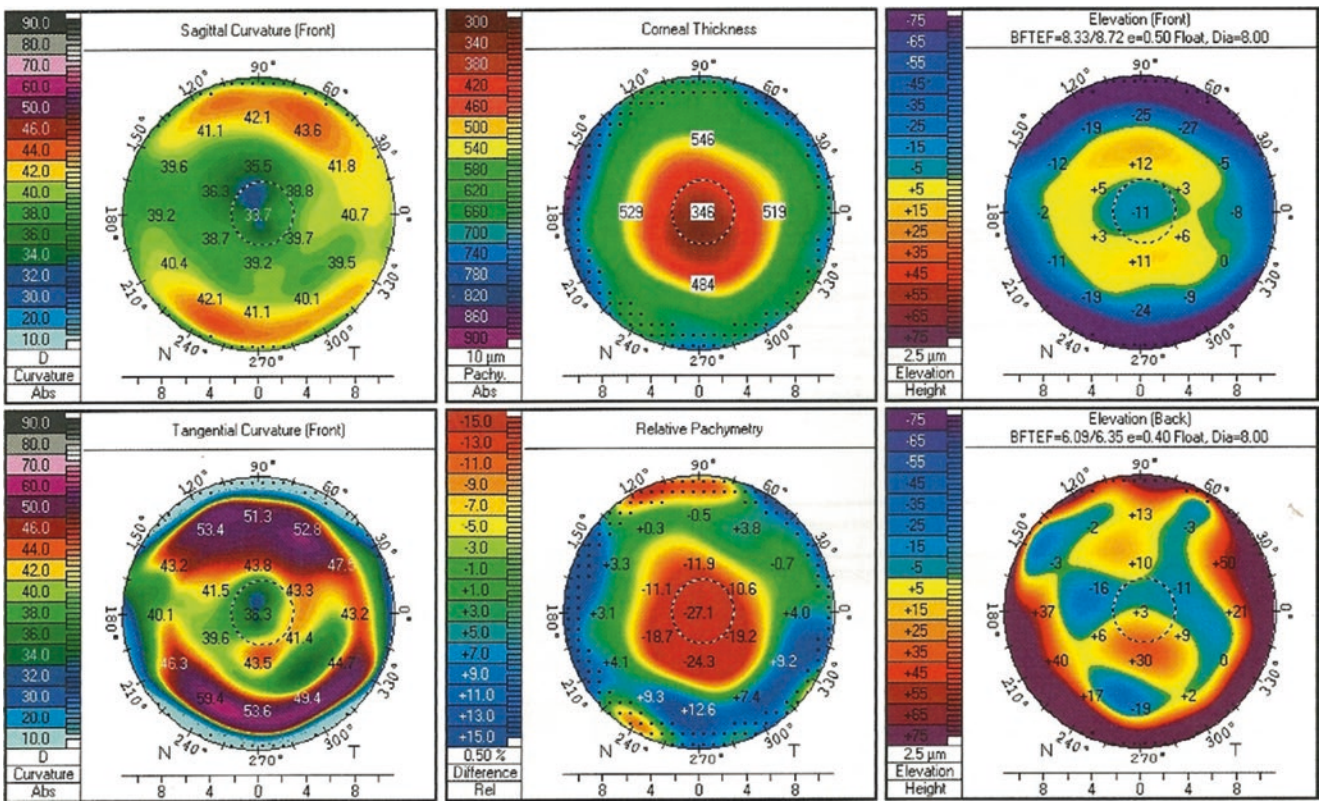

Fig. 28.2 Tomography scan of an eye that developed ectasia 2 years after LASEK, which was stable for 10 years following 250 µm inferior Intacs insertion and CXL and retained a visual acuity of 20/20 unaided

Over recent years, CXL has been used in combination with other procedures, such as topography-guided PRK, to optimize visual and refractive outcomes in keratoconus and even in post-LASIK ectasia [112–114]. Combined CXL and limited topography-guided PRK, with ablation depths less than 50 micrometres (μm), in eyes with moderate keratoconus and post-LASIK ectasia, has been shown to be effective with significant improvements in visual, refractive and topographic parameters and stabilization of the ectatic process in the vast majority of eyes [112–114]. Labiris et al. demonstrated that such combined procedures are associated with significant improvements in quality of life scores [115]. Follow-up of these combined PRK CXL treatments in what are chronic progressive conditions, however, is limited to only 1–3 years so that long-term biomechanical stability has not really been fully elucidated. It is known that PRK itself reduces the biomechanical strength of the cornea [104], and progression of ectasia after PRK with CXL has been reported [112] as well as the occasional occurrence of visually significant corneal haze/scarring [116]. Despite these unknowns in carefully selected cases with contact lens intolerance, limited ablation depths, adequate corneal thickness and low-grade ectasia, with adequate counselling and fully informed consent as to the risk of progression, combined CXL and topographic-PRK treatments might, on the basis of the recent published literature, be considered.

Take-Home Pearls

- In the event of alcohol escape during LASEK, the ocular surface should immediately be irrigated with balanced saline solution, the conjunctiva and corneal surface dried, and the well reapplied for the remainder of the application time.
- If flap adherence is encountered, replacing the flap and applying alcohol for 10 more seconds usually facilitate improved flap creation.
- It is not unreasonable to discard the epithelium in cases of free or poor flaps as the ultimate refractive and visual outcomes may not be affected.
- Patients must be carefully counseled as to the importance regarding the correct dosage of anesthetic drops for pain, as keratopathy after LASEK may occur.
- Patients with conjunctival cicatrizing conditions and limbal stem cell deficiencies are not candidates for keratorefractive surgery.
- In eyes with epithelial basement membrane dystrophy preoperatively, the surgeon should not only warn the patient of the increased risk of recurrent erosion syndrome, but should also combine LASEK with a peripheral stromal puncture technique.
- If corneal melting should occur, management is required with intensive topical preservative, free corticosteroid, and systemic immunosuppressive therapy. Further, surgical interventions such as amniotic membrane grafting and keratoplasty may be necessary.
- In patients that develop labial herpes simplex during the early/medium postoperative period, it is recommended that they are prescribed systemic prophylactic acyclovir.
- When using MMC, it is necessary to undercorrect the spherical and cylindrical component of the intended refractive correction by 10%.
- CXL and topographic PRK treatments might be considered in patients with contact lens intolerance, limited ablation depths, adequate correct thickness, and low-grade ectasia. Adequate counseling and a full informed consent regarding the risk of progression of ectasia must be given to the patient.

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Corneal Haze After Refractive Surgery

29

David Fahd, Jose de la Cruz, Sandeep Jain, and Dimitri Azar

Core Messages

- Loss of corneal clarity (haze) after refractive surgery can be a serious condition leading to decrease in VA, myopic regression, and irregular astigmatism.
- Haze is due to abnormal collagen deposition and decreased corneal refractivity.
- Most cases of post-PRK haze are clinically insignificant and self-resolving.
- Haze can also be seen following LASIK, epi-LASIK, and LASEK.
- Adequate follow-up post-op can detect and help prevent development of haze.
- MMC can adequately prevent and also treat haze after refractive surgery.

29.1 Introduction

Laser vision correction (LVC) surgery is extremely common today, with a prevalence of around 3%/year of the general population [1]. The number of LVC procedures performed has increased dramatically over the last 20 years. Photorefractive keratectomy (PRK) was the first technique employing an ophthalmic excimer laser for the correction of refractive errors, effectively correcting moderate myopia, astigmatism, and hyperopia by surface ablation. This was later followed by further modifications to the technique, including LASEK, epi-LASIK, and transepithelial PRK (tPRK), all of which are surface ablation LVC. In addition, intrastromal ablation emerged, with LASIK (laser in situ keratomileusis) and later femtosecond LASIK, remaining the most common refractive surgery performed today, since it has a faster visual recovery and is associated with a considerably lower incidence of corneal haze compared to PRK. Despite the marked prevalence of LASIK, surface LVC is resurfacing with the advent of tPRK. One of the common side effects of corneal surface excimer laser ablation is haze; however, significant haze is seen in less than 5% of the cases [2].

29.2 Definition of Haze

Different definitions of haze include: (1) a decrease in tissue transparency, (2) a marginal loss of corneal clarity, and (3) a subepithelial stromal opacity [3].

Haze can be completely asymptomatic—as is the fact in most cases; however, it can also lead to starbursts and visual loss or, more seriously, to a stromal reaction that induces refractive regression and increases corneal surface irregularity and thus irregular astigmatism. It is often accompanied by myopic regression which affects visual quality and quantity and also can be shocking to see on slit lamp exam to the non-refractive surgeon.

The slit lamp assessment of haze magnitude in clinical studies is subjective. Different studies report different incidences following PRK as will be discussed later. In brief, clinically *insignificant* corneal haze is present in most eyes after PRK and may last for 1–2 years after surgery. Clinically *significant* haze only occurs in a small percentage of eyes, usually less than 0.5–4%, depending on the level of correction and other factors (more of this later). Lohmann et al. worked on developing an objective method of haze assessment in 1992 and reported an overall incidence of 4% at 6 months [2].

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In 1998, Moller-Pedersen et al. used the confocal microscope to assess haze and reported an incidence of 3% at 12 months [4]. These results and others are summarized in Table 29.1.

29.3 Grading System

Fantes et al. [5] described five stages of corneal haze ranging from 0 (no haze) to 4 (total obscuration of anterior chamber). (See Table 29.2 for a full description of stages.)

Two types of haze are observed after PRK, the typical transitory haze and the late haze [6, 7]:

Typical transitory haze: This is more common; however, it is rarely associated with clinical symptoms. It is noted between 1 and 3 months postoperatively and disappears within the first year after surgery. It is proportional to depth of ablation and quality of laser ablation.

Late haze: This is a haze in an eye that initially had a clear cornea postoperatively but with haze appearing between 2 and 5 months postoperatively. Though less common, this type of haze may severely compromise vision. The result is a decrease in the corneal transparency and myopic regression. It usually resolves over time; however, it may stay longer and may persist for up to 3 years.

29.4 Course

Typically, transitory corneal haze appears a few weeks after surgery, plateaus, and then decreases slowly and becomes visually insignificant over time [8]. Different authors report different time courses with many intervening factors affecting its incidence and progression: Winkler von Mohrenfels et al. initially noted subepithelial haze 3–4 weeks postoperatively as a diffuse zone of altered light reflex. Haze then increased progressively to a maximum at 3 months and then slowly regressed [9]. Mohan et al. reports that it tends to peak 6–9 months after PRK and then gradually diminishes over time—taking years to resolve in some patients [10]. Rajan et al., in a study published in 2006, described it as increasing during the first months after surgery, reaching a maximum between 3 and 6 months after surgery, and thereafter declining [11]. In the article by Netto et al., also published in 2006, haze was noted to begin 2 weeks after PRK and peak at 4 weeks postoperatively [12]. In tPRK, Fadlallah et al. reported persistence of grade 1 or more haze after 3 months in only 10% of patients [13].

Table 29.1 Subepithelial haze at 6–12 months post-treatment with PRK (stages according to Fantes et al. [5])

Study	Time of examination (months)	0 (%)	0.5–1 (%)	2 (%)	3 (%)	4 (%)
el Danasoury 1999	6	41.7	54.2	4.2	0	0
el Danasoury 1999	12	54.2	37.5	4.2	0	0
el Maghraby 1999	12	83	83	13	0	3
SUMMIT	6	45.6	44.1	5.9	4.4	0

Table 29.2 Haze staging (stages according to Fantes et al. [5])

Stage	Description of image by slit lamp
0	No haze, completely clear cornea
0.5	Trace haze seen with careful oblique illumination
1	Haze not interfering with visibility of fine iris details
2	Mild obscuration of iris details
3	Moderate obscuration of the iris and lens
4	Complete opacification of the stroma in the area of the scar, anterior chamber is totally obscured

29.5 Pathophysiology

Haze is the end stage of a cascade of events secondary to corneal epithelial and stromal injury (Fig. 29.1). Many different molecular growth factors, cytokines, and chemokines

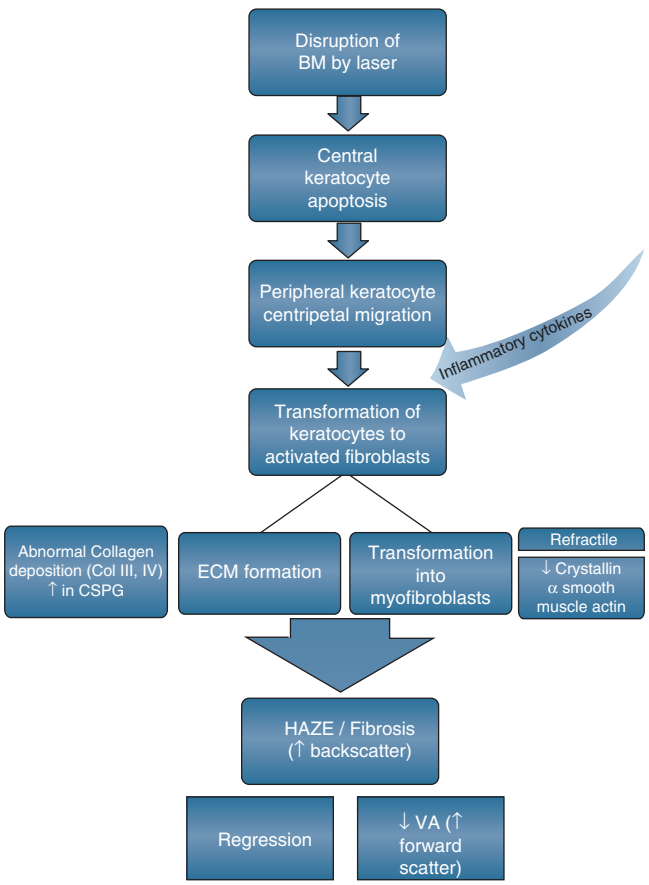

Fig. 29.1 Pathophysiology of haze development. *CSPG* chondroitin sulfate proteoglycan, *ECM* extracellular matrix, *VA* visual acuity, *Col* collagen

(interleukin-1, tumor necrosis factor-α, chondroitin sulfate proteoglycans, and others) interplay to promote regeneration instead of fibrosis after wounding [7]. Surgical trauma leads to disruption of the basement membrane and apoptosis/necrosis of the surrounding corneal cells. This will result in keratocyte activation and further transformation into fibroblasts. These fibroblasts then migrate centripetally to the site of injury. Their role is multiple, namely, (1) they lay down the ECM, (2) they transform into myofibroblasts, (3) they cause stromal edema, and (4) they lead to an irregularity of the stromal surface.

In normal clear corneas, collagen types I and VI are arranged in a repeating orthogonal arrangement [14]. In contrast, postoperatively, fibrillar type IV collagen, normally not present in this region of the corneal stroma, increases. In addition, type I and III fibrillary collagen molecules become arranged in a non-orthogonal pattern. These two changes are thought to lead to the development of subepithelial haze observed clinically postoperatively. Myofibroblasts, highly contractile cells with reduced transparency attributed to decreased intracellular crystallin production [15], invade the stroma. The extracellular matrix is also altered in the anterior stroma. The integrity of the epithelial membrane is necessary in proper wound healing and prevention of haze development; hence, the presence of an intact epithelial barrier immediately after laser ablation has an important role in curbing subepithelial haze and myofibroblast differentiation [3]. Haze is seen when light from highly reflective myofibroblasts within the photoablated region is scattered randomly, forward and backward [4, 16].

Late apoptosis may have a role in disappearance of myofibroblasts and haze over time [12]. Disappearance of haze is correlated with disappearance of myofibroblasts and remodeling of disorganized stromal collagen.

29.6 Risk Factors

In order to prevent haze occurrence after refractive surgery, many studies have been conducted to assess the possible risk factors. These risk factors include depth of ablation [17], diameter of ablation [11, 18], slope of wound surface over the entire area of ablation [19], volume of stromal tissue removed [20], level of correction [12], length required for corneal healing, irregularity of post-op stromal surface [12], basement membrane integrity, Bowman's layer ablation, and tear fluid TGF-β levels [21].

Depth of ablation: The depth of ablation, the diameter of ablation, and the attempted error of correction are contributing factors to the volume of tissue removed. Braunstein et al. noted that there is a significant increase in light scatter and haze in patients with ablation depths >80 μm compared to those with ablation depths less than 80 μm [17]. The study, conducted on 34 patients, found a significantly higher amount of haze in patients with ablation depths greater than 80 μm. Conversely, however, O'Brart et al., in a study on 33 patients, found that increasing the depth of ablation has no significant influence on haze [22].

Slope of wound surface over the entire area of ablation: Corbett et al., on a review of 100 patients, found that the factor with greatest apparent influence on the development of haze and regression was the slope of the wound surface over the entire area of the ablation. Tapering the wound edge provided no additional benefit and contributed to night vision problems [19]. However, the ablation profiles of the laser machines incorporate transition zones to curb the difference between ablated and non-ablated stroma and thus decrease the slope of the wound surface.

Diameter of ablation and volume of tissue removed: Different authors have attempted to correlate the diameter of ablation and the volume of stromal tissue removed with haze, as mentioned before. Objective measurements of haze were lower with 6.0 mm compared with 4.0 and 5.0 mm treatments ($P < 0.001$) [11, 18]. An important regulating factor for haze postoperatively, according to Moller-Pedersen et al., is the increased volume of stromal tissue removed [20]. This is also seen in areas of maximal ablation in astigmatism ablation profiles.

High levels of correction: It is well known and established that haze rarely occurs in eyes that have lower levels of myopic correction (<6 D) treated with PRK [12]. Clinically significant haze incidence after PRK increases with higher levels of myopic corrections, as refractive error goes beyond −6.00 D [23–27]. This is also related to distance from equator and UV exposure—the closer you are to the equator, the more you are likely to develop postoperative haze.

Irregularity of post-op stromal surface: There is an increase in the irregularity of the ablated surface as the depth of the ablation increases [28]. Surface ablation disturbs the stroma and increases its irregularity. Haze post-PRK is proportional to the stromal surface irregularity remaining after ablation [12]. Studies on rabbits suggest that PRK smoothing reduces haze after PRK and demonstrates conclusively that haze and myofibroblast density increase as surface irregularity is artificially increased [10]. In a study on 80 human eyes, Vinciguerra et al. noted that there is a clinical correlation between the irregularity of the ablated surface after PRK and the incidence of corneal haze; haze decreased when PRK included a stromal PTK smoothing procedure [29, 30].

Tear fluid TGF-β levels: Long et al., in a search to find a method to predict which patients will develop haze postoperatively, found that those who had a higher degree of TGF-β1 in tears on day 1 had a greater incidence of haze after 1 month [21].

Other factors: Removal of the epithelial basement membrane, ablation of Bowman's layer, and length of time

required for epithelial defect healing have also been ascribed as risk factors for haze development. In addition, surgical method and laser type used influence haze incidence. Haze is more common in PRK than in the other surgical models. Its incidence is less with the use of small flying spot laser as compared to the use of the old, broad-beam lasers [31].

29.7 Clinical Assessment

Haze can be measured by different methods, some of which are widely used and others have been abandoned. Table 29.3 summarizes the different techniques that have been used. These methods can be divided into subjective and objective methods of assessment.

Subjective assessment is carried out via a slit lamp biomicroscope. It is graded from 1 to 4 as described in Table 29.2. Figure 29.2 shows the different stages of haze as seen by a slit lamp. Though this method is easy and doesn't require any additional equipment, it is very subjective and not reproducible, with high intrasession (4%) and day-to-day variation (7%) [32].

Objective measures use additional equipment, either mounted on the slit lamp or as stand-alone machines to measure haze. These can be further subdivided into "reflected light methods" that measure forward scatter and those that measure backward scatter of light. (Backward scatter is defined as scattering of light toward the origin of the incident light. Forward scatter is when light is scattered toward the retina.) Recently, corneal optical coherence tomography (OCT) has been used to measure reflectivity of the cornea and thus measure haze (since myofibroblasts and fibroblasts have higher refractivity than regular keratocytes).

Using the law of conservation of energy and basic physics, the following formula can be generated: (This formula forms the basis of the rationale of scattered light measurement.)

Incident white light = reflected light + light absorbed by haze + scattered light + transmitted light

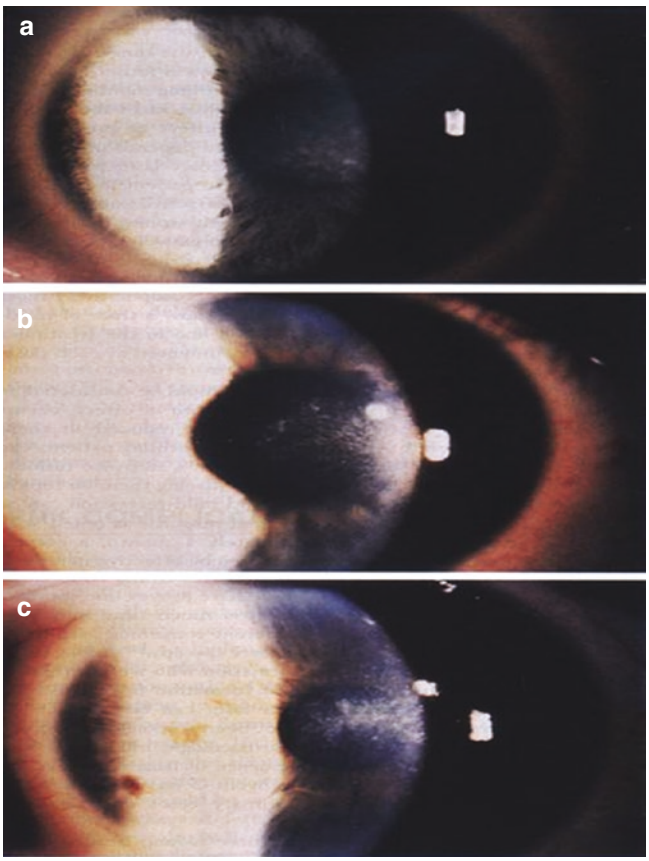

Fig. 29.2 Stages of haze. (**a**) Trace haze, (**b**) mild haze, (**c**) moderate haze (From Thompson V, Seiler T, Hardten DR [2007] Photorefractive keratectomy (PRK). In: Azar DT (ed), Gatinel D and Hoang-Xuan T (associate eds) Refractive Surgery, 2nd edition. Elsevier, Dordrecht, pp. 223–237)

The value of the incident white light is known and constant. Reflected light of the cornea is constant and was measured to be equal to 2% [33]. Since haze appears white—and from basic physics, white is obtained when all incident light is reflected—then absorbed light by haze can be considered to be equal to zero. The light that is transmitted goes to the retina. Simplifying the above equation will lead to the conclusion that scattered + transmitted light should remain constant as long as the incident white light is constant. Haze is

Table 29.3 Objective methods to measure haze

Mechanism	Method	Advantage(s)	Disadvantage(s)
Slit lamp biomicroscope	Subjective grading	Easy, no special tools required	Subjective, low reproducibility
Opacity lensometer	Two-color scattering response	Better than slit lamp	Poor discrimination of low haze
Scheimpflug -EAS1000	Backward light scatter	Subjective measure	Small magnification
TSPC-3 hazemeter	Backward light scatter	Can objectively measure subtle changes, more magnification, wide area of coverage	Not reflective of forward scattered light
van den Berg stray light meter	Forward light scatter	More reflective of retinal image quality	Not practical
Confocal microscope	Backward light scatter	High magnification, good resolution	Cannot be used clinically

inversely proportional to backward scatter and directly proportional to forward scatter.

The following is a description of the different machines that have been developed and used:

- Reflected light
  - Scheimpflug anterior eye segment analysis system EAS-1000 [34]
    This is the method of choice and the first method that was developed. It can measure mild to moderate corneal haze well, but severe haze cannot be adequately quantified [33]. It uses a charge-coupled device camera mounted on the slit lamp to measure reflected light and assess corneal haze. Limitations to this technique include:
      Only a narrow area of the cornea is covered.
      There is a lack of sensitivity in measuring low grades of haze.
      Photographic processing is required (which may increase result variability).
      There is possibly a background scatter light from the lens contamination.
      It is impossible to focus on the entire depth of the cornea in a single image.
      The magnification is too small for a detailed analysis of the corneal subepithelial region.
      Zero calibration is not confirmed in the background area [33].
  - TSPC-3 hazemeter [33]
    This is a modification of the EAS-1000 system which can objectively measure subtle changes in haze levels. It has good detail assessment and has 6.25 times more magnification than does the EAS-1000 system. A xenon flashlight source and a charge-coupled device camera are used. The light source generates a vertical slit beam of 7 × 0.08 mm, which is projected perpendicularly onto the cornea. The charge-coupled device camera is placed 45° to the plane of the slit light and focuses on the entire depth of the cornea by using the Scheimpflug principle. The flashlight power can be set to 50, 100, or 200 W by changing the electrical current, thus enabling coverage of a very wide range of scattering (haze) intensity by simply altering light illuminance. The image is then captured and digitized. Latex microsphere solution is used for calibration. Advantages include the ability to cover a wide area of the cornea and the ability to obtain results without the need for photographic processing.
  - Confocal microscope
    This method can measure corneal haze quantitatively and objectively and is considered the gold standard for assessing haze, despite the fact that it is not widely used clinically. The basis of the confocal microscope is the focusing of the illumination and observation systems on the same point. This dramatically improves the axial and lateral resolution of the microscope and enables it to reach a magnification of 600× [35]. The amount of backscattered light given in intensity units or in intensity thickness units can be used to assess and monitor the relative transparency of the corneal stroma and provides an estimate of corneal haze [36–40]. Changes in the appearance of the corneal stroma, keratocytes, and corneal nerves can be visualized over time at high resolution. This method can also be used to characterize cellular changes associated with the wound healing response. Sublayer thickness can also be measured, allowing for in vivo monitoring of subepithelial haze depth after excimer PRK.
- Forward-scattered light (Van den Berg stray light meter)
  Though more accurate and more reflective of actual haze magnitude, this technique is not widely used clinically because of its impracticality. The forward scattering in the eye is what reduces the contrast of the retinal image and thus influences contrast sensitivity. This is more likely to affect retinal image quality and visual acuity measurements.

29.8 Preventive Measures

29.8.1 MMC

MMC (mitomycin C) is an antibiotic derived from *Streptomyces caespitosus*. Its alkylating properties enable it to cross-link DNA between adenine and guanine, thereby inhibiting DNA and RNA replication and protein synthesis. Although its actions are exerted primarily during the late G1 and S phases, it is non-cell cycle specific. Rapidly dividing cells are more sensitive to its action, and as a consequence, it may inhibit proliferation of corneal epithelial cells, stromal cells, endothelial cells, conjunctival cells, and Tenon's capsule fibroblasts [41–43]. It also induces keratocyte apoptosis and may lead to myofibroblast death by inducing apoptosis and necrosis. This results in myofibroblast differentiation blockade [44]. It is directly responsible for triggering corneal cell apoptosis and/or necrosis in vitro. The death of some keratocytes in the anterior stroma typically results in proliferation and activation of remaining keratocytes. This chemotherapeutic agent inhibits fibroblast proliferation and differentiation. It has been used to modulate scarring in different areas of ophthalmology. Topical application has improved the results of glaucoma surgery and pterygium excision and treatment of conjunctival and corneal intraepithelial neoplasia. Modulation of wound healing with the use of MMC was first suggested by Talamo in 1991 [45]; since then intraoperative MMC has been used to prevent haze formation after PRK for high myopia [46–48]. A meta-analysis of the use of MMC in corneal surface LVC was conducted by

Majmudar and colleagues and got to the conclusion that the majority of the articles surveyed support the role of MMC as an adjunctive treatment in surface ablation procedures and that the incidence of haze is reduced [49].

The usual concentration of MMC is 0.02%. It is applied to the corneal surface for a maximum of 2 min, followed by copious irrigation with balanced salt solution [50]. Initially application was done using a circular sponge disc; however, the higher recurrence of haze in the periphery led to Azar and Jain [51] proposing the use of rings instead of discs (Fig. 29.3).

MMC has higher efficacy in preventing haze formation than in treating it after it has formed [50, 52]. This is more pronounced in PRK patients with a spherical equivalent correction between −6.00 and −10.00 D [44]. The concentration of MMC is constant; however, the time of application can be varied according to need.

MMC is far from being perfect. In some cases, haze may recur after its application, which may lead to secondary astigmatism. In addition, there might be a progressive decrease in keratocyte density and decreased collagen production leading to late corneal melting and keratectasia. Another problem is that in the presence of previously existing corneal opacification, MMC may not completely eliminate haze due to an eventual persistence of myofibroblast cells.

29.8.2 Vitamin C

Vitamin C (ascorbic acid) prevents UV damage produced by excimer laser and reduces keratocyte activation. Oral supplementation preoperatively might have a prophylactic effect in decreasing haze development after PRK [53]. However, this is not widely accepted due to the difference in results following its prescription postoperatively.

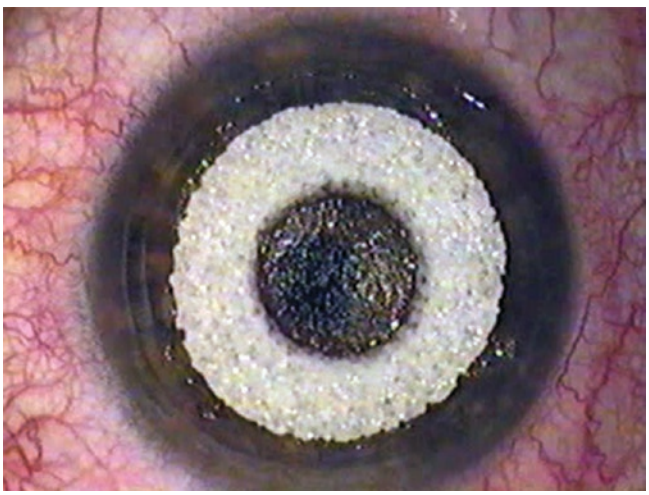

Fig. 29.3 MMC application using a ring-shaped sponge

29.9 Control and Treatment

A variety of therapeutic regimens have been used to prevent corneal haze after PRK, including topical corticosteroids, nonsteroidal anti-inflammatory drugs, plasmin inhibitors, antimetabolites, interferon-α, and growth factors. Unfortunately, use of these pharmaceuticals results in minimal, if any, reduction in corneal haze after PRK [54, 55].

Increasing the ablation zone size from 4 to 6 mm and using MMC intraoperatively have been shown to improve the refractive outcomes and reduce corneal haze after PRK [11, 18, 56, 57].

Different studies report that treatment with MMC proved effective in preventing the recurrence of fibrosis when combined with superficial keratectomy. In all cases, there was an improvement of corneal clarity [56, 57]. Although better results are obtained after using MMC as a preventive measure, Epstein et al. reported that the majority of PRK can be retreated successfully by a redo surgery with MMC or by PTK [58].

Raviv et al. describe a technique for eliminating haze and myopic regression [57] by removing the subepithelial haze using a no. 64 blade or a pterygium burr. A MMC-soaked sponge is then placed on the cornea for 2 min followed by copious irrigation of the cornea and conjunctiva with a balanced salt solution. A pressure patch or a bandage contact lens is then applied, and the patient is given antibiotics and steroids qid for 1 week. The steroid drops are then tapered over 1–3 months.

Reports by Horgan et al. [59], Serrao et al. [60], Ma et al. [61], and Choi et al. [62] reported on the use of PTK to treat stromal irregularity after PRK.

29.10 Haze in Other Types of LVC (Refer to Table 29.3)

We were focusing on PRK in our above discussion. However, haze can also occur in eyes treated by different refractive surgery techniques.

PRK: The corneal wound healing response that occurs after PRK is usually more intense than that after LASIK for the same level of correction. This is why corneal haze is much more common after PRK than LASIK and is typically localized to the subepithelial anterior stroma.

LASIK: The creation of a flap during LASIK maintains a zone of normal cornea between the epithelium and the stromal bed. This probably diminishes interactions between activated stromal cells and the overlying epithelium that are required for the generation of myofibroblasts; hence, the incidence of haze is less. There seems to be a protective value for the intact epithelium covering the ablated stroma. Haze is noted in the central interface post-LASIK in the following cases: diffuse lamellar keratitis, donut-shaped flaps, and retention of epithelial debris in the interface. It is likely that each of these is associated with increased access of TGF-β and other cytokines from epithelial cells to the activated keratocytes. Circumferential haze is seen around the edge of the flap due to direct contact between normal and activated keratocytes in the stromal tissue and epithelium at the incision site. Haze is also seen in areas of maximal ablation in astigmatism ablation profiles.

LASEK: LASEK is a modified PRK technique that involves the use of ethanol for the creation of an epithelial flap. After excimer laser ablation, the epithelial flap is repositioned. LASEK has been reported to produce faster visual recovery and less haze than PRK [63] and less corneal haze noted compared to epi-LASIK [21].

Epi-LASIK: An epitome is used to create an epithelial flap. However, contrary to LASIK, the integrity of the basement membrane over the central cornea is preserved. Microfocal damage to the lamina densa of the basement membrane is still seen in some eyes with this method. Dai et al. reported an incidence of haze lower than that in LASIK [64].

T-PRK: Transepithelial PRK is an all-laser technique where the stromal and the epithelial ablation profiles are done by the laser. It has been reported to induce less haze formation than traditional PRK [13].

29.11 Algorithm for the Approach to a Patient with Haze (Fig. 29.4)

Figure 29.4 shows an algorithm to approach a patient found to have haze >1 month after refractive surgery. If the procedure performed was LASIK, then check if the haze is central or circumferential. If it is central, then diffuse lamellar keratitis, a donut-shaped flap, and debris retention in the interface should be ruled out. Each of these entities should then be treated adequately. If haze is circumferential, then the situation becomes similar to that of a PRK patient: grade the haze. If it is ≤stage 2, then observation and follow-up are all that need to be done, since the entity resolves over time. If stage is >2, then start with topical steroids and assess response. If there is no improvement, then treatment with a mitomycin C ring should be attempted.

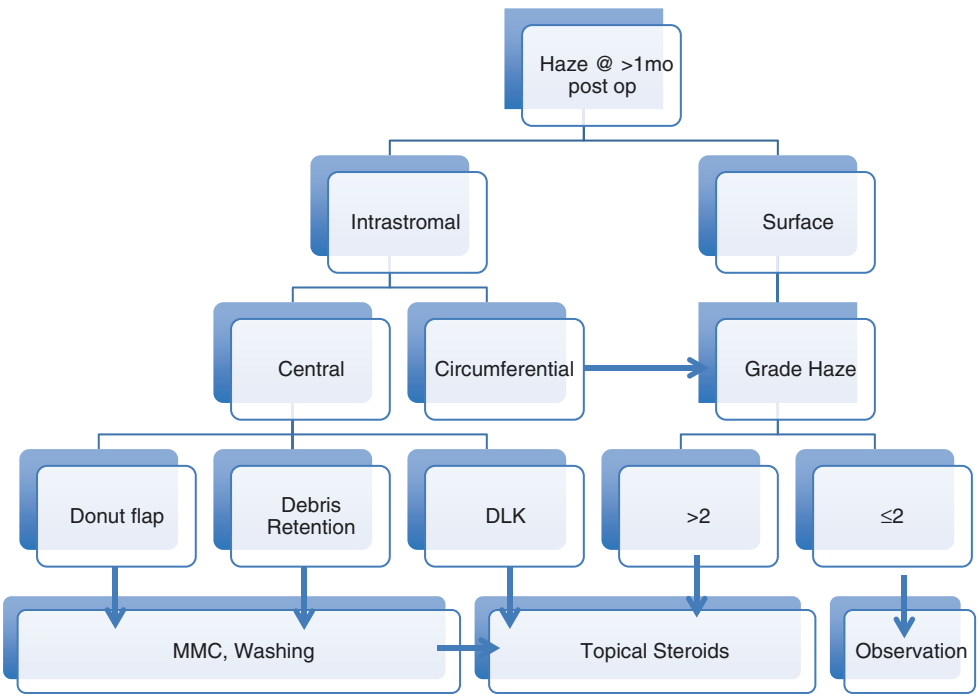

Fig. 29.4 Algorithm to approach a patient found to have haze

Conclusion

Though refractive surgery is safe and very prevalent, it is not without complications. The most common complication of PRK is haze. Despite the high incidence of mild haze, it is clinically significant in less than 5% of cases and resolves on its own. The most prevalent method of assessment is slit lamp subjective assessment; however, the gold standard is confocal microscopy. Care should be taken in selecting patients and assigning them to different refractive surgery models. In the case of high myopic and/or high astigmatic patients to be treated by PRK, MMC should be administered before completion of the procedure. In the event of development of clinically significant haze and visual compromise, a repeat MMC procedure or a repeat PTK/PRK is the way to go.

Take-Home Pearls

- Haze postoperatively should be graded.
- Fantes grades ≤2 require only observation.
- For more advanced stages, more aggressive treatment is necessary.
- Steroids are used effectively, with a course of topical steroids qid for 1 week, as the first-line treatment in stage 2 or more haze post-refractive surgery.
- MMC can adequately prevent and also treat haze after refractive surgery. Though it is more effective as a preventive measure, redo surgery with MMC can re-treat the majority of cases.

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Part VIII

Phakic Intraocular Lens Complication

Complications of Anterior Chamber Angle-Supported Phakic Intraocular Lenses: Prevention and Treatment

30

Antonio Renna and Jorge L. Alió

Core Messages

In this chapter, the complications of AS-PIOLs will be reviewed as follows:

- Intraoperative and early postoperative complications.
- Late postoperative complications and their management.
- Complications that lead to explantation of the AS-PIOLs.
- Explantation techniques of AS-PIOLs.
- The ideal PIOL design.
- Anterior segment OCT and aging.

AS-PIOLs have been widely used for a long time. They were the first PIOLs to be used and the first to be abandoned, according to long-term evaluations made by several authors [1–5]. The reason AS-PIOLs have remained popular is primarily due to the ease of implantation. The anterior chamber (AC), especially in myopic eyes, is the largest space in the anterior segment of the eye and its anatomy can be studied easily both preoperatively and postoperatively. Other reasons for PIOLs popularity are that they do not induce for glaucoma, if properly selected, and that they do not induce cataract formation because they are not in contact with the lens at any given moment [6–20]. Despite these features, all models of AS-PIOL, some in early stages and others in later stages, face the risk of central corneal endothelial loss [21–35]. Excluding the Kelman Duet lens, all the AS-PIOLs were phased out of the market because of unacceptable complication rates. Angle-supported lenses were developed initially with different models. Charles Kelman and Jorge Alió in Alicante co-developed the Duet Lens (Fig. 30.1). Its design includes a tripod support of PMMA that can be implanted through a <2.75 mm incision that allows the implantation of the haptic and the injection of the silicon optic that later is attached to the haptic into the anterior chamber. This represents the best example of an AS-PIOL that adapts to the concept of minimal incision providing very good outcomes for the patients initially and in the long term, even if it is no longer in use [36]. This lens was followed by a foldable model, the Alcon Cachet, that is injectable through a 2.6 mm incision and follows almost all the rules of small-incision surgery with the advantage of using the AcrySof material. All models of AS-PIOL have revealed to be either unsafe in the early postoperative, from 1 year to 3 years or in the long term. All of them are affected by the anatomy of the anterior segment and other issues related to the behavior of the patients, such as rubbing or the position

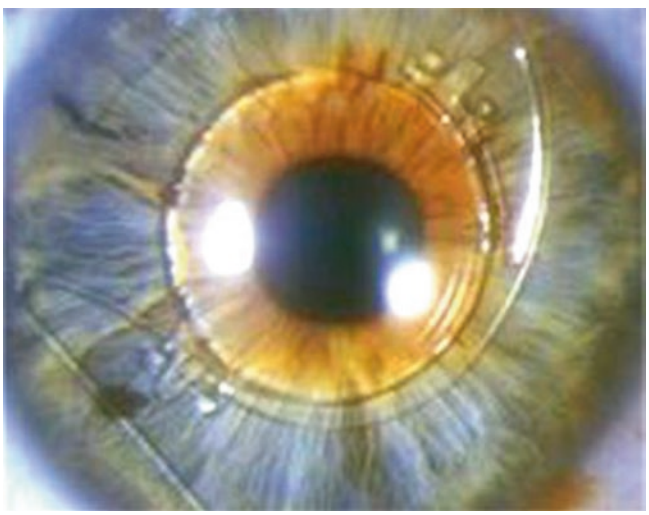

Fig. 30.1 Kelman Duet angle-supported phakic intraocular lens

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during sleeping. Additionally, all of them are affected by the evolution of the anatomy of the anterior chamber that has the trend to be shallower with time, specially after 15 to 20 years [28].

Therefore, treatment and prevention of complications are essential for patients implanted with these types of PIOLs.

30.1 Intraoperative and Early Postoperative Complications

Intraoperative complications included ocular hypotony (iris prolapse, choroidal hemorrhage) and damage to the natural lens, endothelium, or iris. These were usually due to inappropriate surgical techniques or IOL size and design [25].

Early postoperative complications include:

- Ocular hypertension due to incomplete viscoelastic removal, related to corticosteroid eye drops prescribed postoperatively, or pupillary block due to decreased anterior chamber depth (ACD) and incompetency of iridotomy or iridectomy [9, 12–16].
- Acute uveitis due to surgical trauma, contact with the trabecular meshwork, and iris root, leading to some degree of erosion, vessel disturbance, pigment dispersion, and synechiae formation, hence the concern about glaucoma, iridocyclitis, and breakdown of the blood-aqueous barrier [12–16].
- Decentration, displacement, or rotation of the IOL usually due to an inappropriate surgical technique or IOL sizing.
- Endophthalmitis can complicate any open-eye procedure, reported with an exceedingly low incidence [16].
- Corneal edema, usually transient and secondary to excessive manipulation during surgery, inflammation, or ocular hypertension.
- Residual refractive error requiring replacement of the lens or correction by means of a corneal procedure (PRK, LASIK, or intracorneal rings).

30.2 Late Postoperative Complications and Their Management

The most common complications to all kinds of AS-PIOLs are cataract formation (Fig. 30.2), endothelial cell loss, and pupillary ovalization. Other less frequent complications addressed are anterior chamber inflammation, patients complaining about halos and night glare, elevated intraocular pressure, lens decentration or rotation, corneal edema, and iris cyst formation [7–9, 16, 28–36].

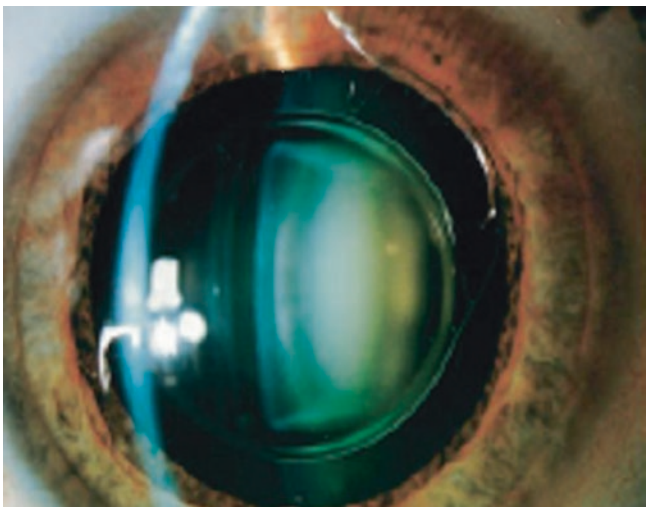

Fig. 30.2 Nuclear cataract in patient implanted with the Baikoff ZB5M angle-supported anterior chamber phakic intraocular lens

30.3 Complications that Lead to Explantation of the AS-PIOLs

PIOL explantation reflects a major failure in the concept of IOL implantation and is always due to a significant problem. It may be caused by reasons related to the IOL design, biomaterial, or anatomical location and to the anatomical evolution of the implanted eye. The analysis of the causes and outcomes of PIOL explantation and of the condition of the PIOL-implanted eyes many years after the implantation provides useful information about the timing and the criteria of PIOL explant.

Recently Alió and coauthors evaluated 240 eyes that have undergone explantation of PIOLs, 140 of which were AS-PIOLs. The models of AS-PIOLs included in this study were Baikoff ZB and ZB5M (Domilens, Lyon, France), Kelman Duet IOL (Tekia, Inc., Irvine, CA), ZSAL-4 (Morcher, Stuttgart, Germany), Phakic 6 IOL (Ophthalmic Innovations International, Ontario, CA), and AcrySof Cachet PIOL (Alcon Laboratories, Inc.) [34].

Cataract was the main cause of explantation (51.39%) of AS-PIOLs, endothelial cell loss in 23 eyes (15.97%), corneal decompensation (Fig. 30.3) in 15 eyes (10.42%), PIOL dislocation in 11 eyes (7.64%), and ovalization of the pupil in 9 eyes (6.25%). Other causes such as retinal detachment, halos and glare, and incorrect lens power were found less frequently. The mean time interval between AS-PIOL implantation and explantation surgery was 7.89 ± 5.62 (range, 0.06–29.76) years. The mean age of the patients at the time of explantation surgery was 49.02 ± 11.71 (range, 25–80) years. In cases that developed cataract, the mean time between PIOL implantation and cataract formation was

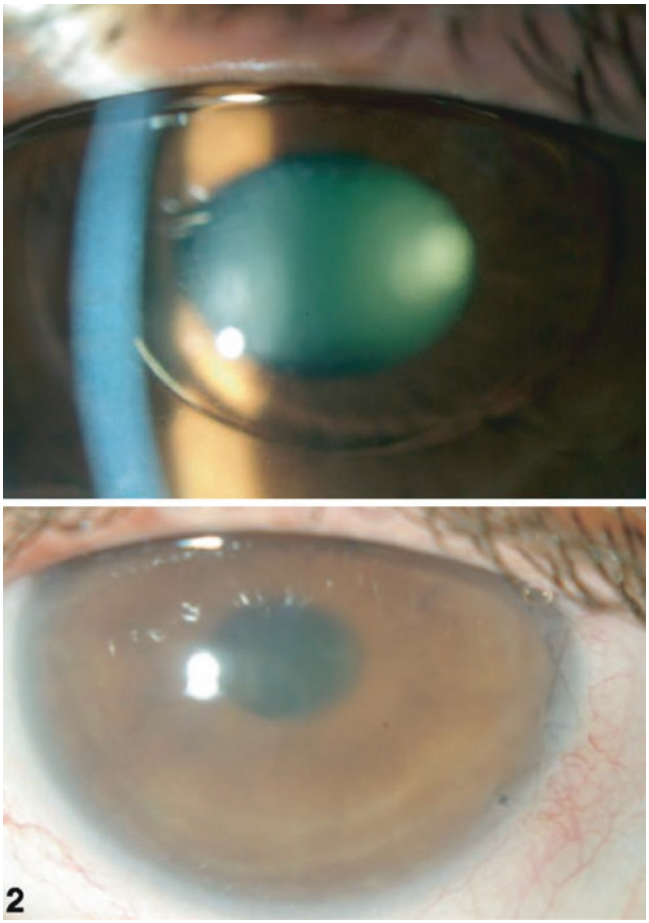

Fig. 30.3 Corneal decompensation in a patient implanted with the Phakic 6 intraocular lens (IOL). *Bottom*, the same case 1 week after phakic IOL explantation

8.56 ± 4.89 years. Patients with a decrease in CDVA by at least two lines from the CDVA measured after PIOL implantation and related to evident lens sclerosis or cataract were explanted. In almost all of these cases, cataracts were nuclear according to the LOCS III.

Previous reports have not demonstrated a relationship between AS-PIOL implantation and cataract development but instead have shown that the probability of cataract development increases when an eye with an axial length of over 30 mm is implanted in patients older than 40 years, leading to nuclear cataract development in the following 2 years [24]. Surgery also might increase the speed of nuclear cataract development because of surgical trauma, postoperative inflammation, and the postoperative use of topical steroids [10, 12]. Phakic IOL implantation in eyes with early changes of the nucleus might promote the progression of these changes into the development of a clinically significant nuclear cataract [24]. Hence, the physician should pay careful attention to recent changes in refraction and density of the lenses of highly myopic eyes before this surgery is recommended [34].

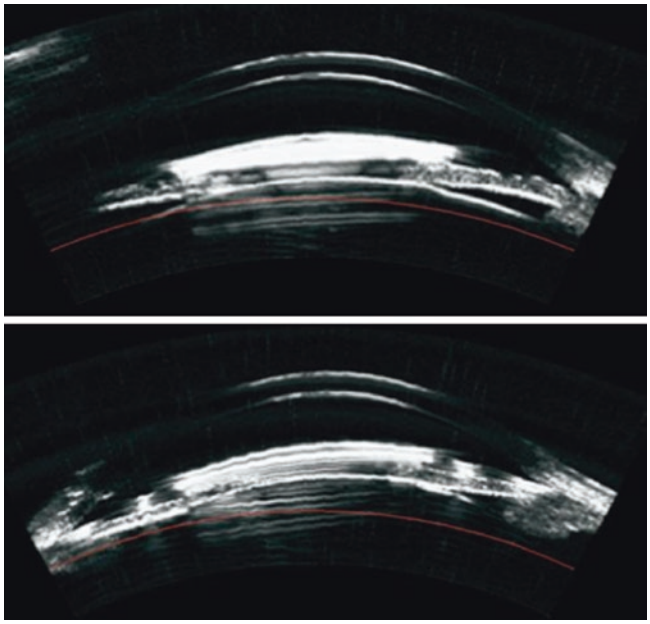

Fig. 30.4 Artemis pictures of two cases which developed severe endothelial cell loss as a result of Phakic 6 intraocular lens implantation

Endothelial cell loss was the second most frequent cause of angle-supported PIOL explantation and is related to PIOL design, inadequate anatomy of the anterior chamber, and patient behavior (Fig. 30.4). PIOLs were explanted in case of marked decrease in endothelial cell count to 1500 cells/mm^2, with evidence of progressive deterioration during the previous 6 months. PIOL decentration/dislocation might occur due to lens undersizing. Explantation surgery was performed in these cases when the PIOL was dislocated peripheral to the visual axis, causing symptoms, or when there was a destructive effect on the anterior chamber structures such as the cornea, anterior chamber, angle, or iris due to this dislocation. Pupillary ovalization is produced as a consequence of ischemia due to compression of the haptics at the iris root and can extend beyond the edge of the PIOL (Figs. 30.5 and 30.6). Some of these cases may suffer from intraoperative complications related to PIOL explantation surgery due to adhesions between the PIOL, iris, and anterior chamber.

30.4 Explantation Techniques of AS-PIOLs

30.4.1 Bilensectomy

Bilensectomy surgery is recommended when best spectacle-corrected visual acuity (BSCVA) decreases by at least two lines from the BSCVA documented after AS-PIOL implantation and related to evident lens sclerosis or cataract. Bilensectomy is also recommended, even without development of cataract, when the endothelial cell count decreases

Fig. 30.5 Severe pupil ovalization in a patient implanted with the Baikoff ZB5M angle-supported anterior chamber phakic intraocular lens (or page 101)

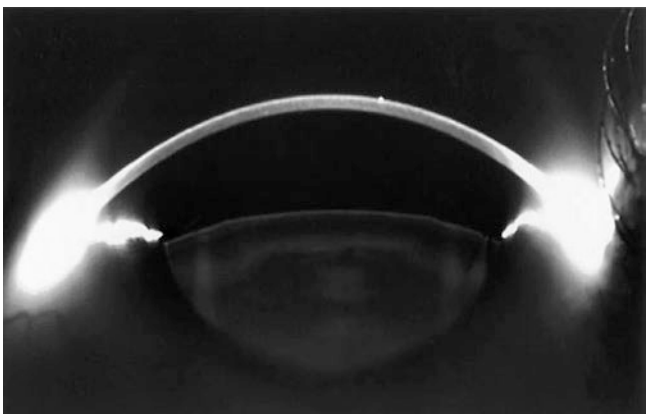

Fig. 30.6 Scheimpflug image of anterior chamber. Note the corneasclera junction zone is overexposed because of the extreme whiteness of the scleral tissue

markedly to approach 1500 cells/mm^2 and the patient has lack of motivation to wear spectacles or contact lenses or when severe pupillary ovalization develops in patients older than 45 years.

Bilensectomy can be performed using coaxial phacoemulsification or MICS in order to increase surgical control during the phacoemulsification procedure [37, 38]. The AS-PIOL can be explanted through a 6 mm incision and then can be sutured after PIOL removal. Afterward, MICS surgery can be performed through two 90° apart 1.5 mm incisions. After phacoemulsification of the nucleus and cortex removal, the initial 6 mm incision is reopened, and a PC IOL can be placed in the capsular bag. In a previous study, Alio and coauthors found that the use of the MICS technique in bilensectomy surgery enhanced intraocular fluid control. They observed that the AC was more stable, with less liability to iris prolapsed, when MICS was used [39].

30.4.2 Phakic Intraocular Lens Exchange

This procedure can be performed when the PIOL is improperly sized, in case of refractive error, because of subjective visual symptoms (e.g., halos and glares) or when significant endothelial cell loss occurred related to the PIOL. To exchange the PIOL, peribulbar anesthesia is usually preferred. Then, using steps similar to those previously described for bilensectomy but with only one side port, the PIOL can be explanted and the new PIOL can be implanted [39].

30.4.3 Bilensectomy Followed by Penetrating Keratoplasty

This procedure can be performed when there is severe corneal endothelial decompensation. After PIOL explantation, the crystalline lens is removed using coaxial phacoemulsification from the superonasal clear corneal incision, and a posterior chamber lens is implanted in the capsular bag. Finally, penetrating keratoplasty is performed [34].

30.4.4 Simple Phakic Intraocular Lens Removal

This procedure can be performed when significant endothelial cell loss occurred related to the PIOL when refractive lens exchange was not indicated or accepted by the patient or to enhance posterior segment visualization when retinal surgery is indicated. Simple PIOL explantation is usually eventless [39].

30.5 IOL Design: Looking for the Perfect PIOL

Until recently the incision size of most of the phakic IOL models was large enough to create at least some astigmatism. In addition, insertions of phakic IOLs were sometimes traumatic to the endothelium and the iris. The danger of inducing opacities in the natural lens is not only theoretical but has been documented. The long-term effects of the redirection of aqueous flow and its clinical significance have yet to be determined. If the implant has to be removed, the surgery becomes quite extensive, and the damage to endothelium and natural lens is more likely.

Successful PIOLs should have some properties which are defined by Charles Kelman [35]:

1. Not putting pressure on the angle
2. Not moving in the anterior chamber
3. Not flexing against the peripheral endothelium
4. Not rubbing against the iris
5. Not causing damage to the natural lens on insertion
6. Not requiring an incision of more than 1.5–2 mm
7. Not difficult to insert
8. Not difficult to remove
9. Not difficult to exchange

30.6 Anterior Segment OCT and Aging

The anterior chamber optical coherence tomography (AC-OCT) enables all the required anterior chamber measurements (anterior chamber diameter, anterior chamber depth, corneal pachymetry, crystalline lens thickness, and iridocorneal angle opening). It is shown to have accurate, repeatable, and reproducible measurements of the anterior segment. Since the infrared light beam is stopped by the pigments, a satisfactory view of the structures situated behind the iris is not possible. The advantages of the AC-OCT are easy no-contact examination and simple anterior chamber measurements and accommodation can be induced. With these advantages, AC-OCT seems to be the most convenient device to scan the anterior chamber for AS-PIOL monitoring [40].

When surgeons used to implant AS-PIOLs, the better choice had to respect three parameters: perfect adjustment to the internal diameter of the anterior chamber, minimum distance from the endothelium, and no contact with the iris and the crystalline lens. Despite respecting these parameters, PIOL explantation cannot be avoided due to the age-related anatomical changes of anterior segment [27].

30.6.1 Anterior Chamber Depth

The clearance between the endothelium and AS-PIOL is critical. Therefore, determination of ACD is very important. Measurement of the internal depth of the anterior chamber (crystalline lens to endothelium) should be preferred over the measurement of the ACD between the crystalline lens and the epithelium. The clearance between the IOL and the endothelium is not the distance from the center of the optic to the posterior face of the endothelium along the eye's axis but the shortest distance from the optic to the endothelium (Fig. 30.7). It was clearly demonstrated that there should be a minimum of 1.50 mm distance between the edge of the optic and the endothelium to prevent the risk for corneal damage. If the edge of the optic is less than 1.50 mm from the endothelium, corneal distortions that occur during eye rubbing can give rise to endothelial alterations by contact with the edge of the IOL. If the IOL is closer than 1.0 mm from the endothelium, explantation should be considered [40–48]. A biometrical study that led to the elaboration of predictive models of endothelial cell count and ACD reduction, provided very useful indication about the timing of AS-PIOL explantation [27]. The distance between the anterior pole of the crystalline lens and the line joining the 2 iridocorneal angles along the horizontal corneal diameter is considered the crystalline lens rise (Fig. 30.8). In addition, with every diopter of accommodation, the anterior pole of the crystalline lens moves forward 30 μm, and the natural lens thickens with age with a mean of 18–20 μm forward movement of its anterior pole every year that corresponds to an anterior chamber (AC) reduction of approximately 18.3 μm per year. This means that after 20 years, the anterior pole of the crystalline lens has moved forward by 400 μm. The safe mean lens height in a young subject, selected for a phakic IOL implantation, was approximately 300 μm. This would imply a 700 μm safety margin for phakic IOL vault (300 μm mean crystalline lens rise +400 μm mean 20 year safety delay = 700 μm). Explantation of angle-supported phakic IOL (Fig. 30.9) is recommended before 30 years after implantation because the endothelial cell count would be less than 600 cells/mm^2 in patients with a preoperative spherical equivalent of −25 D or before 40 years in patients with spherical equivalent of −20 D.

Furthermore in patients with a preoperative spherical equivalent of −20 D, a reduction of anterior chamber depth of 0.6 mm 30 years after implantation is expected and in

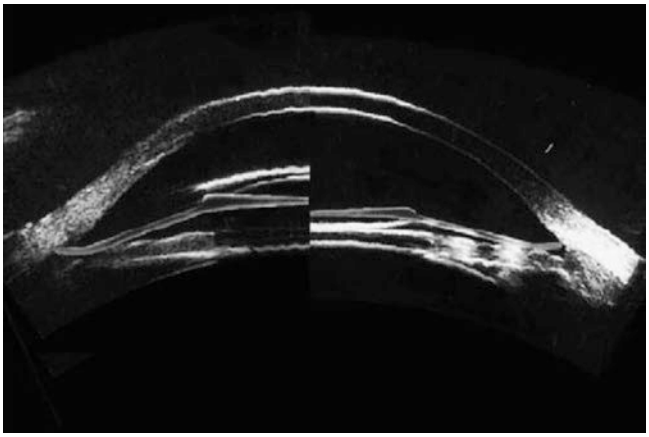

Fig. 30.7 Four superimposed VHF echographic images (Artemis 2) showing the evolution of the "safety distance," that is, the clearance from mid-peripheral endothelium and edge of the myopic optic of different generations of angle-fixated phakic IOLs. Compared to the old ZB (*top left*) and ZB5MF (*bottom left*), the Nuvita (*top right*) and the foldable GBR/Vivarte (*bottom right*) show the modern trend for a significantly lower vault to respect the corneal endothelial cell layer

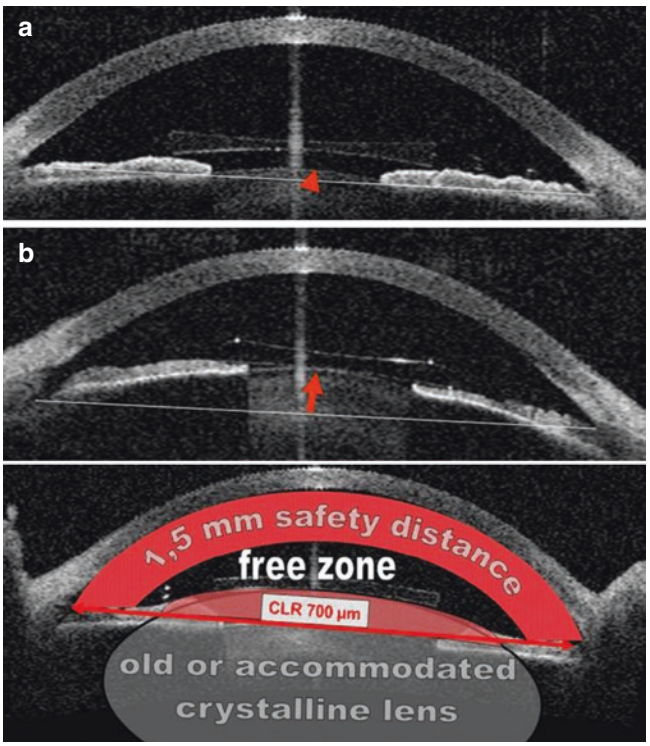

Fig. 30.8 Safe (**a**) and unsafe (**b**) CLR (crystalline lens rise). Bottom: safety distances from the endothelium and the crystalline lens for angle-supported phakic intraocular lens implantation demonstrated in the anterior segment optical coherence tomography image

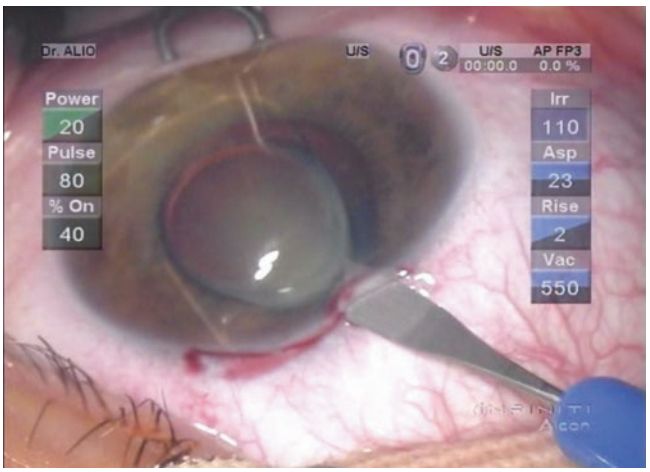

Fig. 30.9 Explant of a Baikoff AS-PIOL through a 6 mm clear cornea incision

patients with a preoperative spherical equivalent of −25 D a reduction of 0.8 mm following 25 years of implantation is expected.

Baikoff ZB (Domilens, Lyon, France) had 1-year mean percentage change in endothelial cells of −4.3 to 5.3%. Cachet AcrySof phakic IOL had a similar 1-year endothelial cell loss about −4.77 ± 8.04%. This suggests to extend this predictive model to new angle-supported phakic IOLs.

Take-Home Pearls

- AS-PIOLs are no longer used because of long-term risks associated with AC aging.
- However given their earlier use, the refractive surgeon should be prepared to deal with their long-term complications.
- The results of explantation of AS-PIOLs are usually excellent with the appropriate surgical techniques.
- PIOLs explantation is recommended in case of marked decrease in endothelial cell count to 1500 cells/mm^2 with evidence of progressive deterioration during the previous 6 months.
- AC-OCT is important for early detection of complications:
  - Sufficient clearance with the endothelium (more than 1.5 mm)
  - Sufficient clearance with the crystalline lens (more than 700 µm)
- Explantation of AS-PIOLs is recommended before 30 years after implantation in patients with a preoperative spherical equivalent of −25 D or before 40 years in patients with spherical equivalent of −20 D.
- As long as meticulous care is given to the prevention or treatment of the complications reviewed above, more invasive surgical procedures can be avoided at the time of AS-PIOL explantation, achieving good results with the least damage to the patient.

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Complications of Iris-Supported Phakic IOLs

31

Antonio A.P. Marinho

Core Message

- Phakic IOLs have been used in refractive surgery for more than 20 years. All types of phakic IOLs are associated with very good refractive results and patient satisfaction. However, complications (mostly long term) have been associated with these IOLs, leading to a constant change in design and location inside the eye. In this chapter we look at the complications associated with phakic IOLs and provide guidance on how to avoid them.

31.1 Introduction

In this chapter, we will present the possible complications associated with implantation of iris-supported phakic IOLs. As many of the complications found are related not to the lenses themselves but to surgical and patient characteristics, we will cover briefly both of these aspects after presenting the available models of iris-supported phakic Iols.

31.2 Iris-Supported Phakic Intraocular Lenses

The concept of implantation of an intraocular lens supported by the mid-periphery of the iris was developed by Jan Worst, for aphakia in 1979. The great success and safety of this implant led Jan Worst and Paul Fechner [1, 2] to implant the first iris-supported phakic IOL for myopia in1986. It was originally a biconcave lens that was sometimes too close to the corneal endothelium possibly causing damage. In 1991 the phakic IOL was redesigned to a safer plano-concave shape. This IOL has been renamed "ARTISAN" in 1997. We will now describe in summary the different available iris-supported phakic IOLs pointing to their material, optic diameter and powers. All these lenses have in common the following characteristics [3–10]:

(a) Anterior chamber lenses consisting of an optic and two haptics.
(b) The haptics are in the form of a "claw" (lobster claw) to receive the enclavation of iris tissue.
(c) The overall size of these lenses is 8.5 mm for all eyes (except for a very rarely used paediatric model), so it is independent of the size of the anterior chamber. This is what we call "one size fits all."
(d) All these lenses are manufactured by OPHTEC (Netherlands) and distributed worldwide by OPHTEC (Artisan/Artiflex) and AMO (USA) under the brand names of Verysize/Veryflex.

31.3 Characteristics of Different Models of Iris-Supported Phakic IOLs

(a)	Model 206	Artisan myopia 5/8.5 mm	
	Material, PMMA	Optic: 5.0 mm	Power: −3.00 to −23.50 (Fig. 31.1)
(b)	Model 204	Artisan myopia 6/8.5 mm	
	Material, PMMA	Optic: 6.0 mm	Power: −3.00 to −15.50 (Fig. 31.2)
(c)	Model 203	Artisan hyperopia 5/8.5 mm	
	Material, PMMA	Optic: 5.0 mm	Power: +1.00 to +12.00 (Fig. 31.3)

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(d)		Artisan toric 5/8.5 mm	
	Material, PMMA	Optic: 5.0 mm	Power: Cylinder from −2.00 to −7.50 and +2.00 to +7.50. Both negative and positive cylinders are available at 0° (type A) and 90°(type B) (Figs. 31.4 and 31.5)
(e)		Artiflex myopia 6/8.5 mm	Material, Polysiloxane (silicone) optic/PMMA haptics
		Optic: 6.0 mm	Power: −2.00 to −14.50 (Fig. 31.6).
(f)		Toric Artiflex 6/8.5 mm	
	Same material as Artiflex. Like toric Artisan, both types A and B are available. Correct cylinders from −1.00 to −7.50 provided the total power (sphere + cylinder) does not exceed −14.50. For example, if the sphere is −13.00, only −1.50 can be corrected. On the other hand, if the sphere is −8.00, the cylinder can be corrected up to −6.50		

31.4 Selection of Patients

Patient selection for implantation of Artisan/Artiflex follows the general rules of refractive surgery, like 18 years minimum age (exception for paediatric anisometropia) and a stable refraction. The absence of intraocular vascular (diabetes) or inflammatory (uveitis) diseases are also mandatory. As the IOL is going to be implanted in the anterior chamber, it is very important to be sure that no damage is inflicted to the corneal endothelium. The anterior chamber depth must be carefully measured. Classically it was stated that an anterior chamber depth (from endothelium to natural lens) should be at least 2.8 mm. However the central anterior chamber depth is not the main issue, but also because of the shape of the cornea (dome shaped) and the greatest thickness of the lens in the periphery (myopia lens), the critical distance between the IOL and the endothelium must be at least 1.5 mm [3] (Fig. 31.7).

This measurement is not available by ultrasound biometry, Orbscan (B&L USA) or Pentacam (Oculus, Germany).

There are tables that can extrapolate this distance from the central anterior chamber depth, and the power of the IOL to implant is much safer today to simulate the implantation and measure the distances using devices like the anterior chamber OCT (Visante, Zeiss, Germany).

Despite the safety of these lenses to the corneal endothelium, we must not implant Artisan/Artiflex in eyes with endothelial disease. Endothelial cell count of at least 2400 cells/mm and the absence of significant polymegathism and polymorphism are criteria for implantation (except in eyes after penetrating keratoplasty, where lower counts can be accepted).

One last very important point concerning the inclusion/exclusion criteria for implantation of Artisan/Artiflex deals with the shape of the iris. Eyes with a convex iris (mostly hyperopes) should not be implanted with this kind of phakic IOLs [11, 12].

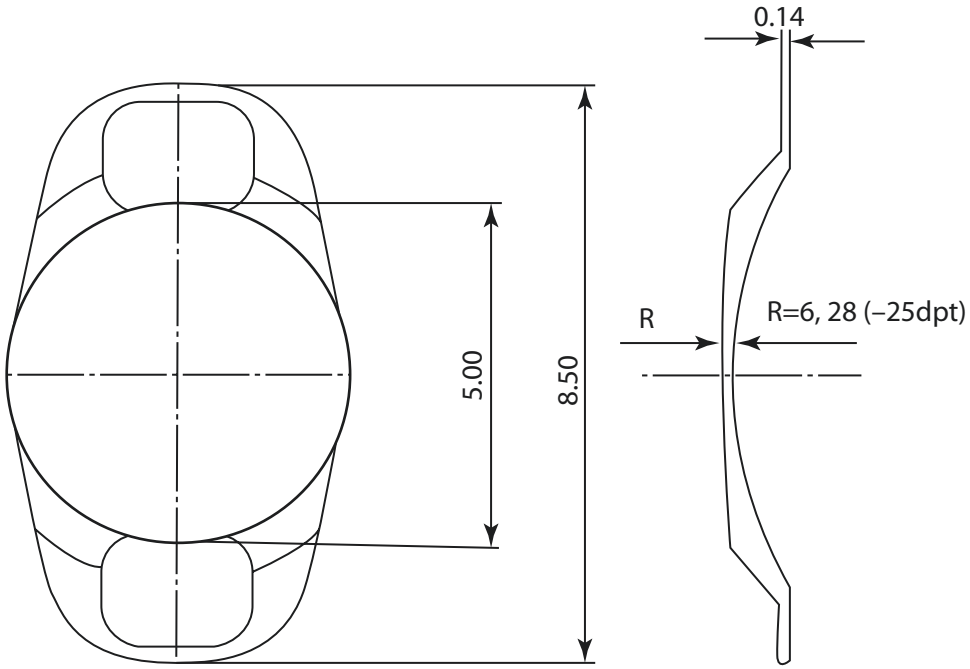

Fig. 31.1 Artisan model 206 (myopia PMMA 5.0 mm)

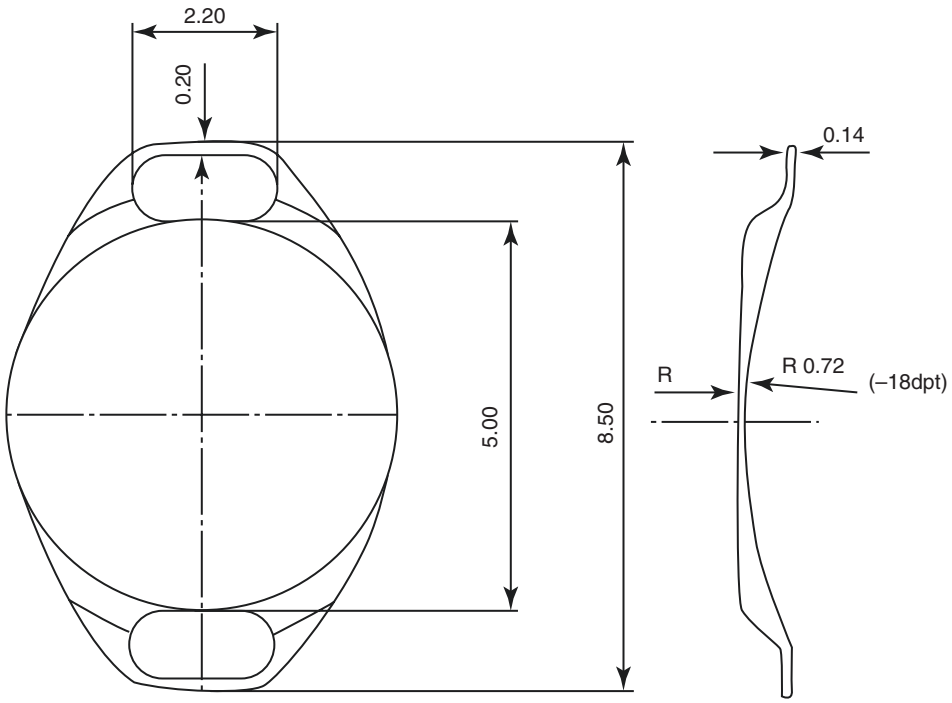

Fig. 31.2 Artisan model 204 (myopia PMMA 6.0 mm)

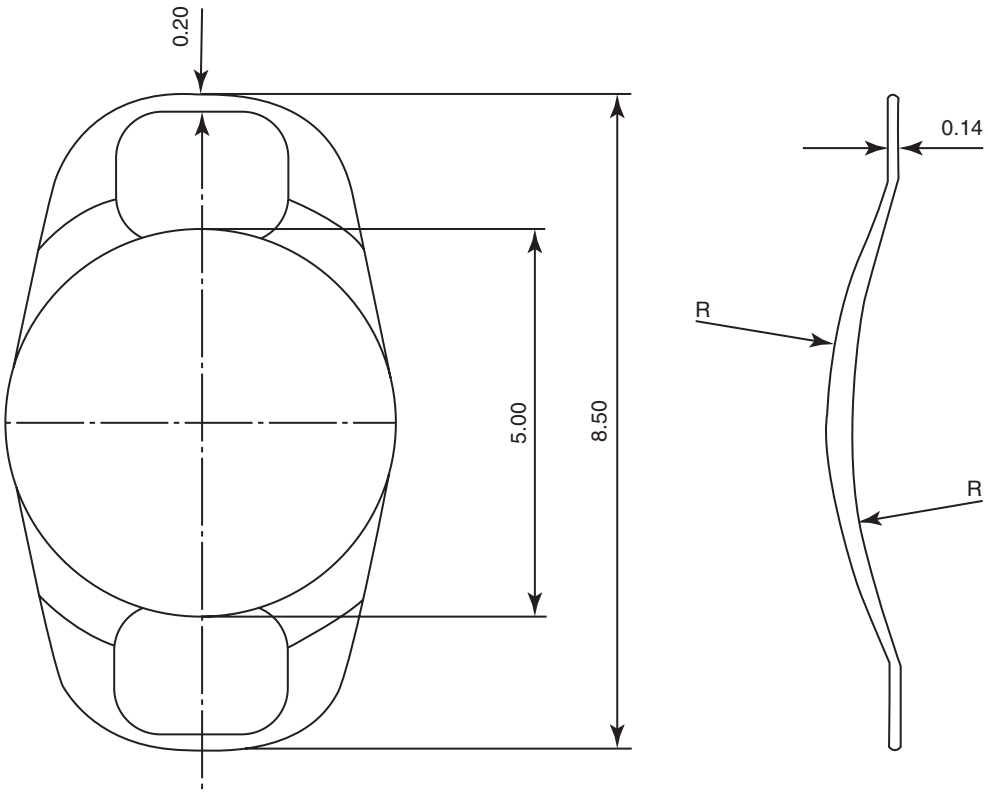

Fig. 31.3 Artisan model 203 (hyperopia PMMA 5.0 mm)

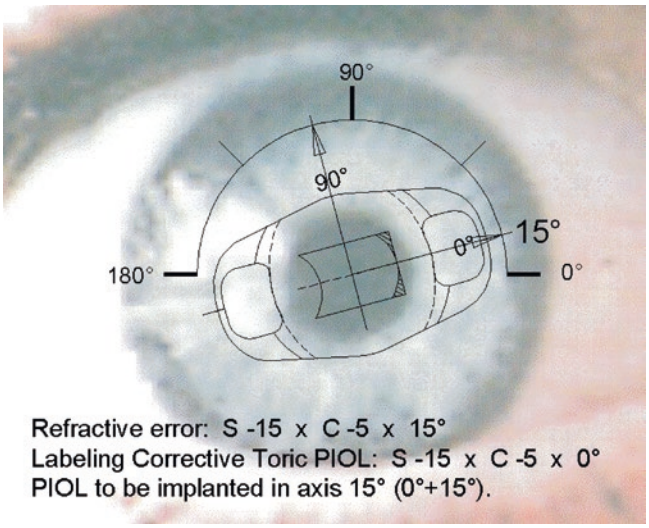

Fig. 31.4 Toric Artisan (type A)

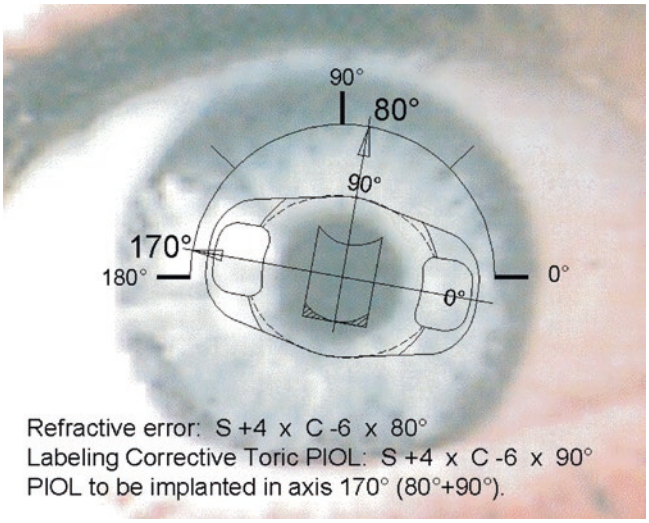

Fig. 31.5 Toric Artisan (type B)

31.5 Surgery

It is very important to review in detail the surgical technique of implantation of Artisan/Artiflex IOLs, because many of the complications associated with these IOLs are caused by an imperfect surgery and so are avoidable if the rules are strictly followed for each step [13].

31.6 Preoperative Preparation

The pupil must be constricted prior to surgery. In most patients, two or three drops of 2% pilocarpine are enough. Alternatively, you may achieve the same goal by using intracameral acetylcholine. If you are planning a peribulbar/retrobulbar anaesthesia, a perfusion of IV mannitol may be useful to reduce vitreous pressure (see Sect. 31.7).

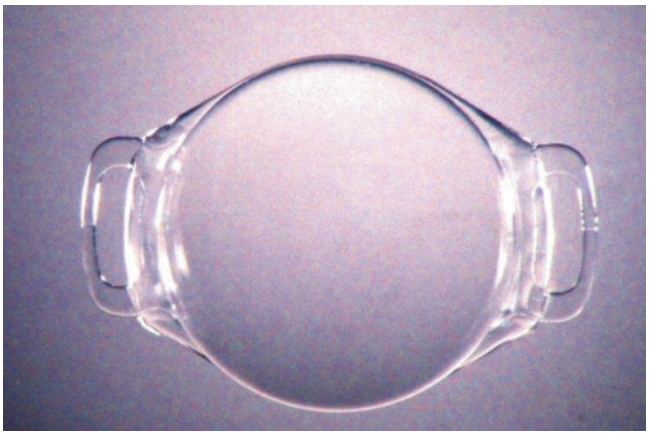

Fig. 31.6 Artiflex (foldable)

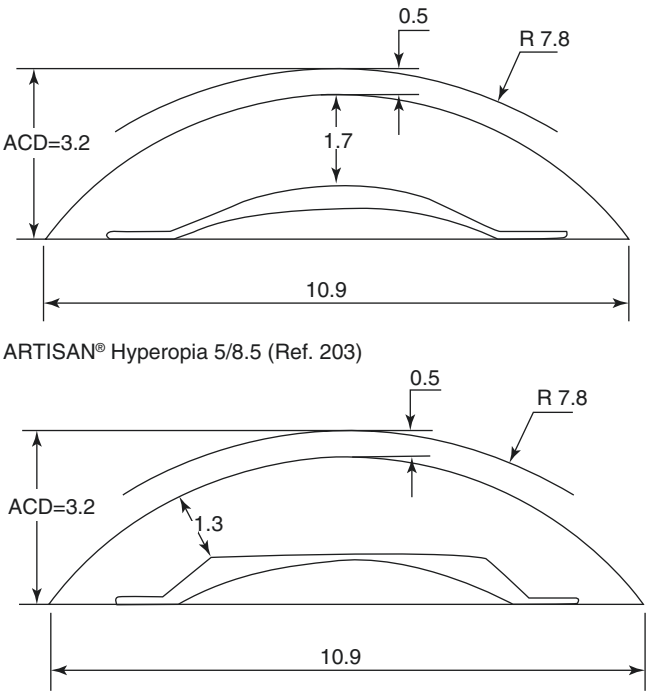

Fig. 31.7 Critical distances to the endothelium in myopia (*bottom*) and hyperopia (*top*)

31.7 Anaesthesia

Artisan/Artiflex IOLs can be implanted with different types of anaesthesia. As a general rule, we think that general anaesthesia is the most adequate for this procedure, and it is mandatory to the inexperienced surgeon. Retrobulbar/peribulbar block is not recommended, because it is usually associated

with increased vitreous pressure and consequent shallowing of the anterior chamber, turning the surgery more difficult and risky. Topical anaesthesia is possible with Artiflex (small incision) but should only be attempted by experienced surgeons.

31.8 Surgical Steps

The first surgical step (common to all these lenses) is to perform two side ports. These side ports are classically done at 10 and 2 o'clock positions (assuming the main incision is at 12 o'clock), but their location can change according to the desired position of the IOL. The side ports must be 1.5 mm wide. After completing the side ports, the anterior chamber is filled with cohesive viscoelastic material. Dispersive viscoelastics should never be employed. The next step is the main incision. When using PMMA IOLs, the incision is 5.2 mm or 6.2 mm according to the model. The incision can be clear corneal, sclerocorneal or scleral, with or without a tunnel. The importance of the location of the incision relates to the possible induction of astigmatism with these large incisions. Slightly posterior incisions give better results. When implanting Artiflex IOLs, a clear cornea with 3.2 mm incision is the rule [5, 6]. The IOL is then introduced in the anterior chamber and rotated to the desired position. This position is critical when implanting toric Artisan or toric Artiflex [7–9, 13]. In this case we must define the axis of implantation, by marking the limbus with a surgical pen (preferably in the sitting position to avoid cyclotorsion). In all the other models, the axis of implantation is irrelevant. Once the Artisan/Artiflex is in the proper position, we proceed to the most critical point of the surgery—the enclavation. In this step the Artisan/Artiflex IOL is fixated to the mid-periphery of the iris. We achieve this fixation by a bimanual technique (Fig. 31.8). One hand holds the IOL with a forceps. In Artisan the forceps holds the optic of the lens [13], while in Artiflex, as the optic is soft, special forceps were designed to hold the haptics [5, 6]. With the other hand, a blunt "needle" is introduced through the side port which introduces (enclavate) a sufficient amount of iris tissue in the claw of the haptic. This is repeated in both haptics. It is very important at this stage to check the correct and the perfect centration of the Artisan/Artiflex with the pupil. In this type of phakic IOLs, the centring of the IOL is of exclusive responsibility to the surgeon. The next step consists of performing a small iridotomy or iridectomy (this can also be done with YAG preoperative). After completing the iridotomy/iridectomy, the viscoelastic material must be completely removed. We usually use passive irrigation to achieve this goal. The last step of the surgery is the suture of the incision for Artisan and simply hydration of the wound for Artiflex (sutureless surgery).

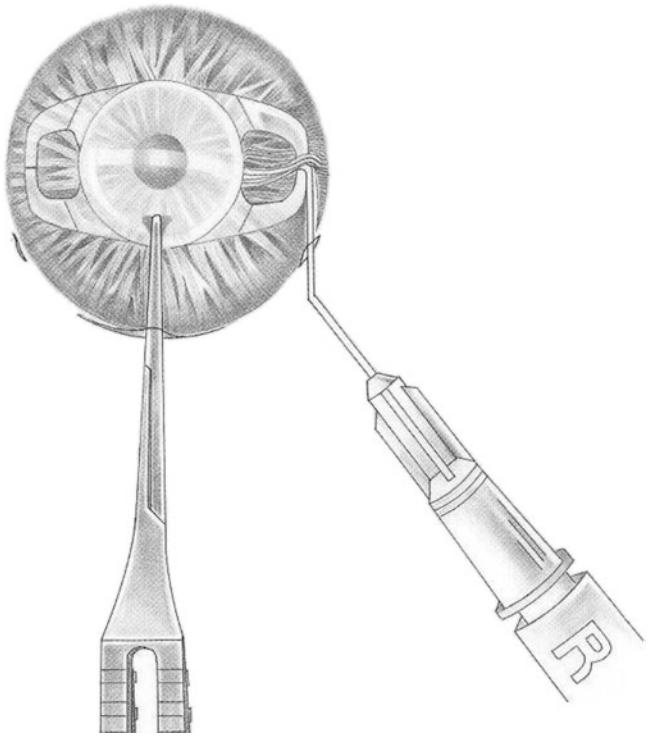

Fig. 31.8 Fixating the IOL to the iris (enclavation using the needle)

31.9 Postoperative Care

At the end of the surgery, a subconjunctival injection of antibiotic and steroids is recommended. The post-op regimen consists of topical ofloxacin and topical prednisolone acetate 4×/day for 2 weeks. Oral prednisolone for a week is recommended in patients with heavily pigmented eyes, mostly in Artiflex (material concerns).

31.10 Complications

The complications related to the implantation of iris-supported phakic IOLs can be divided in three groups. Short-term complications are those found during surgery or in the first postoperative days. Medium-term complications occur during the first 3 weeks post-op, and long-term complications are those beyond that period of time [14–16].

31.11 Short-Term Complications

The most common complications found during implantation of Artisan are the iris prolapse and the loss of anterior chamber [14]. These problems are related to the large incision (5.2 mm or 6.2 mm) and mostly to high vitreous pressure. This high vitreous pressure is related mostly to patient anxiety and high volume of

retrobulbar/peribulbar anaesthetic. This loss of anterior chamber makes the surgery very difficult and usually leads to other complications. The best way to avoid it is to use general anaesthesia, and if peribulbar is needed, association of pre-op mannitol can help. In the presence of iris prolapse, an iridectomy/iridotomy should be performed immediately, and usually the eye calms down, and the surgery may continue. These two complications are very rarely observed with Artiflex as the small incision (3.2 mm) allows us to work in a closed system [5, 6, 10].

Bleeding can occur during surgery. If the iris is pulled too vigorously during the enclavation process, we can observe some bleeding from the root of the iris. Also, when performing iridectomy, bleeding is possible. Generally this complication is avoided with gentle surgery, and if bleeding does occur, it is usually easily stopped putting some viscoelastic in the bleeding site. Postoperative hyphaema is exceptional.

Centration of the IOL and sufficient amount of iris tissue enclavated in the haptic (grasp) are very important, and failure to do so will lead to later complications. The suture, when needed (Artisan), must be astigmatic free.

Corneal edema may be present in the first day after surgery. It is usually caused by a traumatic surgery with excessive manipulation. It is a more common complication during the learning curve of the procedure or if the surgical conditions of the eye were not perfect (loss of anterior chamber). This edema generally goes away in a matter of days, but later damage to the endothelium is possible. It is easily avoidable with good surgery and adequate surgical conditions.

Another complication seldom seen, but possible in the first days post-op, is a flat anterior chamber with possible touch of the IOL to the cornea. This flat anterior chamber can occur in two different settings. We can observe a flat anterior chamber with low ocular pressure or with high ocular pressure. In the first case, it is due to inadequate closure of the surgical incision. In this case the suture must be fixed. More serious is the situation of flat anterior chamber with high ocular pressure. This can be related to retained viscoelastic but more often to not patent iridectomy. In this situation, we must act immediately to avoid the risk of a permanent dilated pupil (Urrets-Zavalia syndrome). Yag laser iridotomy usually solves the problem.

The most feared complication in the first days post-op is infectious endophthalmitis. In this complication (common to every intraocular surgery), routine endophthalmitis treatment (systemic and intravitreal) must be used.

31.12 Medium-Term Complications

In the first 3 months after the surgery, some complications may occur. As we are going to see, they are mostly related to poor surgery or failure to follow the guidelines for patient selection.

During the first 2 weeks post-op, sometimes a high ocular pressure is present. This is due to the topical steroids. Suspension of the steroids brings the pressure to normal levels, and no further treatment is needed.

However, the most important complications in this period are optical and inflammatory. The most common optical complication is the complain of halos and glare. This is more frequent if the optic is small (5.0 mm) or the one pupil is large. Decentration of the IOL (even slight) (Fig. 31.9) may cause a lot of halos and glare, especially if the lens is decentred superiorly. To avoid (or to minimize) this problem, centration of the IOL must be carefully done, and we should not implant patients with mesopic pupil larger than the optic of the Artisan/Artiflex [14, 15]. If we find a decentred IOL with symptoms in the post-op, surgical recentring of the lens is advised. Although halos and glare may be present in patients with perfect surgeries and normal pupils, these symptoms tend to wane over time, and it is unusual to have to explant the lens.

Another optical problem we may find is the induction of astigmatism. This can occur with toric Artisan if the IOL is not implanted in the right axis or in Artisan if the suture is poorly constructed. Doing slightly posterior incisions (avoiding clear cornea) reduces the risk. It is also very important in toric Artisan to mark carefully (sitting position) the axis of implantation. To manage this complication, we may try to do a new suture, but most often more reliably, we manage the residual astigmatism with laser corneal surgery (if corneal conditions allow). With Artiflex we never observed any significant change in astigmatism [5, 6, 10].

However, the most feared complications in the first 3 months after surgery are inflammatory [11, 12]. Acute uveitis immediately after surgery is a rare event and is almost always associated with a very traumatic surgery. Standard uveitis treatment solves the problem. Pigment deposits on the surface of the lens are commonly observed between

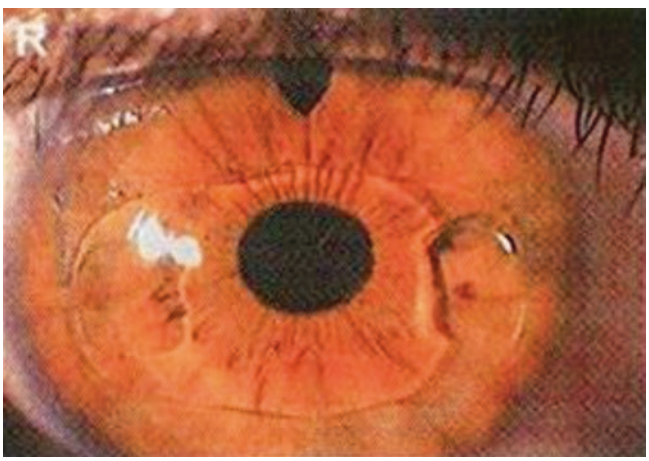

Fig. 31.9 Decentred Artisan

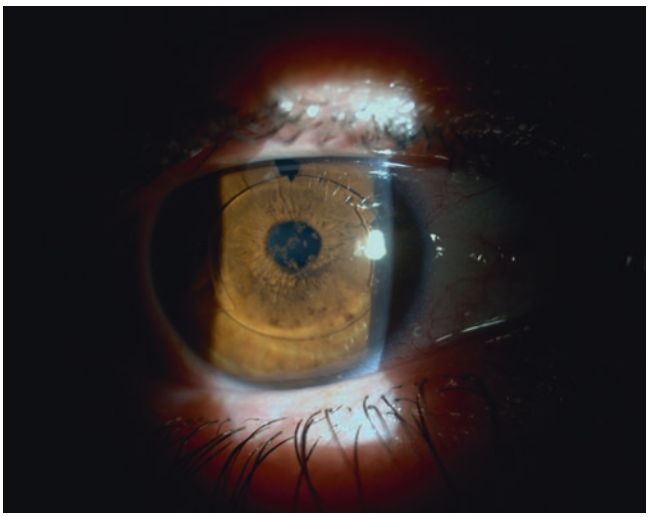

Fig. 31.10 Artiflex with pigment deposits

2 weeks and 3 months. These pigment deposits are asymptomatic, tend to disappear with time and do not require treatment. Additionally, these pigment deposits are seen in both Artisan and Artiflex lenses. Giant-cell deposits have also been observed in some eyes implanted with Artiflex (Fig. 31.10). In these cases there is normally a decrease of visual acuity, with only very mild inflammatory signs. In our series of 400 eyes implanted with Artiflex, these giant-cell deposits have been observed in four eyes [5, 6, 10]. To avoid this complication, we suggest the subconjunctival injection of steroids at the end of the surgery. If these deposits occur, topical and oral steroid treatment leads to full recovery.

Late-onset uveitis (after 3 weeks of surgery) associated with cyclitic membranes and posterior synechia have been described mostly in hyperopic eyes. This is due to special anatomic conditions of the iris (convex iris) [11, 12]. As it was stated above (patient selection), this form of the iris is a contraindication for the implantation of these lenses. In the presence of such a situation, aggressive therapy with oral and topical steroids must be implemented. If the treatment does not succeed or the situation recurs, explantation is recommended.

31.13 Long-Term Complications

One possible complication observed later than 3 months after surgery (may also be seen sooner) is the luxation of the IOL [14, 15]. This means that one (Fig. 31.11) (exceptionally both) haptic of the IOL became free from the iris tissue, leading to the luxation of the IOL. This is always due to insufficient amount of iris tissue enclavated in the claw of the lens (weak grasp). A good grasp definitively avoids this problem. In the event of a luxation of an iris-supported phakic IOL, surgical repositioning must be done immediately, as the loose lens may damage the corneal endothelium.

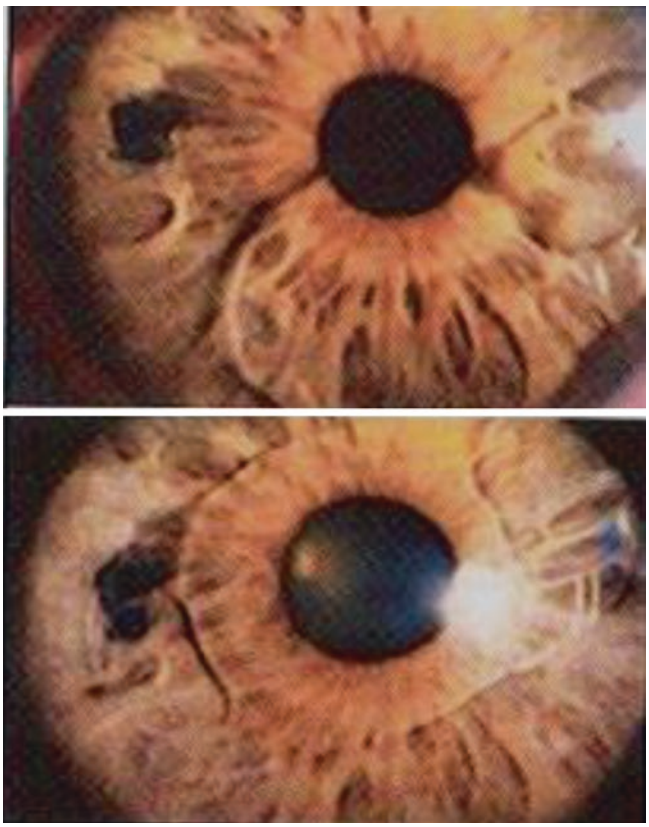

Fig. 31.11 Luxation of Artisan (*top*) and after management (*bottom*)

The relationship between phakic IOLs (mostly anterior chamber) and corneal endothelium has been widely discussed. Several studies concerning the impact of Artisan implantation and endothelial cell loss have been done. The most complete study is the European Multicenter Study published in 2000 [17], where 518 eyes implanted with Artisan showed a loss of endothelial cell count of 4.8% at 3 months (surgically induced) but only a further loss of 1.7% at 2 years and a 0.4% at 3 years. Most other published studies (however much smaller) show similar results [9, 10, 18–20].

A classic paper by Perez Santonja et al. [21] in 1996 stated that there are important losses in endothelial cells in eyes implanted with Artisan. In this paper, however, there is no relationship of these losses with power of the implanted IOLs and the anterior chamber depths. Of course if the anterior chamber is not deep enough, endothelial cell loss will occur.

Our data show that Artisan/Artiflex is safe for the corneal endothelium as long as the selection criteria for implantation are met [5, 6, 15]. Nevertheless, it is advised to check the corneal endothelium yearly after surgery and to explant if endothelial cell count or shape (polymorphism, polymegathism) degrade significantly.

Being at a safe distance from the natural lens, the iris-supported phakic IOLs do not induce anterior subcapsular cataract, as the posterior chamber phakic IOLs. However,

some nuclear cataracts have been observed in eyes implanted with Artisan. These nuclear cataracts are age related but in implanted eyes tend to be present at a younger age (late forties, early fifties). The reason for this is not clear, but it has been suggested that the opening of the eye during surgery or the misdirection of the aqueous humour (due to the iridectomy) may account for the earlier development of nuclear cataracts [16, 22, 23].

31.14 Explantation of Phakic IOLs

Most of the phakic IOLs are to be explanted. In our series, as well as in data published in the literature [24], the mean time between implantation and explantation is from 5 to 12 years. The main cause of explantation is cataract (50% of cases). These cataracts can be related with the age of the patient (nuclear cataracts) or directly with the phakic IOL (anterior subcapsular cataracts in ICL). In anterior chamber phakic IOLs, endothelial cell loss is the second cause for explantation. Other causes are:

(a) Pupil distortion and iris atrophy (anterior chamber angle-supported PIOLs)
(b) Chronic inflammation (Artiflex)
(c) Wrong sizing (ICL)

After explantation of phakic IOLs, phaco with a pseudophakic IOL in the bag is the most common approach. However, if the patient is young (<45 years) and no cataract or endothelial cell damage is present, exchange for another phakic IOL may be indicated.

Conclusions

Like any surgery, the implantation of iris-supported phakic IOLs can be associated with many complications. What is important at this point is to differentiate the complications related to the IOL itself, from those arising from other factors such as the selection of candidates for implantation or the surgical technique.

As we clearly see from the presentation of possible complications, most of them are not related to the IOL but to other factors. Let us summarize the most frequent complications relating to their origin:

1. Complications due to incorrect surgery (or anaesthesia):
   (a) Iris prolapse
   (b) Hyphaema
   (c) Endothelial touch (corneal oedema, endothelial cell loss)
   (d) IOL decentration (glare)
   (e) Induced astigmatism (Artisan)
   (f) IOL luxation (weak grasp)
   (g) Acute uveitis
2. Complications due to bad selection of candidates for implantation:
   (a) Late-onset uveitis with posterior synechia (convex iris)
   (b) Endothelial cell loss (shallow anterior chamber)
   (c) Glare and halos (large pupils)

This clearly shows that a good selection of candidates and a gentle and precise surgical technique allows us to implant iris-supported phakic IOLs with almost no complications. Artisan/Artiflex is the safest phakic IOLs available in the market.

Take-Home Pearls

- Proper patient selection is most important in avoiding complications with Artisan/Artiflex IOLs.
- The surgical technique also plays a role in avoiding complications.
- The surgeon (not the IOL) is the only responsible for perfect position of the lens.
- With Artisan/Artiflex "one size fits all".
- There are very few (if any) complications related to the IOL.

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Complications of Posterior Chamber Phakic IOLs

32

Carlo F. Lovisolo and Roger Zaldivar

Core Messages

- Collamer posterior chamber phakic IOL (*Visian ICL*™, STAAR Surgical Inc., Monrovia, CA) implantation is a predictable and effective method to correct high myopia and hyperopia. Toric phakic IOLs (*TICL*™) are currently available to correct high combined astigmatisms, including stable keratoconus and post-keratoplasty eyes.
- Current implantable collamer lens (ICL) models show better clinical outcomes and a decrease in the incidence of cataracts postoperatively.
- To guarantee their long-term safety, these lenses require a thorough preoperative anatomical evaluation of the anterior segment with specialized high-resolution biometry technologies, such as very high-frequency (VHF) ultrasonography and dedicated software to size their overall length.
- Most of the complications related to the use of modern ICL models may be avoided by adequate preoperative implant sizing and a proper surgical technique.

32.1 Introduction

Posterior chamber IOLs, also called sulcus or lens-supported phakic IOLs, are widely used today. Their implantation through minimally invasive procedures is likely to produce excellent results in terms of precision, predictability, and stability of the refractive outcome [1–14]. When compared to eyes that receive a myopic conventional LASIK procedure, the postoperative quality of vision has been shown to be better in the implanted eyes, yielding significantly less higher-order aberrations [15–17]. The outstanding outcomes reported after implantation of toric optics have allowed refractive surgeons to expand indications to highly astigmatic patients, including stable keratoconus and post-keratoplasty eyes [18, 19]. Refractive inaccuracies may be easily adjusted with complementary fine-tuning excimer laser corneal surgeries [20–25]. In the event of implanting a lens with an inadequate size or with reported visual symptoms, the implants can be removed or exchanged with an anastigmatic small incision, permitting potential reversibility to the preoperative [8, 26, 27].

However, as a consequence of the anatomic site of fixation—posterior chamber phakic IOLs are vaulted between the iris posterior pigmented layers and the anterior crystalline lens with the anterior zonules—these implants may possibly cause acute angle-closure and/or malignant glaucoma, ischemic "blown" pupil (the Urretz-Zavalia syndrome), pigmentary dispersion syndrome, anterior subcapsular cataract, damage to the zonules with dislocation, and chronic uveal inflammation [10, 27–37].

32.2 Posterior Chamber Phakic IOLs

Since the original "collar button" silicone lens introduced by Fyodorov in the early 1980s [28, 32], some different models have been proposed through the years, but only one has reached successful, widespread use: the Visian ICL™ (STAAR Surgical, Monrovia, CA) [7, 8]. The "top hat" elastomer lenses provided by Adatomed (Munich, Germany) in the mid-1990s [38–41] have been abandoned due to significant inflammatory complications and to the fibrotic changes induced to the anterior crystalline lens, though no convincing evidence has been published as to whether these complications were due to hydrophobic properties of the low refractive index silicone material or to the design contour [38, 42].

Although thousands of new-generation silicone models (*PRL*™, Zeiss Meditec, Jena, Germany) were implanted in Europe with satisfactory refractive outcomes, a significant decentration rate (about 10% in our experience versus 0% of the ICL) and the concerns about some design-related severe complications anecdotally reported at meetings, mainly

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zonular damage and dislocation into the vitreous chamber, are the reasons why the PRL is now slowly falling into disuse worldwide [39, 43, 44].

At the time of writing, acrylic material models, like the *Sticklens*™ (IOLTECH, La Rochelle, France), the *Epi. Lens*™ (AcriTec, Hennigsdorf, Germany), and the *ThinOpt-X*™ (Medford Lakes, NJ, USA), are in the very early phases of experimental trial application, and only preliminary reports have been issued.

This chapter summarizes the use of ICL and its most relevant complications. Particular attention will be paid to lens implant sizing and the new safety guidelines based on internal anatomy provided by specialized biometry techniques, such as very high-frequency (VHF) ultrasonography and a dedicated software [34, 45, 46].

32.2.1 The Visian ICL™

The ICL is made of *Collamer*™, a so-called collagen-copolymer material where the addition of 0.2% collagen to the silicone (60% poly-HEMA) makes the implant more hydrophilic (36% water) and more permeable to gas and nutrients. This ICL, by attracting the deposition on its surface of a monolayer of fibronectin, which inhibits aqueous protein binding, is more biocompatible with the nearby structures [47].

After the first prototypes were implanted in Italy, Austria, and Argentina in fall 1993, several clone models followed, with variations of the built-in vault height (Fig. 32.1a) [2, 3, 6, 7, 48]. Current ICL models (V4 or Version Four for myopia, V3 or Version Three for hyperopia) marketed in Europe are measured in a bath of NaCl solution. The ICL is a rectangular, 7.0-mm-wide lens implant, available in four overall lengths (11.5, 12.0, 12.5, and 13.0 mm for the myopic lenses, called ICM; 11.0, 11.5, 12.0, and 12.5 mm for the hyperopic ones, called ICH). The optic diameter ranges from 4.65 to 5.5 mm in the ICMs, depending on the dioptric power, and is always 5.5 mm for ICHs. The basic design change of the most used V4 ICM is in the vaulting. In an attempt to increase the clearance from the anterior crystalline lens surface, and therefore to minimize the risk of iatrogenic subcapsular anterior opacities, the V4 has an additional 0.13–0.21 mm of anterior vault height, due to the steeper radius of curvature of the base curve and depending on the dioptric power (Fig. 32.1b) [7]. When implanted into the intraocular environment or immersed into BSS, the ICL swells, thus increasing its dimensions to about 5.2%. So the lens implant width becomes 7.37 mm, an optic of 5 mm corresponding to 5.26 mm, and an overall length of 13.0 mm–13.6 mm. In the US market, the lenses are labeled based on measurements taken in balanced salt solution (BSS) rather than NaCl.

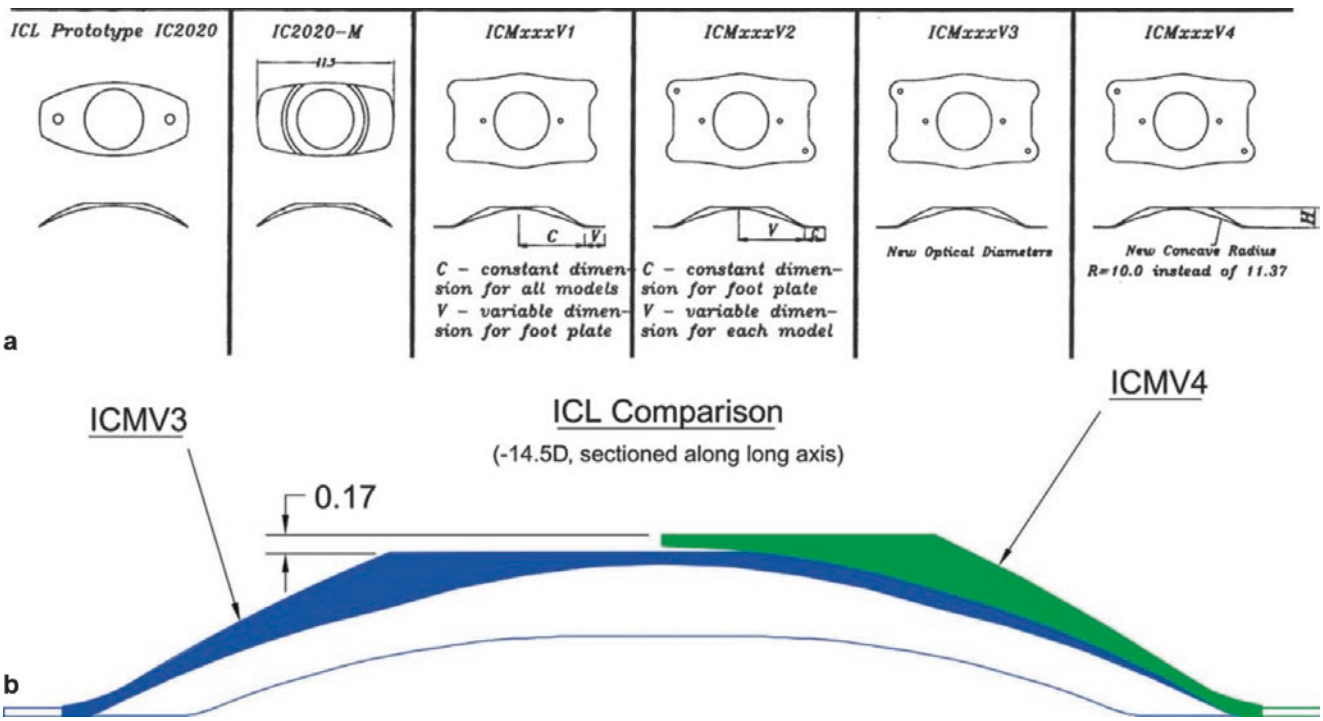


Fig. 32.1 Technical drawings of successive generations of myopic ICL (**a**) and direct comparison of the last model (V4) versus the previous one (V3) (**b**)

For comparative reasons, the overall ICL patient population was divided into three groups based on the lens model implanted and the method utilized for choosing its overall length:

1. Group A: 139 myopic eyes implanted with first to third-generation ICL (41 ICLs implanted with the forceps, 98 lenses injected), from September 1993 to April 1998, with a mean follow-up of 39 months (maximum of 14 years).
2. Group B: 401 myopic eyes implanted with the last-generation (V4, Version Four) ICL sized according to the white-to-white +0.5 mm rule of thumb (from April 1998 to December 2003). The mean follow-up was 37 months (maximum of 9 years).
3. Group C: 287 myopic eyes implanted from January 2002 to June 2007 with the last model (V4), including toric correction (V4 TICL), whose sizing was made with a software based on the ciliary sulcus dimensions (sulcus-to-sulcus) obtained with the Artemis 2 (Ultralink, St. Petersburg, FLA, USA) VHF echographer and the Lovisolo Custom ICL Sizer [34, 40]. The mean follow-up was 29 months (maximum of 65 months).

Table 32.1 shows a comparison of complication rates among the three groups and Group D (data provided by the STAAR International Vigilance Office on the eyes implanted with the pre-V4 generation of ICL, September 1993 to January 1998), and Group E (the results of the post-V4 ICL eyes enrolled in the long-term, multicenter STAAR Myopic Implantable Contact Lens trial, which led to FDA approval in late 2005) [7, 11, 39].

Table 32.1 Synopsis of complication rates in different populations of ICL-implanted myopic eyes

Complication (%)	Group A *N* = 139	Group B *N* = 401	Group C *N* = 287	Group D *N* = 1285	Group E *N* = 526
Safety index	91.7	108.9	127.4	N.R.	105
Eyes in the ±1.00 D range at 6 months	73.1	91.4	100	78.4	99
Disabling visual symptoms	0.8	0	0	0.2	0.6
Intraoperative ICL tear	2.6	0.5	0	N.R.	N.R.
Inverted implantation	1.7	1	0	N.R.	N.R.
Explantation-replacement	2.6	0.5	0	0.4	1.7
Corneal haze/edema after 1 week post-op (endothelial cell loss >30%)	0.8	0.25	0	N.R.	0
3-year cumulative endothelial cell loss	11.6	5.8	2.8	7.7	8.4–9.7
Nondisabling halos	7.9	4.75	5.8	N.R.	N.R.
Decentration >0.5 mm	7.9	0	0	1.2	0
Late anterior chamber dislocation	0.8	0	0	0	0
Late vitreous dislocation	0	0	0	0	0
Maculopathy	1.6	1.5	0.9	0.2	N.R.
Retinal detachment	0.8	0.25	0.3	0.2	0.6
Atonic pupil (Urretz-Zavalia syndrome)	3.2	0.25	0	0.4	N.R.
Pupil ovalization—iridopathy	1.6	0.75	0	N.R.	N.R.
Endophthalmitis	0	0.25	0	0	0
Malignant glaucoma	0.8	0	0	0.1	0
Angle-closure glaucoma	6.4	3	0.6	0.9	N.R.
Open-angle/pigmentary glaucoma (IOP >25 mm hg or >10 mm hg increase)	0.8	0	0	0.6	0.2
Increased IOP on medications	16.9	2.5	0	N.R.	0.4
Anterior subcapsular lens opacities	8.2	1.75	0	1	2.7[a]
Clinically significant cataract	5.6	0.75	0	0.4	1.4[b]

N.R. not reported
[a]Most of these opacities are early, presumably surgically induced
[b]All the cataracts are found in the subgroup of myopia >10 D

32.3 Intraoperative Complications

Intraoperative complications are extremely rare and almost exclusively connected to human error in the surgical technique (Fig. 32.2) [7, 8]. Given their reduced thickness (less than 100 μm in the footplate and the thinnest part of the optic), ICLs are extremely delicate and should be handled with great care to avoid splits and tears. The most frequent cause of a *torn lens* is an incorrect loading technique (Fig. 32.3). In our learning curve (our first 30 cases when we used a metal head injector designed for aphakic "top hat" silicone lenses), we registered an incidence of one out of ten damaged ICLs, from minor (allowing for safe implantation) to major damages (requiring postponement of intervention). In our last 500 cases, the incidence of that complication was zero. In certain cases, we must deal with sticky, *upbent haptics*, tricky to detach inside the eye and always requiring the patience of an expert "butterfly surgeon" for additional manipulations (Fig. 32.4). The injection of an upside-down lens may also happen. With the first ICL models, whose footplates had no landmarks, the *inverted implantation* was more frequent and difficult to recognize. Thus, many surgeons preferred using the forceps technique to achieve maximum control of the intraocular opening of the lens. With the latest models, the surgeon can easily intervene by pronosupinating the hand, keeping the monomanual shooter before the optic has completely unfolded and overturn the implant. If, however, an inverted implantation does occur, the surgeon should never try to turn the lens around inside the anterior segment, because of the high risk of damaging the crystalline lens or the corneal endothelium. The recommended solution is to enlarge the incision to 3.5–4.0 mm, to remove the lens with specially textured forceps (Lovisolo ICL removal forceps, ASICO) under the protection of a viscoelastic substance, and to reimplant it with appropriate forceps. Then a suture could be required to ensure incision tightness and astigmatic neutrality. The same technique should be used in the event of an ICL exchange, when replacing is needed because of inadequate optical performance or sizing, or alternatively, if the surgeon has to perform a cataract extraction procedure (bilensectomy) (Fig. 32.5) [7].

Intraoperative pupillary block can occur if the surgeon does not perform complete patent YAG peripheral iridotomies in the preliminary workout, or alternately, if he overfills the globe with an excessive amount of viscoelastic or the irrigation bottle is placed too high. It may be useful to avoid

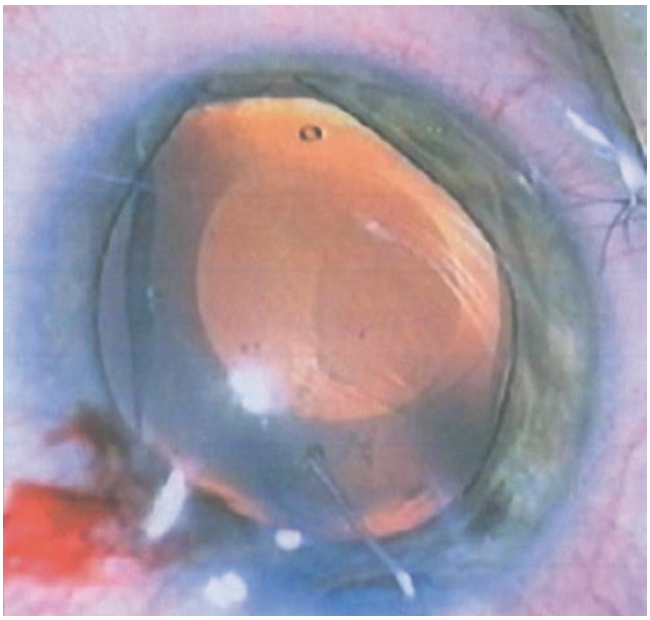


Fig. 32.2 Iatrogenic intraoperative Y-shaped lens opacity that appeared immediately following unwanted contact between the tip of the spatula and the anterior lens capsule

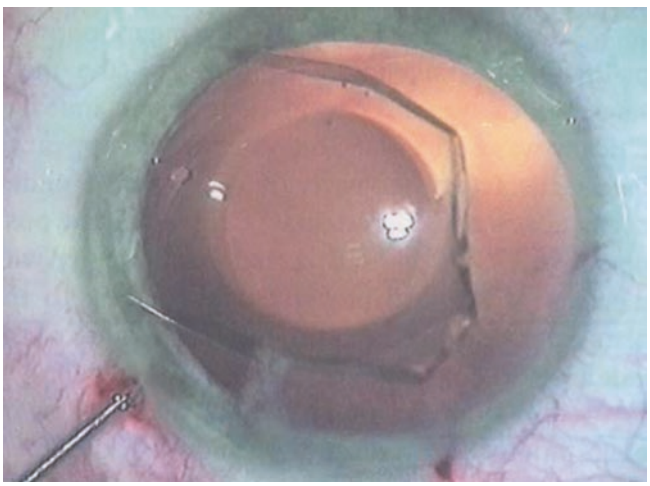


Fig. 32.3 Total fracture of the proximal haptic. The ICL must be removed and replaced

Fig. 32.4 Upbent haptics

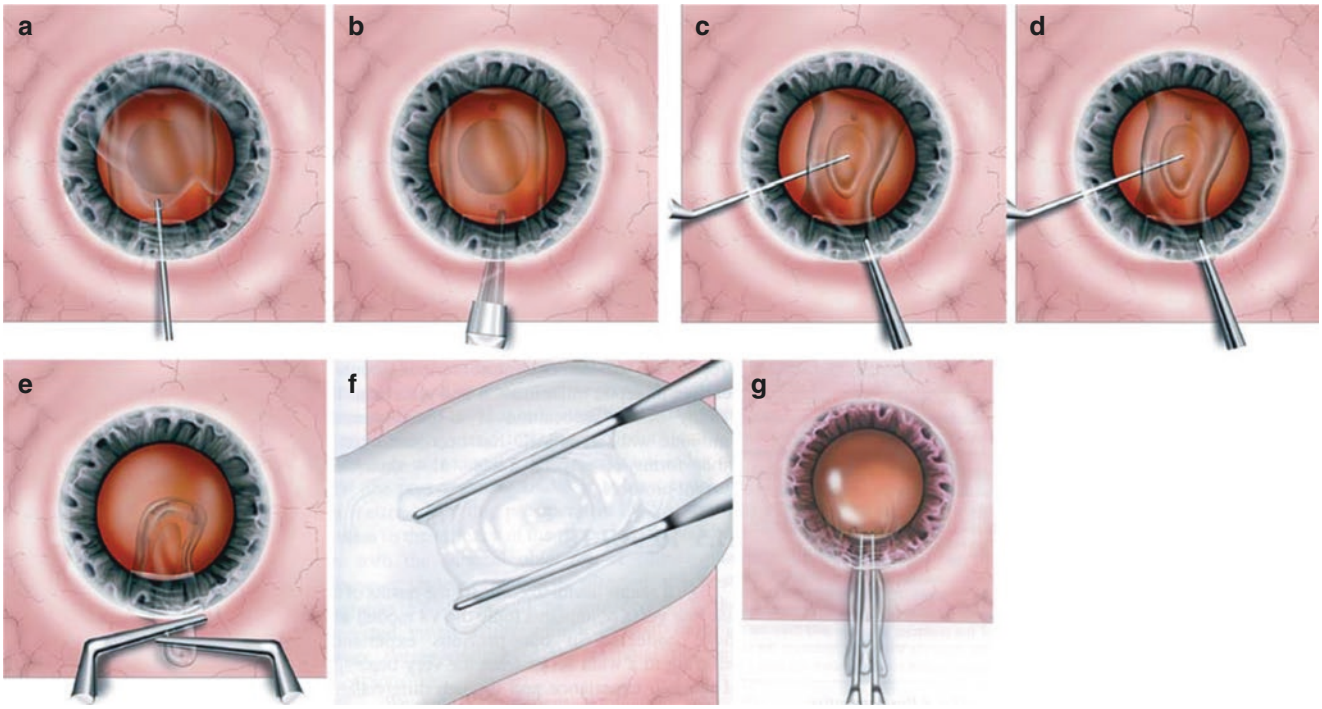


Fig. 32.5 Suggested ICL removal technique. (**a**) Inject Healon above and below the ICL. (**b**) Enlarge the incision to 4.0 mm with a calibrated knife. (**c**) Catch the right proximal footplate with Lovisolo ICL Removal Forceps and pull it toward the incision. The finely sandblasted tips firmly grasp the lens without damaging it, (**d**) As soon as the haptic starts to appear from the incision, using a second forceps, catch the footplate perpendicular to the first (tangentially to the limbus), and continue pulling outwards. (**e**) Release the first hold, and catch with the other hand in a direction parallel to the second, repeating the maneuver 2–3 times, until the most part of the lens is outside the eye. Never go below the ICL with the forceps arms in the central zone to avoid damaging the anterior crystalline lens. (**f**) Extract the lens and wash it with BSS. (**g**) Fold it using Lovisolo ICL Loading Forceps, and reinsert it with the forceps technique

the pressure thrust linked to fluids (viscoelastic and balanced saline solution), lower the height of the irrigation bottle, and relax the patient. If this does not help, the surgeon must perform a surgical iridectomy.

32.4 Postoperative Complications

32.4.1 Visual Outcomes

32.4.1.1 Loss of Best-Corrected Visual Acuity

We evaluated the safety of the ICL procedure by comparing the postoperative best spectacle-corrected visual acuity (BSCVA) in Snellen lines with the preoperative values of BSCVA. A safety index ≥100 would indicate that BSCVA lines are not lost as a result of surgery—in contrast with a value of <100 that indicates BSCVA was better prior to surgery—and that the procedure can be reasonably considered safe. Respectively, the mean safety indexes were 91.7 ± 21.6, 108.9 ± 17.1, and 127.4 ± 26.3 in Groups A, B, and C, respectively. In Group C the index was ≥100 for all patients. The differences between Groups A and B, B and C, and A and C were statistically significant ($p < 0.001$).

32.4.1.2 Over- and Under-Correction

Toric ICLs (*TICLs)* require an astigmatically neutral surgical incision and robust fixation site to provide rotational stability over time, as the cylinder correction decreases with increasing deviation of the lens implant from the target axis by following a nonlinear relationship. To prevent rotation of a small implant, again, precise sizing is essential.

As shown in a study where the position of 30 TICLs sized with VHF echography was documented by superimposable slit-lamp photographs, the mean lens deviation from the original meridian over time (3 years) was less than 5°, i.e., compatible with a maximum of 10% loss of astigmatic correction in all cases [39].

If we consider the threshold range of ±1.00 D as a significant level of over- or under-correction, the predictability of the ICL refractive outcome showed a great improvement, from 26.9% in Group A to 9.6% of Group B and to 2.6% in Group C, where 88.1% of the eyes were within the ±0.50 D range.

As for refractive stability of the ICL, at 6 months almost 97% of the myopic eyes were within the ±0.50 D range, significantly better than the average of 82% obtainable with excimer laser surgery. However, when evaluated at the 2-year

gate, most of the eyes showed a limited regression, such that the ratio decreased to 68% (as a comparison, ±0.50 D range stability with LASIK is 77%), possibly due to a reduction of vault height that we observed over time in all implanted eyes (unpublished data) or a progression of the myopia. We now therefore aim at a slight overcorrection (+0.50 sphere) in all patients younger than 38 years.

32.4.1.3 Quality of Vision Disturbances

Different degrees of nighttime visual disturbances when driving vehicles are spontaneously reported by 5–8% of our ICL patients, although only one patient (one eye in group A) requested the removal of the ICL for these complaints. No significant differences were noticed among the three groups ($p = 0.852$, $p = 0.196$, $p = 0.087$) respectively. Visual symptoms under dim light conditions are caused by mesopic entrance pupil diameters that do not match small optic sizes, whose edges consequently cause higher-order, mainly spherical, aberrations of the retinal image. The deeper the chamber and the steeper the corneal curvature, the greater the effect [41, 49–52]. Binocular infrared pupillometry, a helpful tool to predict these side effects, has shown that scotopic pupil diameter in young myopic patients—the average candidates to ICL surgery—is significantly larger than in the emmetropic group. Our observations on Caucasian myopic eyes, ranging from 21 to 39 years of age, showed a mean scotopic pupil diameter of 6.87 ± 0.72 mm, the range of minimum-maximum values going from 5.6 to 8.9 mm. For surgeons used to judge the pupil size on the corneal plane, an approximate mean conversion rate of 1.26 for the ICL-equivalent optical zone versus the LASIK one should be applied (Table 32.2).

Table 32.2 Corneal versus retropupillary plane equivalent optical zones (mm)

ICL (retropupillary plane)	LASIK (corneal plane)
4.65	5.86
5.0	6.3
5.2	6.55
5.5	6.9

The combination of an additional excimer laser corneal procedure (bioptics) has highlighted the need for a wide functional optical zone [19–23]. For a −16.00 D correction in a patient with a 6.0-mm mesopic pupillary diameter, for instance, postoperative quality of vision is unquestionably better if we select a wide-optic implant (a –12.00 ICL has a 5.5-mm diameter and corrects approximately −9.50) and combine it with a −6.50, 6.0-mm optical zone excimer laser ablation, instead of implanting a −20.00, 4.65-mm optic ICL, fully correcting the ametropia. As a trend, taking advantage of new designs and higher-index materials, it is easy to foresee that the average effective optical zone of future lenses will soon be made larger with an aspherical shape factor to respect physiology.

32.4.2 Clinical Complications

32.4.2.1 Ocular Hypertension and Iridopathy

An early acute IOP rise is relatively frequent (7–8%). When hypertension occurs within the first 24 h and without chamber shallowing, it is almost always moderate (less than 30 mm Hg), asymptomatic, and rapidly transient in 24–48 h. Since it is mainly caused by *trabecular blockage by retained ophthalmic viscosurgical devices (OVD)* (Fig. 32.6a), it

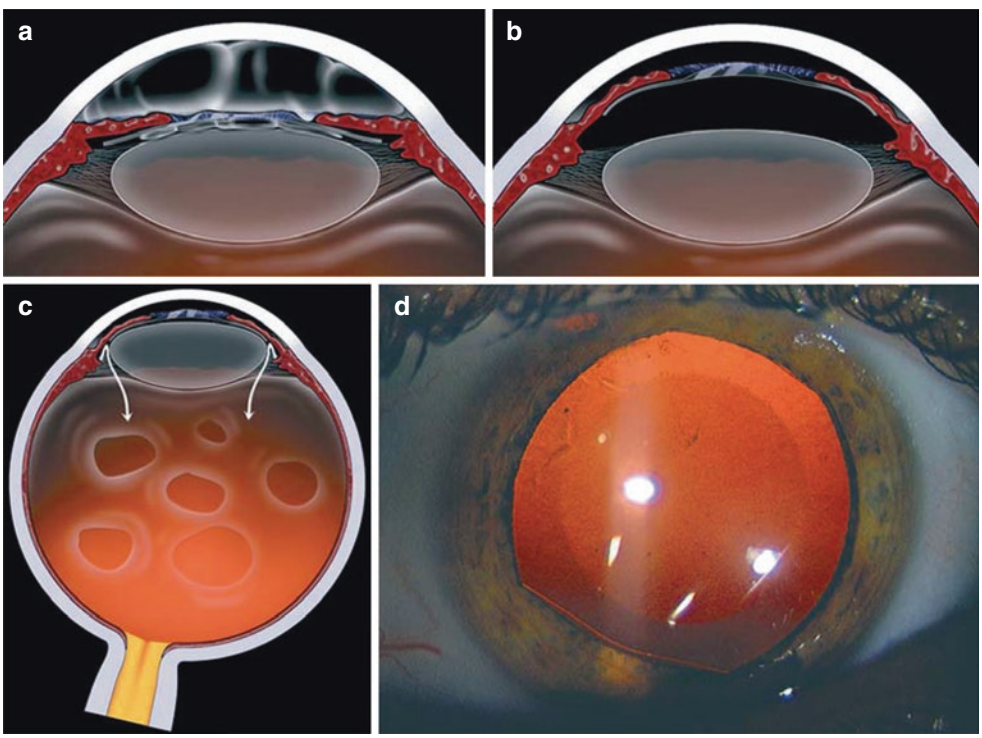


Fig. 32.6 Viscoelastic-related IOP rise with deep chamber and normal expected vaulting (**a**). Pupillary block in an ICL-implanted eye. The chamber is shallow and the lens vaulting exaggerated (**b**). Malignant glaucoma: flat chamber with both crystalline lens and ICL pushing forward (**c**)

should be prevented with thorough intraoperative removal of the viscoelastic gel and carbonic anhydrase inhibitor administration (acetazolamide tablets, per OS, b.i.d.) [53]. ICL surgery should be planned in the morning, to allow a comfortable check after 5–6 h. Very rarely, painful IOP spikes require decompression from the side port at the slit lamp with a blunt spatula.

When peripheral iridotomies (PIs) were not performed or they were not patented or occluded (by the lens footplate or by dense viscoelastic gel), physiological aqueous flow through the pupil is blocked; the iris root is pushed forward leading to *angle-closure glaucoma*. The anterior chamber becomes flat and the ICL overvaulted (Fig. 32.6b) [30, 32, 54]. The surgeon can try to take time, dilating the pupil with isonephrine 30% or phenylephrine 10% and lowering the IOP by dehydrating the vitreous with mannitol or acetazolamide IV infusion, while the OVD is fully reabsorbed. Additionally, the surgeon can re-YAG the eye at the existing sites of PIs, eventually performing a new one at six o'clock, doing a "Y-shape" or a surgical iridectomy. An urgent ICL removal, theoretically necessary in case the previous steps are ineffective, has never been required in our series.

If the acute IOP rise is associated with a markedly flat anterior chamber with the entire iridolenticular block (iris-ICL-crystalline lens) pushed forward (Fig. 32.6c), the block of the aqueous flow is posterior and typically refractory to the iridectomy. The aqueous inverts its physiological direction, moving toward the vitreous, where it accumulates forming pools of fluid (*malignant glaucoma*) [33]. The surgeon must intervene by urgently dehydrating the vitreous with osmotic agents (IV mannitol) and atropinization. If no results are observed after a few hours, the patient must return to the operating room for implant removal. In extreme cases, via pars plana vitreous decompression through a 25-Ga needle or phacoemulsification combined with posterior vitrectomy (the so-called Chandler's procedure) may be necessary.

The *Urrets-Zavalia syndrome* refers to intermittent pupillary block with sudden IOP rise causing iris sphincter muscle ischemia and *atonic* ("blown") *pupil* [55, 56]. The syndrome, described following other intraocular procedures, usually occurs at night with no apparent symptoms. The nonreactive pupil, around 7 mm in diameter, is often irreversible and will not respond to pharmacological treatment. In some cases, the pupil diameter shows a slight tendency to contract under the effect of NSAID eye drops. The most important disturbances are the visual symptoms resulting from optical aberrations induced by the edge of the optic [25, 51]. If the patient does not complain about these problems, the surgeon should leave the lens inside the eye and possibly widen (repeat YAG) the iridotomies. One of our patients benefited from this conservative behavior; after 4 years, although the pupil is still atonic, her pupil diameter improved from 7 to 5.5 mm and does not interfere with night driving. It stands to reason that the removal of the ICL will not change the situation to any great degree; given the fragility of the atrophic iris stroma, a pupilloplasty with Prolene purse-string suture should not be advisable. One alternative solution could be to exchange the ICL with a new wide-optic implant or to perform a clear lens extraction and implant a low-power wide-optic IOL in the capsular bag.

Another alternative to avoid pupillary block was first described in 1994, by Roberto Zaldivar who referred to the use of an ICL model that had a "central hole," designed to facilitate the flow of aqueous humor and thus avoid performing pre- or intraoperative iridectomies. At the beginning the occurrence of dysphotopsia in the visual axis was a problem that required solving, plus the need to improve phakic IOL surgery's safety led the authors and STAAR Surgical to look for different approaches. Together, with Vlad Feingold's, they designed different models of phakic intraocular lenses that favored the prototype that included a central aqua port, due to the belief that its size would not cause diffraction and that at the same time it would avoid pupillary block.

Results from preclinical and clinical studies of the VICMO demonstrated that the addition of the central port maintained the effectiveness equivalent to the FDA-approved Visian ICL and provided equivalent quality of vision and safety without the requirement for preoperative iridotomies. Additional follow-up is still necessary to determine whether the more physiologic central port design will continue to improve the long-term safety profile of the ICL [25, 56–61].

In a recognized steroid responder population like high myopia, it is no surprise that aggressive postoperative cortisone treatment often created considerable IOP rises, which always regressed to preoperative values with the suspension of the therapy (by 2–4 weeks after surgery) but sometimes required the prolonged use of a hypnotizing regimen, topical beta-blocker BID in general. At present, *steroid-induced hypertension* is no longer a problem, given that the postsurgical anti-inflammatory therapy has been greatly reduced. After routine, uneventful surgery, we do not use dexamethasone eye drops for more than 3 days any longer, tapering it soon in favor of NSAID eye drops.

Pigment movement successive to posterior chamber phakic IOL surgery is an undesired but inevitable event, due to the chosen site of implantation. In slit-lamp retroillumination, small window defects, trace deposition in the trabecular meshwork—gonioscopically, a sort of moderate, inferior Sampaolesi line—and pigment spots on the lens surfaces (Fig. 32.7) are frequently seen. However in our experience, the mechanical chafing of the posterior layer of the iris has always been moderate and self-limiting, never reaching a level of clinical importance. The increased pigmentation of the trabecular meshwork observed at the early postoperative period, in particular, returns to the preoperative level after 12–18 months.

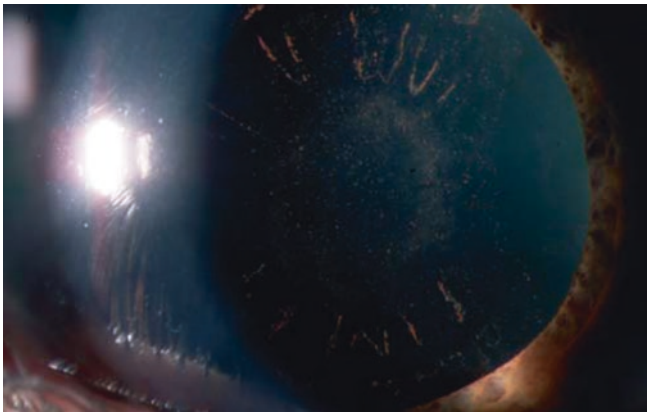


Fig. 32.7 High-magnification image of nonclinically significant pigmentary deposition on the anterior and posterior surfaces of the ICL

Not all experts fully accept our position of reassurance, but the concerns voiced some years ago relative to a long-term risk of *chronic glaucoma* secondary to the *pigmentary dispersion syndrome* have not been confirmed by the recent literature [8, 29, 62]. Prevention of post-ICL glaucoma includes the general rule to always perform at least one, well patented, minimum 500-μm-wide preliminary YAG peripheral iridotomy or an intraoperative surgical iridectomy located perpendicularly at ICL position. The potential for avoiding PIs is being investigated with ICL centrally or peripherally holed ICL implants. Our preliminary results, 3 years after surgery, suggest ensuring a uniform physiological perfusion flow of the aqueous on both sides of the implant (Fig. 32.8).

Following guidelines supplied by the manufacturer (choosing the ICL overall length on the basis of the external white-to-white distance and excluding from surgery the eyes with ACD—central distance between the endothelium and the anterior surface of the crystalline lens—of less than 2.8 mm) is questioned, since it has been artificially derived from old studies in eyes with naturally occurring angle-closure glaucoma (Fig. 32.9) [54, 63–67].

Although an obvious medical-legal reference point, a single measurement of the central anterior chamber depth, done by a conventional A-scan ultrasound biometry or by more or less sophisticated optical devices (slit lamp, IOLMaster®, Scheimpflug camera based of slit-scanning tomographers), is not a reliable predictor of the risk of developing angle-closure glaucoma, as it shows no precise correlation with the shape of the anterior segment and to the width and the occludability of the iridocorneal angle [34, 68]. Similar ACDs often show very different, individual, anterior segment shape, angle aperture, iris configuration, and original asymmetries. Angle-to-angle and sulcus-to-sulcus measurements obtained with very high-frequency ultrasound or anterior segment optical coherence tomography showed significant differences among four meridians analyzed, suggesting that the human eye is not geometrically round [69]. The longest meridian may be located horizontally, vertically, or obliquely (Fig. 32.10). For surgical anatomy, the only rule is that there is no rule. In spite of ACD, only the clinical judgment based on a thorough high-precision examination of the anatomy, provided by very high-frequency ultrasonography and a software showing the statistical risk carried out by certain linear and angular measurements, may help the surgeon to perform safe implantations (Fig. 32.11) [7, 34, 46, 68].

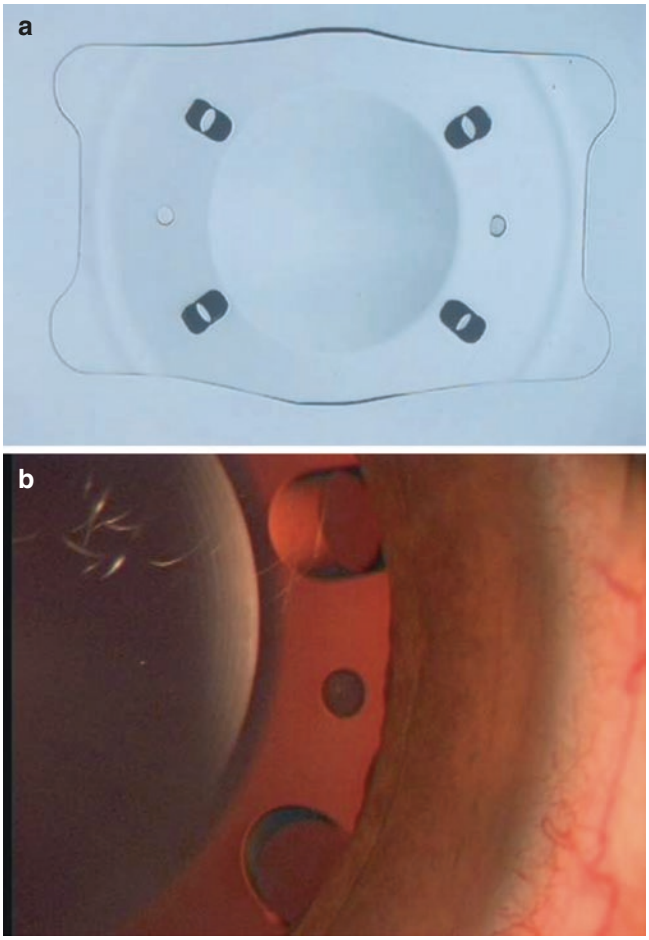


Fig. 32.8 ICL with four oblique through holes in the haptics, 0.6 mm in diameter, outside (**a**) and inside (**b**) the eye

Because of the biometric changes occurring over time, age is a fundamental factor to be considered in the ICL-safety preliminary evaluation. Due to the lifelong mitotic activity of the subcapsular epithelial cells at the lens equator, the thickness of the human lens increases as it gradually grows, with an anterior change in displacement by 0.4 mm during the lifetime of a 90-year-old [70–72]. As a consequence, the anterior chamber depth drops by 0.75 mm over a 50-year span particularly in the periphery. It is thus essential to bear these points in mind when dealing with very young patients. Nobody knows how much the anterior chamber volume available to the aqueous circulation of a normal eye (average 157 μL) can be reduced

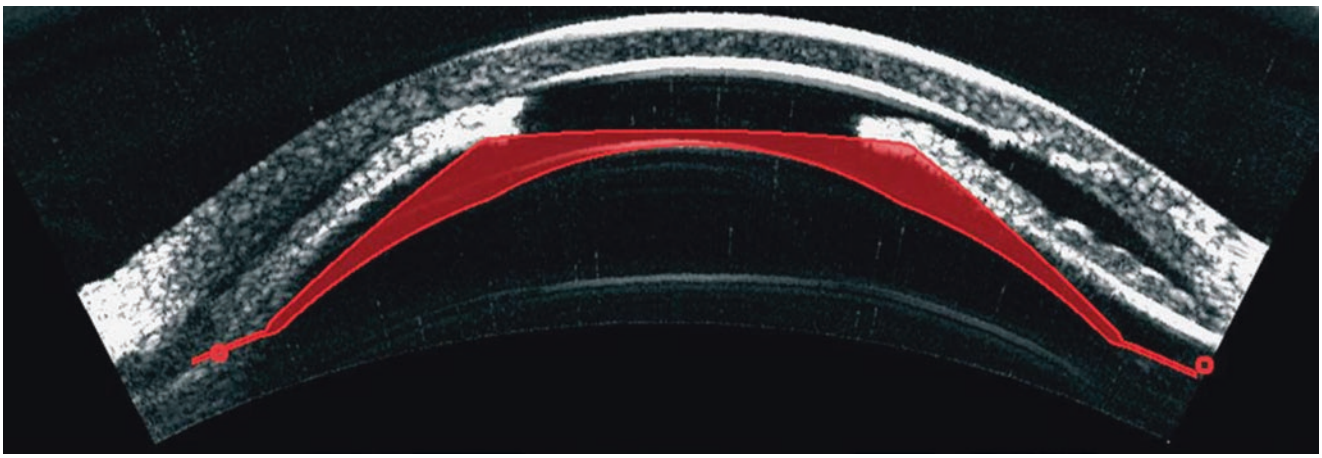


Fig. 32.9 Artemis 2 VHF echography image of an angle-closure glaucoma caused by exaggerated ICL vault height. Preoperative ACD was 3.09 mm. Since the W-to-W was 12.5 mm, the overall length was correctly (?) chosen to 13 mm. Instead, the sulcus-to-sulcus distance was 10.9 mm

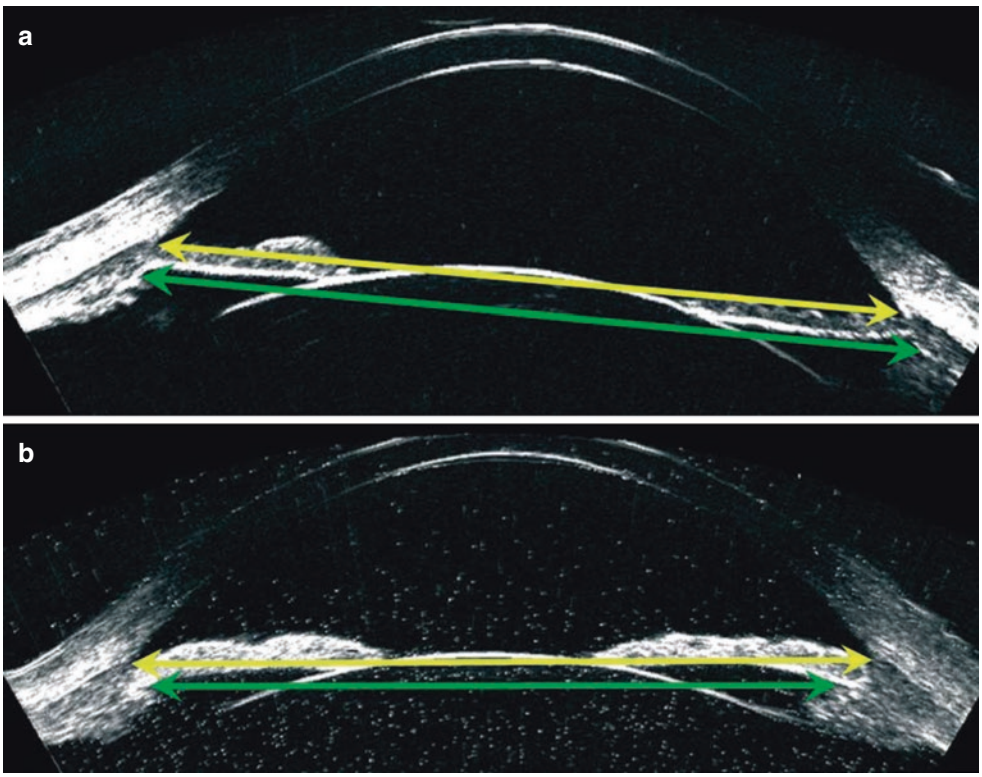


Fig. 32.10 In a sample of 288 eyes scanned with VHF echography (Artemis 2), the largest cross-sectional internal sulcus diameter was found to be horizontal in 27%, oblique in 15%, and vertical in 58%. The horizontal external diameter (*white-to-white*) was found to be the largest in all eyes. *White-to-white* was found to be smaller than sulcus-to-sulcus (a) in 41%, larger (b) in 59% of eyes

by the physical presence of the ICL implant, without risking angle-closure or "crowded" anterior segment glaucoma. The limit of the angle opening to risk pupillary block in pristine eyes has been set to around 15° [73]. According to the Orbscan and echographic data, properly sized myopic ICL, ideally vaulted 500 microns, reduces the post-ICL iridocorneal angle by an average of 25% (from about 42° to 29°) [7, 74]. Long-term effects of potential redirection of aqueous flow have yet to be determined in ICL-implanted eyes.

Moreover, information on the degree of anatomical variability of the hidden ciliary body and the nearby structures is necessary to understand the dynamics after positioning an ICL (intermittent touch during accommodation; chafing of posterior structures, cysts, or abnormalities of the ciliary body; forward rotation of ciliary processes after scleral buckling; etc.) (Fig. 32.11). All candidates should have a complete, in-depth examination of the size and morphology of the anterior segment. This is part of the overall procedure

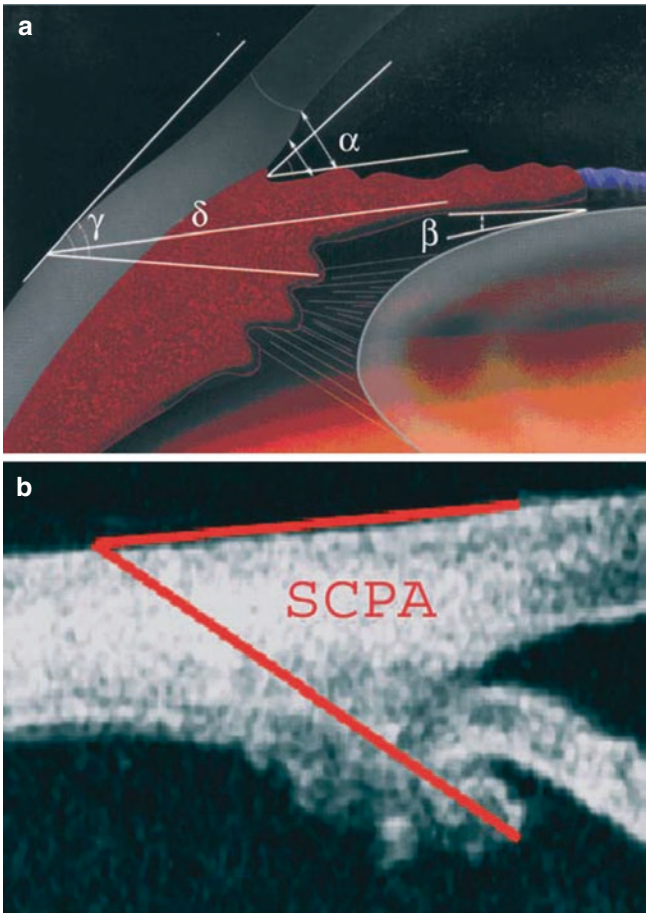


Fig. 32.11 Angle biometric parameters. (**a**) iridocorneal angle; (**b**) iris-lens angle; (**c**) sclera-iris angle; (**d**) sclera-ciliary processes angle (SCPA)

that is often omitted for reasons of cost and substituted with unacceptable, empirical approaches.

32.4.3 Inflammation

Considering the inflammatory response within the eye or the long-term integrity of the anterior uveal barrier mechanisms, evidence to date supports the safety of ICL implantation. Clinical assessments of anterior chamber flare and cellular reaction for up to 3 years after surgery were reported as absent in 99.6–100% of the cases [75, 76]. The inhibition of protein binding provided by the interaction between collagen and fibronectin seems to be the main reason for the superior biocompatibility of the collamer material [77]. One week after surgery, the photometric levels measuring the aqueous flare appeared to have increased by twofold, but by the third month, the values had returned to baseline levels in all implanted eyes [7]. The early leakage of the dye observed with fluoroangiographic examination of the permeability of iris vessels (Fig. 32.12) and the laser flare and cell meter measurements taken between 3 months and 3 years after surgery were within the normal range [7, 75, 76]. In light of this evidence, we no longer consider the preoperative presence of posterior syncline, secondary to low-grade veal inflammation after previous operations (such as penetrating keratoplasty, for instance), as a contraindication to ICL surgery.

On the side of anterior chamber phakic IOL implantation (both angle fixated and iris supported), however, transient low-grade acute postoperative iritis was observed in 3.4–10.7% of

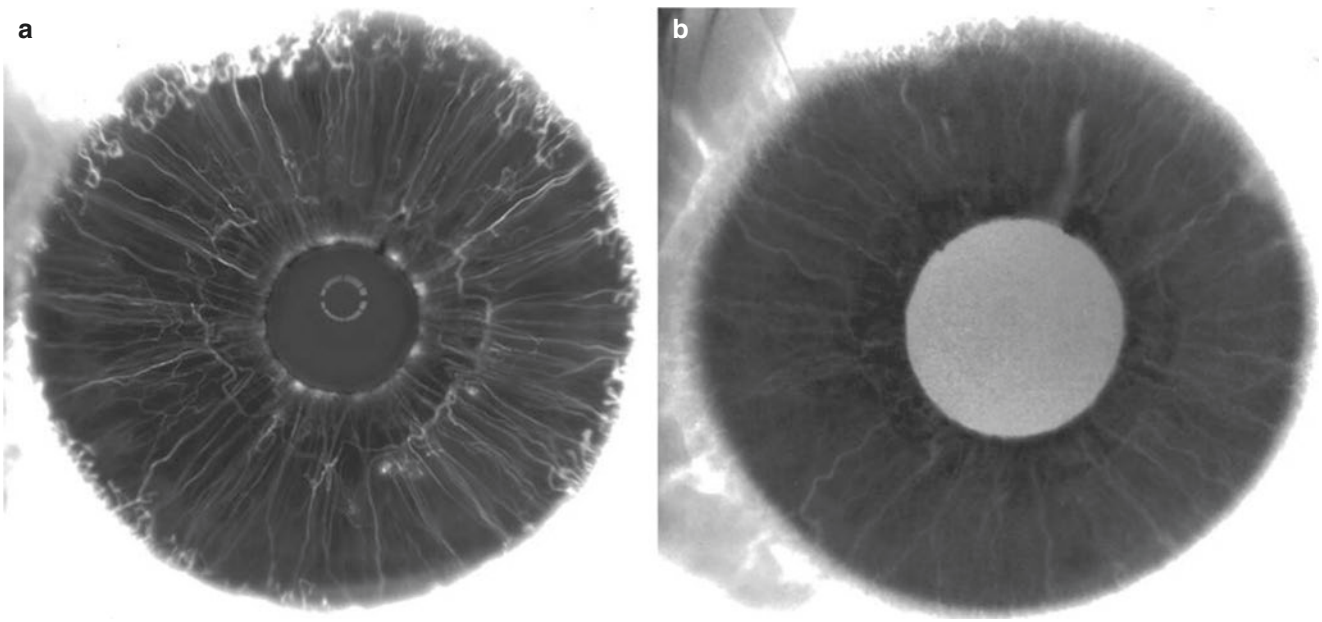


Fig. 32.12 Late phases of iris angiography, 1 month after ICL surgery, following the injection of fluorescein (**a**) and indocyanine *green* (**b**). The dye leakage appears to be moderate to absent

cases [75–79]. Although fluorophotometric evaluations were controversial, some of them indicated a prolonged breakdown of the blood-aqueous barrier and a reduction in the transmittance of the crystalline lens [80, 81].

32.4.3.1 Endophthalmitis

Septic contamination, which may happen in every intraocular procedure, can complicate phakic IOL implantation. Endophthalmitis can occur as an early acute (within 5 days of surgery), subacute (up to 6 weeks after surgery), or late chronic low-grade uveitis of septic origin. Very few cases have been fully described in the peer-reviewed phakic IOL literature, of where a very rare incidence (1/8000) of post-ICL surgery endophthalmitis may be roughly estimated [37, 82–84]. Though endophthalmitis is a potentially blinding complication, it may be prevented with maximum care by using a sterile technique and with early diagnosis and prompt treatment. As compared to what happens on average after a cataract surgery endophthalmitis case, we observed a peculiar clinical outcome (anatomic *restitutio ad integrum* and 20/20 uncorrected 2 weeks after surgery and intraocular antibiotic administration) in the only case we had. This suggests a sort of "barrier" effect provided by the ICL and/or by the crystalline lens to prevent diffusion to the vitreous chamber, therefore determining a better final prognosis [7].

32.4.4 Crystalline Lens Opacity (Anterior Subcapsular Cataract)

Early crystalline lens opacities caused by excessive surgical trauma (highly powered YAG PIs and rough intraocular maneuvers) may complicate the early course of the ICL procedure [4, 8, 10, 35, 36]. These iatrogenic opacities are easy to identify, as they appear at an early stage (up to a maximum of 60 days postoperatively). They are focal and densely white, as they directly involve the anterior capsule. These opacities usually do not progress when visual interference is limited but require follow-up on a yearly basis (Fig. 32.13). Other factors classically recognized as interfering with the lens metabolism, like excessive intraoperative and postoperative IOP rise, air and OVD residuals, and prolonged steroid therapy, do not seem to play a role in determining the formation of a cataract.

Apart from these conditions, the close position of the material to the anterior lens surface is the main criticism against posterior chamber phakic IOLs and is likely to be the main issue of future scientific investigations. Researchers have yet to completely understand the mechanisms of cataract formation. However a few years ago, it was believed that the hydrophilic nature of the Collamer was crucial in avoiding cataract formation, in contrast with what happens with hydrophobic silicone lenses (Fig. 32.14).

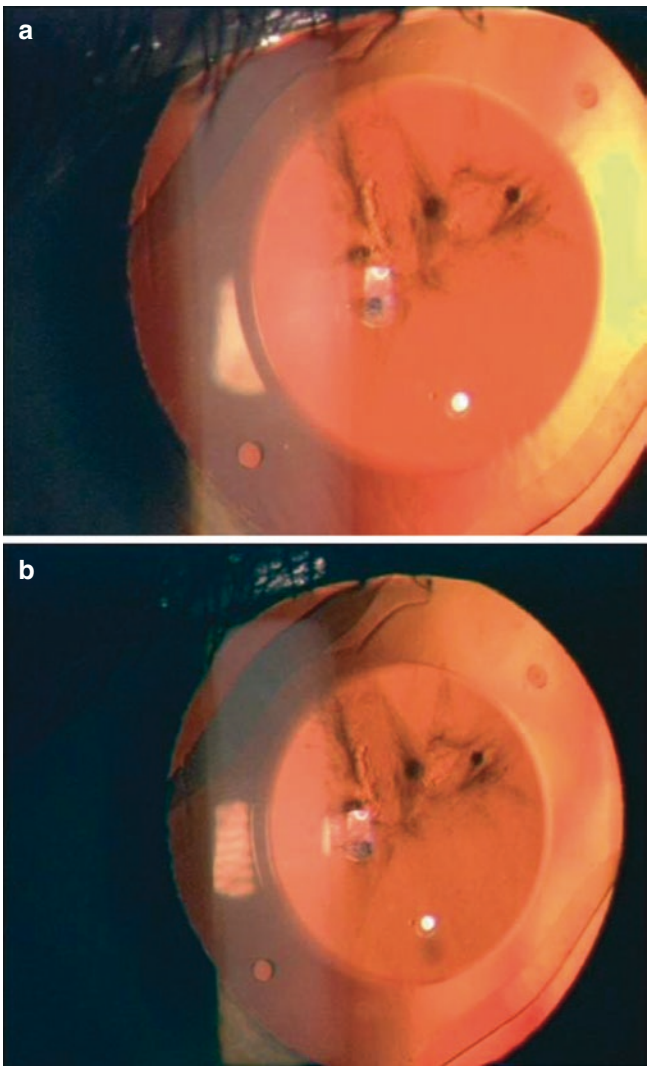


Fig. 32.13 Non-evolutive, iatrogenic, anterior capsular opacities provoked by intraoperative inadvertent touch 2 months (**a**) and 6 years (**b**) after surgery. The uncorrected vision was 20/20^{-}, and only minor interference with the quality of vision was noticed by the patient, who decided to keep the ICL in situ

Now, more attention is given to perfect sizing of the lens, to achieve adequate vaulting, or space separation between the IOL and the crystalline lens that allows aqueous exchange essential to the metabolism of the subcapsular epithelium of the lens. Given the oblate aspherical shape of the anterior crystalline lens surface, the vaulting of myopic lenses is reduced peripherally, especially when higher powers and thicknesses are involved. If the ICL is poorly sized, its short overall length sizing causes circular contact of the edges, with the semi-peripheral regions of the crystalline lens trapping a pool of aqueous. The metabolic stagnation leads to hyperplasia and fibro-metaplasia by the subcapsular epithelial cells of the lens. This theory is confirmed by the fact that in our practice no hyperopic ICL-induced opacities have been documented to date, even if the implant

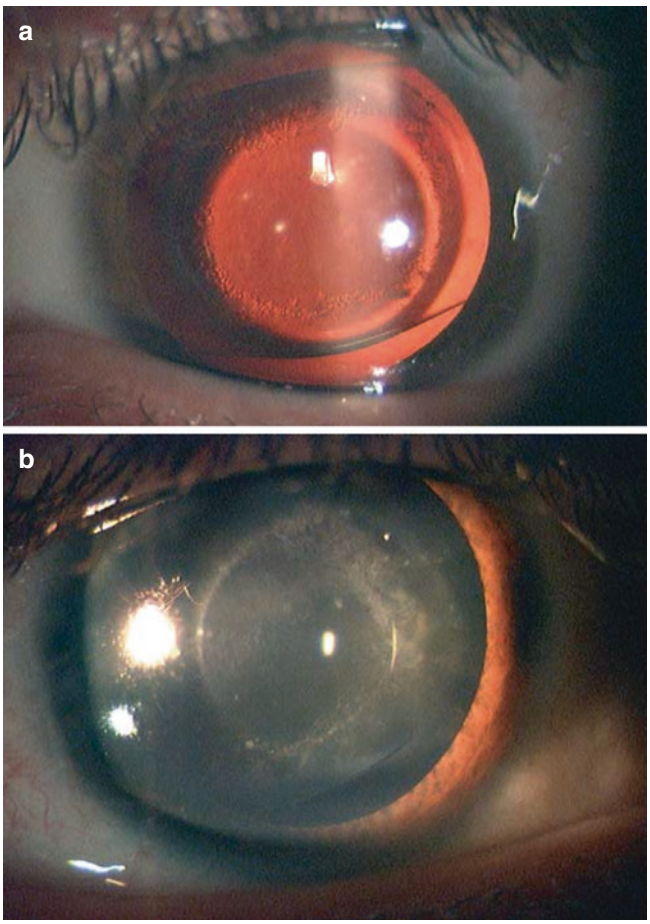


Fig. 32.14 Mid-peripheral anterior capsular and subcapsular opacities 4 years after Adatomed silicone posterior chamber phakic IOL implantation

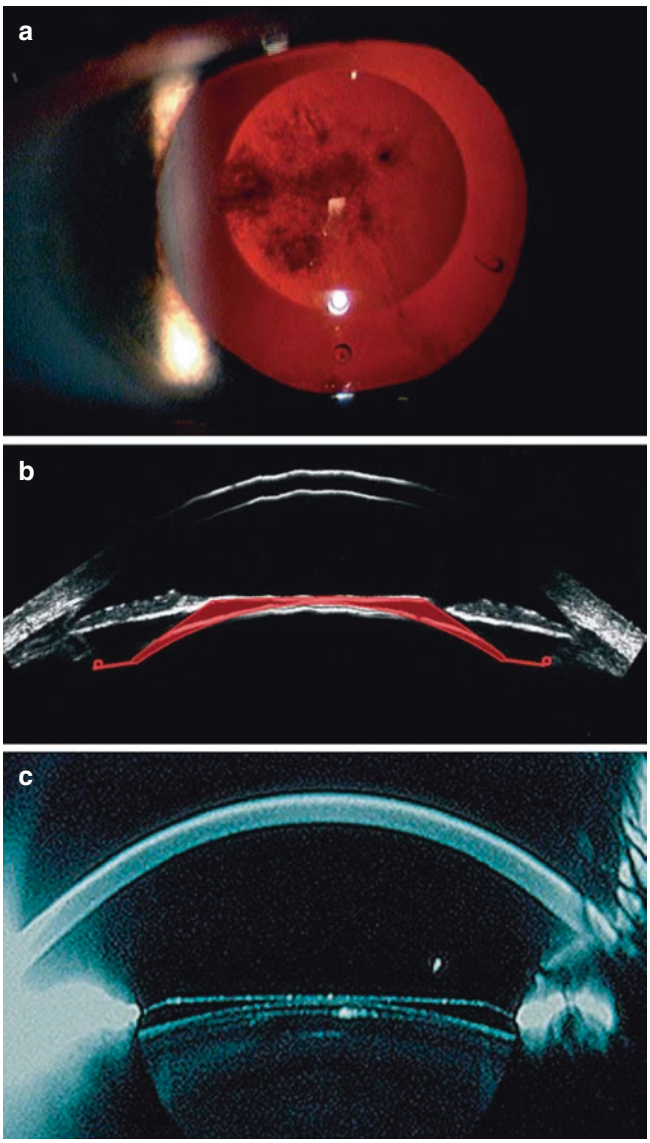


Fig. 32.15 Typical ICL-related iatrogenic subcapsular anterior opacities (**a**) 26 months after surgery; the VHF echography (**b**) and the Scheimpflug camera (EAS 1000, Nidek, Japan) images show the lack of vault between the ICL (V2) and the crystalline lens. The 12-mm V2 myopic ICL, selected on the basis of the 11.6-mm external corneal diameter, turned out to be too small for a sulcus diameter of 12.3 mm

is closer to the crystalline lens in these short eyes. Due to the geometrical shape of the hyperopic optic, aqueous circulation is not impaired. The design of the lens is also critical. In our series, we saw no cataracts with the earlier, more vaulted models, but we reported a significant incidence of cataract—8.2%, with a 5.8% of surgical extraction (bilensectomy) with the flatter base curve of V2 and V3 ICL designs (Fig. 32.15).

Since the introduction of the V4 (April 1998), seven (1.75%) ICL-induced subcapsular opacities and three (0.75%) cataract procedures have been recorded in the group where the lenses were sized following the white-to-white rule; and 0 (0%) opacities have been observed in the group where the overall length was chosen with the Lovisolo Custom ICL Sizer, on the basis of very high-frequency echography measurements of the sulcus dimension.

The issue of potential intermittent touching during accommodation, when the crystalline lens moves forward, was recently addressed with partial coherence interferometry studies [45, 85, 86]. As the sulcus retracts with accommodation, no significant changes in distance between the ICL and the crystalline lens were found; the ICL vaulting increases as necessary, compensating the 200–600-μm forward movement of the anterior lens surface. On the other hand, under photopic environmental conditions or after application of pilocarpine, pupil constriction reduces the vault height by forcing the ICL against the crystalline lens [41, 52].

Although non-conclusive, the evidence provided by more than 14 years of experience in human beings should reassure us about the potential threat of decay of the material, i.e., deterioration of transparency, permeability to nutrients, and biocompatibility of the collamer that could occur in the long term.

32.4.4.1 Corneal Decompensation

Maximum long-term preservation of the corneal endothelium has always been an important issue for the entire area of phakic IOL implantation, in view of the high rates of corneal decompensation reported after the first implantations [87]. Our data allows us to state that currently refined ICL surgical techniques can minimize the sacrifice of endothelial cells [88]. Almost 40% of the postoperative cell counts and morphologies of Group C actually improved at the month 3 follow-up gate. Beyond the actual bias of the instruments measuring the endothelium, the apparent paradox can be explained by cell centripetal migration and enhanced metabolism after stopping wearing contact lenses.

In the long run, the protective role of the iris barrier to prevent ongoing endothelial cell loss through mechanical chafing has been almost unanimously recognized by different authors [7, 89]. Although metabolic interference was hypothesized by Dejaco-Ruhswurm and coauthors, their report is the only one in the literature with worrying rates of progressive loss (5.5% at 1 year, 12.3% at 4 years) during a 4-year follow-up of ICL-implanted eyes [90]. In their study, however, only the first year data were statistically significant, and the cell morphological indices (polymorphism and polymegathism) remained stable during the follow-up period.

In our long term ($\geq$ 6 years of follow-up), the mean annual loss is very similar to the 14 cells/mm^2 (0.5%–0.6%) a year that is considered physiological in non-implanted healthy eyes. Therefore, we believe that the current cell density limits proposed for ICL implantation should not be shared with anterior chamber (angle-fixated or iris-enclavated) phakic IOLs, which have proven to be less safe for the corneal endothelium [78, 91–93].

Moreover, beyond the usual recommendations of taking into consideration the patient's age to assess the minimum cell density, asking patients not to rub their eyes and checking yearly the endothelial images with specular or confocal microscopy, we feel comfortable to safely implant eyes that are presently excluded from surgery, such as post-penetrating keratoplasty, keratoconus, and chronic contact lens wearers with poor endothelial cell count.

32.4.4.2 Vitreoretinal Complications

The overall incidence of vitreoretinal complications in ICL-implanted eyes is approximately 1–2% and seems generally caused by predisposition more than by surgery or by the presence of the implant itself [1, 94]. By the way, it is well known that the high myopic population suitable for phakic IOL implantation is at high risk for:

1. Progressive posterior retinal atrophy, secondary to mechanical and vascular stress from congenital scleral weakness and deterioration of choriocapillary and retinal pigmented epithelium
2. Spontaneous or neovascular macular hemorrhage (the risk is 6%, compared with 0.002% in normal young persons)
3. Rhegmatogenous retinal detachment secondary to vitreous liquefaction, asymptomatic peripheral retinal breaks or degenerations, and posterior vitreous detachment (the risk is 2.4% in the first 60 years of life, compared with 0.06% in the normal population)

To minimize the risk of coincident pathologies, the role of the vitreoretinal expert should be emphasized, as he is the person who will be entrusted with providing documentation, treatment, and prophylaxis of any pathology that may complicate the natural history of such vulnerable eyes. Potential negative influences during surgery (iridotomy and shallowing of the anterior chamber) may stimulate the vitreous to contract, potentially generating avulsion of the base and giant retinal tears [95]. For that reason we feel more comfortable operating on an eye with an already detached posterior vitreous [96].

ICLs seem to be well tolerated by the myopic retina. They do not disturb fluoroangiography or the observation of the retinal periphery since the pupil dilates normally and the haptics do not interfere with the display of the image. In eyes operated with episcleral procedures, great care must be taken. Scleral buckles generate an anterior displacement of the ciliary body and crystalline lens and reduce the depth of the anterior chamber and the width of the iridocorneal angle [97]. The indentation devices may interfere with peripheral choroidal venous drainage through compression of the vorticose veins, resulting in edema of the ciliary body, in such a way that the surgeon should consider better to remove the buckle before ICL positioning, particularly if the chorioretinal scars are old and no vitreal traction is visible.

32.4.5 Zonular Damage, Decentration, and Anterior and Posterior Dislocation

Although further studies are necessary to definitely prove this statement in the long run, well-sized, recent design, and carefully implanted (no dialing maneuvers for retro-iris positioning!) ICLs can be safely implanted even in eyes with a limited (less than 60°) encoche of the Zinn apparatus. We have implanted six high myopic eyes with moderate zonular disruption, taking care to put the haptics in the "healthy" areas; after more than 3 years of follow-up, we did not observe even a minimal decentration.

Although we saw decentration, also spontaneous dislocation into the anterior chamber years after unremarkable clinical course (Fig. 32.16) with the old generation of lenses, with the latest models of ICL, decentration larger than 1 mm has never been an issue even when the sizing has been patently inaccurate [7].

For another posterior chamber phakic implant (the PRL), instead, the commonly used "one size fits all" 11.3 mm over-

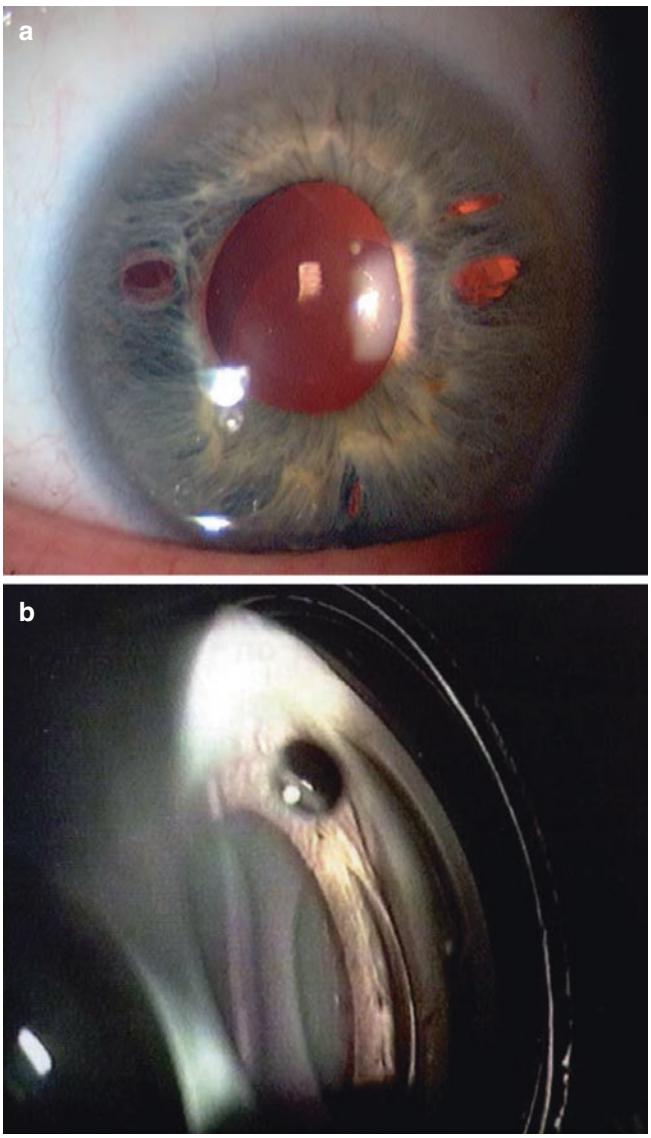


Fig. 32.16 Inferior decentration of the first ICL prototype (IC2020) implanted in the western world in September 1993 (courtesy of Paolo Pesando, MD) (**a**). Gonioscopic view of a V2 ICL spontaneously dislocated in the anterior chamber (**b**)

all length, claimed as "floating inside the posterior chamber with no anatomical fixation sites," frequently (about 10%) decenters of more than 1 mm. Moreover, our experience confirms the concerns of significant (design-related?) risk of cataract, damage to the zonules, and dislocation into the vitreous chamber (Fig. 32.17) [94].

32.4.6 The Lovisolo Custom Phakic IOL Sizer: How to Get Rid of Implant-Related Complications

Since 1999, we have been using proprietary software—the "Lovisolo Custom Phakic IOL Sizer"—(Fig. 32.18) to predict postoperative vault height and the expected clear-

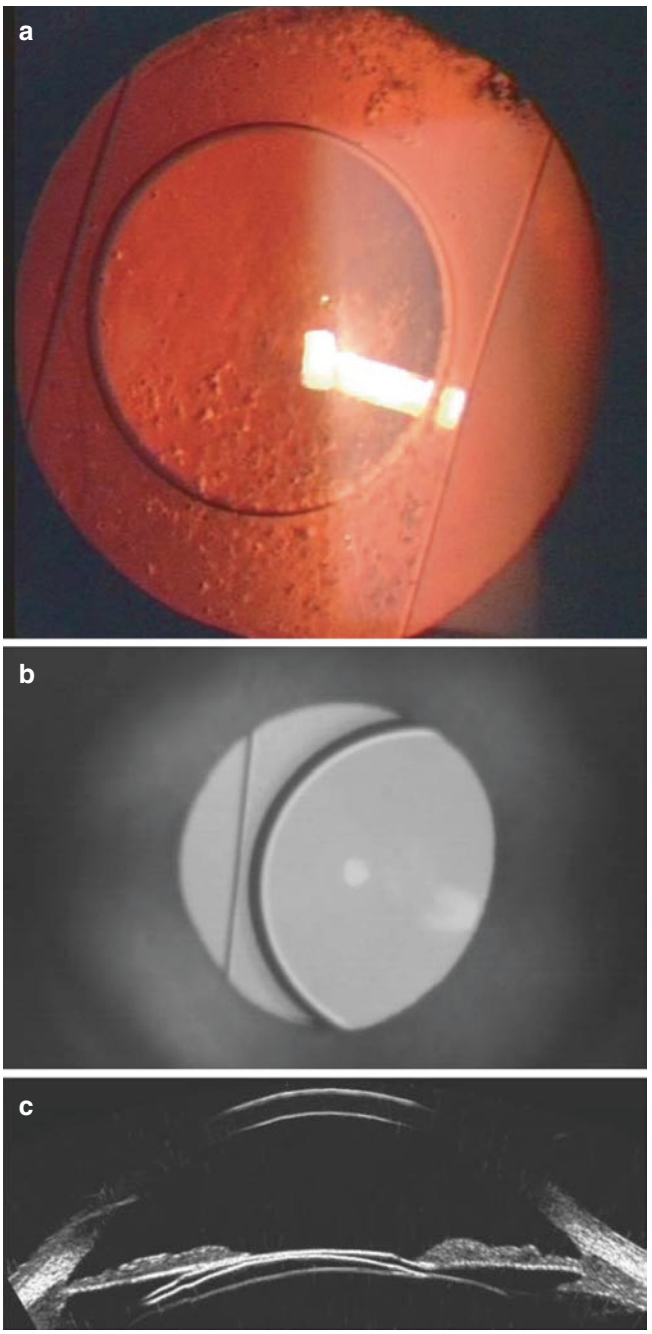


Fig. 32.17 PRL-induced iatrogenic anterior subcapsular opacities 2 years after surgery (**a**); Scheimpflug retroillumination (**b**) and Artemis 2 (**c**) images of a decentered PRL

ances between corneal endothelium, iris, and crystalline lens before implanting phakic IOLs, on the basis of high-resolution images of the anterior segment [98]. Accurate measurements of these parameters may be obtained with instruments that use very high-frequency (VHF) ultrasound waves in the 35–50 MHz range, like the Artemis 2 (Ultralink, St. Petersburg, FL, USA) and the VuMax (Sonomed, New York, NY, USA) (Fig. 32.19a). Optical devices like slit-scanning systems with or without rotating Scheimpflug camera (like the Precisio, Ligi, Taranto,

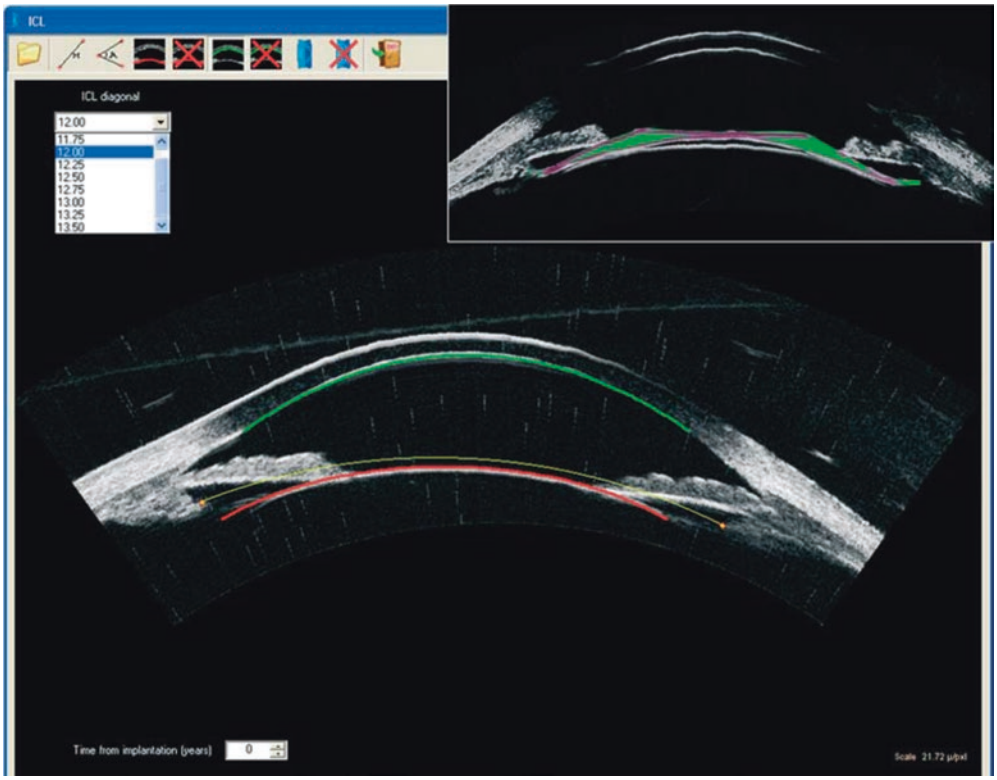


Fig. 32.18 Snapshot of the last version of the Lovisolo Custom Phakic IOL Sizer

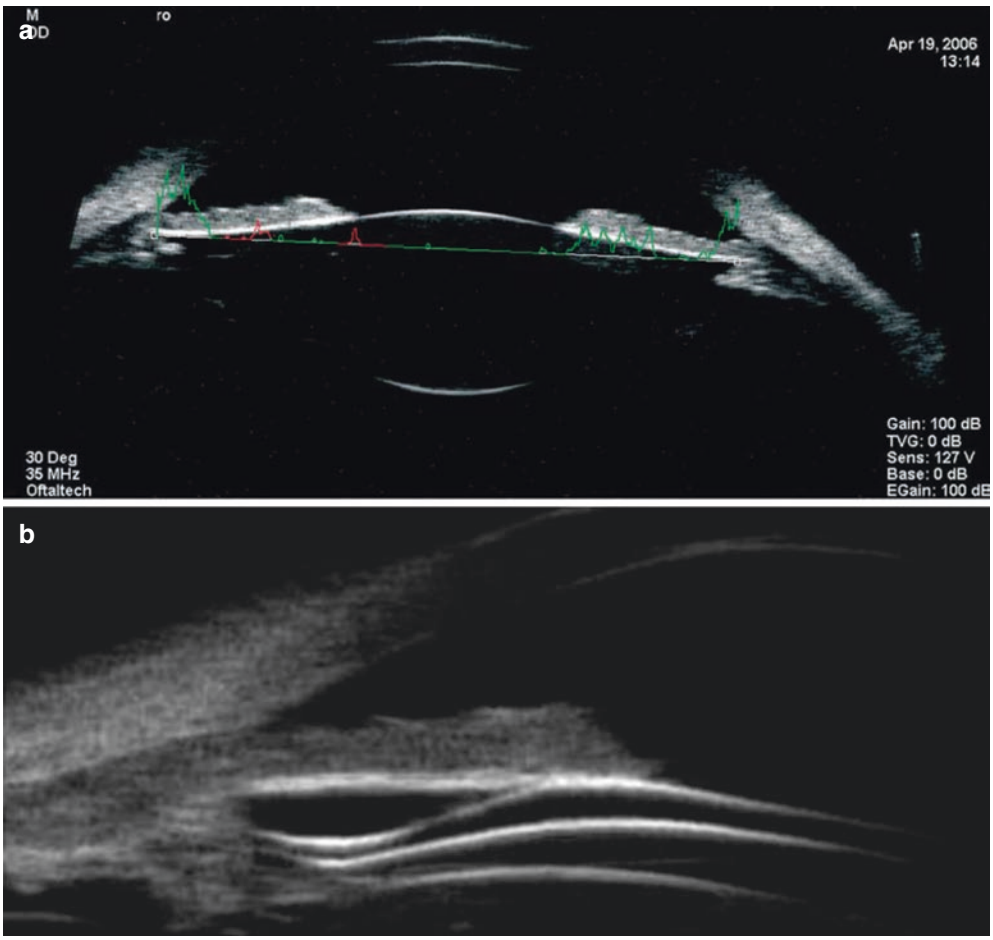
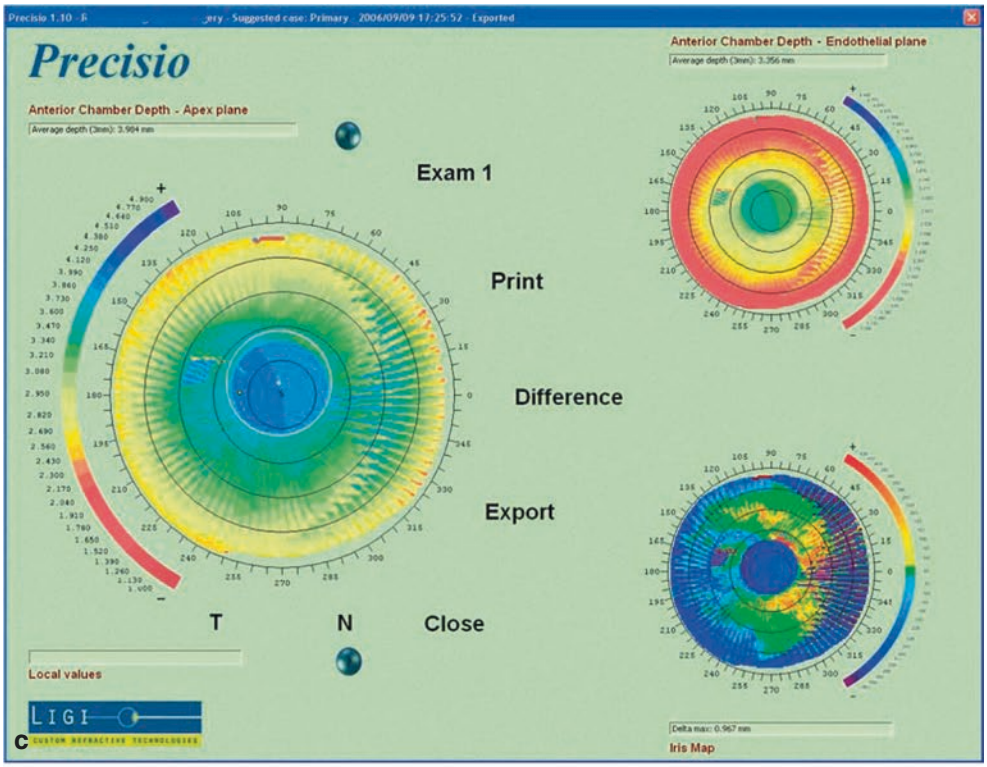
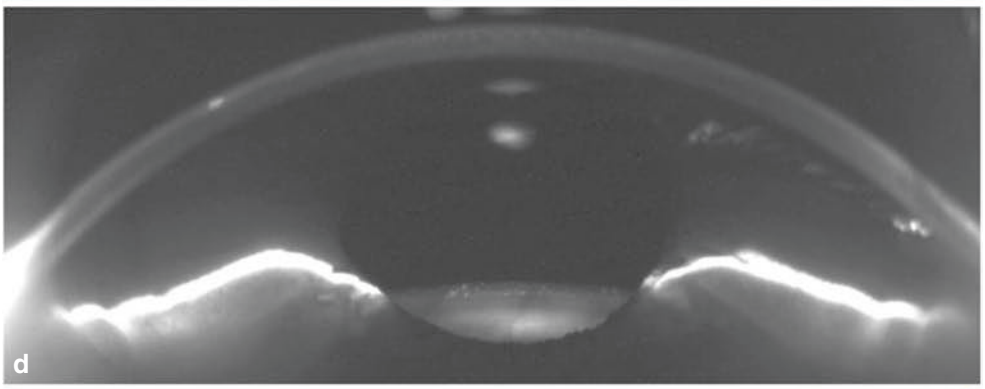
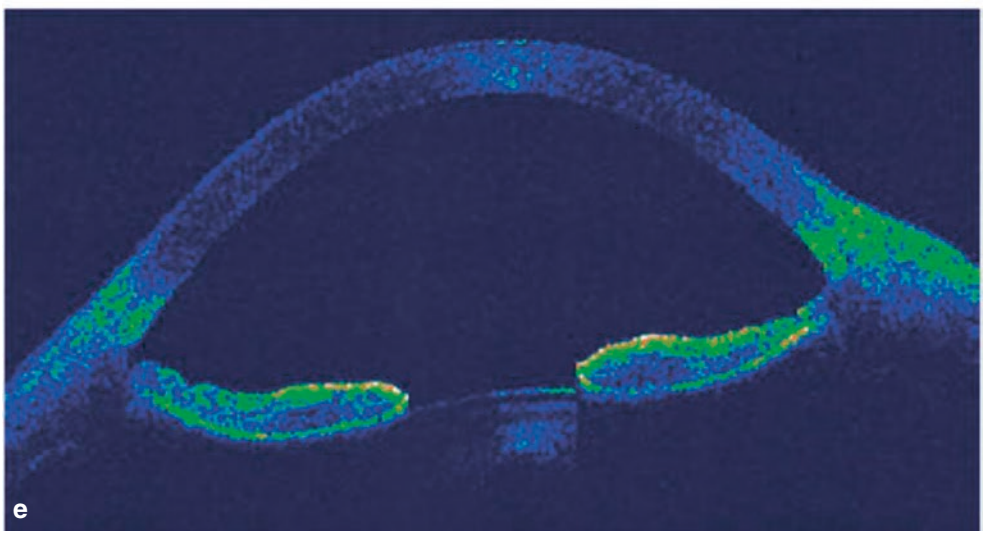


Fig. 32.19 35-MHz VHF echography images (VuMax II): overall image of the anterior segment (**a**) and detail of the site of fixation of the ICL haptics (**b**). Precisio anterior chamber map and Scheimpflug scan (**c**, **d**). Visante OCT scan of the same eye (**e**)

Fig. 32.19 (continued)







Italy, Fig. 32.19b, c; the Pentacam, Oculus, Germany; and the Galilei, Ziemer, Germany) or infrared light optical coherence tomographers (Visante OCT®, Zeiss Meditec, Jena, Germany) (Fig. 32.19d) permit high-definition cross-sectional anterior segment imaging with excellent reproducibility of measurements by using the interference profile of the reflections from the cornea, the iris, and the crystalline lens. However, these methods are not interesting for sizing the ICL, since the retro-irideal space cannot be perfectly visualized by optical devices, and the statistical correlation between angle and sulcus diameters is as poor as between external white-to-white and internal dimensions [69].

For the ICL, the latest version of the software takes into account:

- The position (the sclerociliary processes angle) (Fig. 32.10) and the whole dimension of the ciliary sulcus, as measured under cycloplegic conditions.
- The crystalline lens rise on the iris plane or the sclero-iris angle (Fig. 32.20).
- The iridocorneal angle.
- The specific features of the chosen lens implant (overall length, vault at rest, central and peripheral optic thickness, flexibility).
- A corrective factor for BSS ICL, as those marketed in the USA (the European ICL are labeled as measured in NaCl). Intraocularly, for instance, a European 125 V4 ICL enlarges from 12.5 to 13.2 mm.
- The implant behavior under compression, as predicted by finite element analysis, given the elasticity of the material (Fig. 32.21).
- The age (life expectancy) of the patient. An average reduction of the anterior chamber depth of 0.015 mm per year is calculated to predict the anatomic relationships even after 50 years.
- A warning signal is automatically given if one parameter shows a difference higher than 20% from normal values.

In our most recent personal series (Group C) on 287 eyes implanted with the ICL V4, with a mean follow-up of 29 months, we have not yet observed any cases of iatrogenic cataract, pigmentary dispersion, or angle-closure glaucoma. The mean central vault height was 386 μm, with a standard

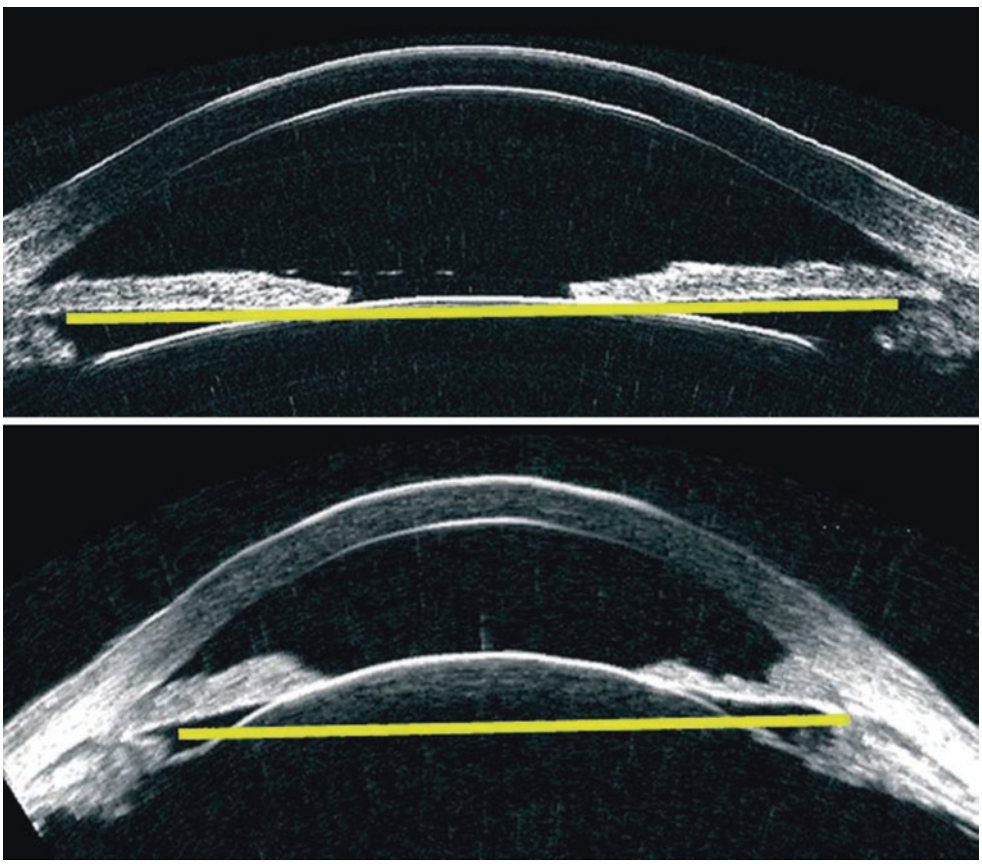


Fig. 32.20 Different shapes of the anterior segment as imaged by the crystalline lens rise on the iris plane

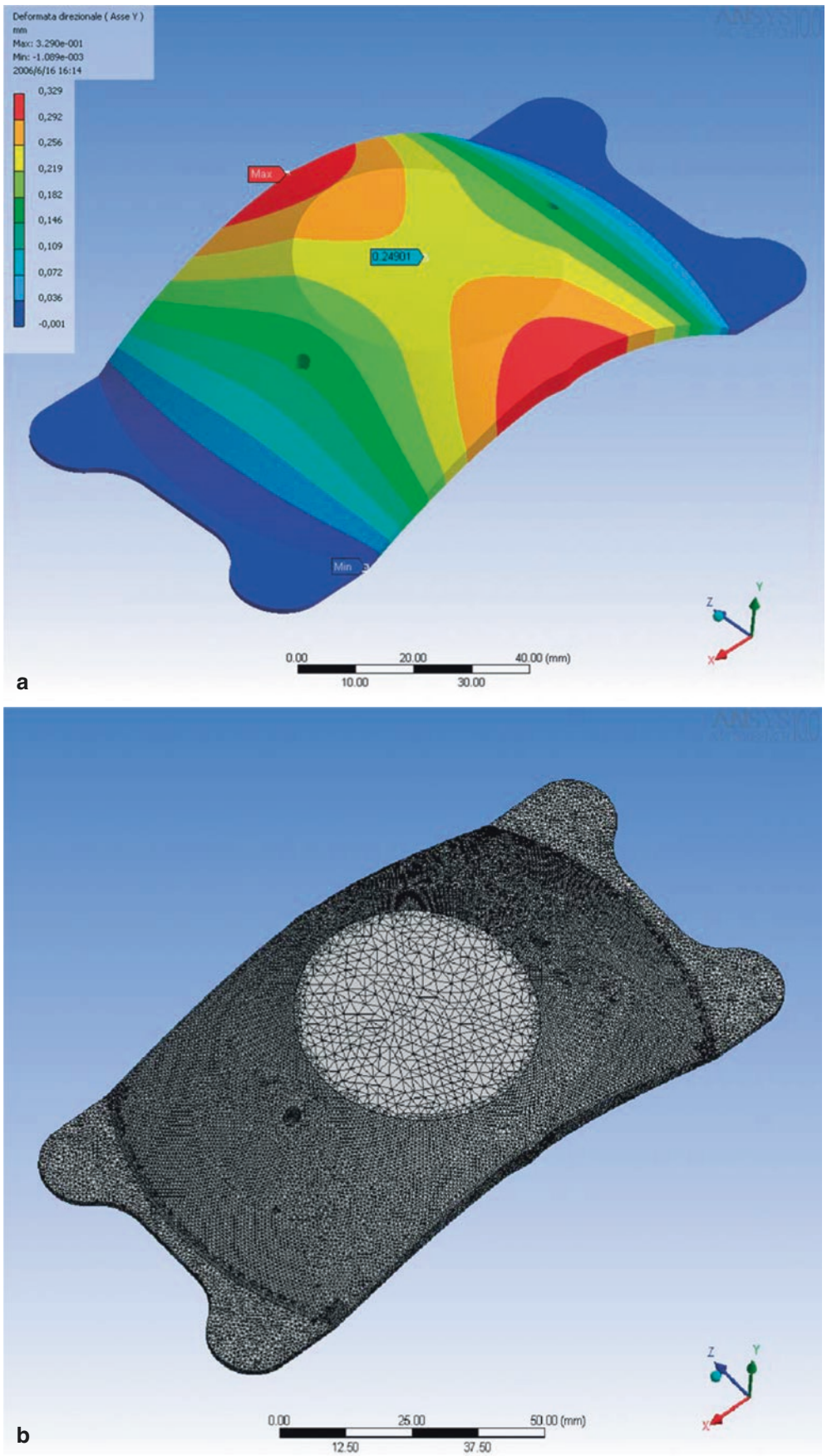


Fig. 32.21 FEA computer simulation representing a 3-D geometrical model of an ICL by multiple, linked representations of discrete regions. Equations of equilibrium are applied to each element, and a system of simultaneous equations is constructed. A set of compressions in order to simulate the intraocular ICL behavior for different powers, lens implant, and sulcus sizes is performed and ICL deformation recorded in every point

deviation of ±113 μm. The minimum vault obtained was 189 μm. An expected vs. achieved vault height in the ±150 μm range was obtained in the 95% confidence interval. In comparison with the group control (Group B), where the ICL was implanted on the basis of the W-to-W, the mean central vault height was 406 μm (the difference was not statistically significant), but the standard deviation was highly significant (±667 μm). The minimum vault achieved was 0 μm, and the incidence of size-related complications (angle-closure glaucoma, cataract, and clinically significant pigmentary dispersion) was around 8%. The reference point of the 95% confidence interval as referred to the expected vs. achieved vault height was reached for the range of ±730 μm [14]. Similar values are obtained from multivariate regression analysis by sizing the ICL on the basis of anterior chamber depth, corneal pachymetry, opening of the iridocorneal angle, angle-to-angle distance, and axial length, but also shoe, hat, or glove size!

Take-Home Pearls

- Posterior chamber phakic lenses (ICLs) are safer for the corneal endothelium than other models of phakic lenses.
- Adequate and specific surgeon training is mandatory prior to using ICLs, as this may prevent most of the intraoperative and early postoperative complications.
- Most late postoperative ICL complications (including iatrogenic anterior subcapsular cataract) are size related. Sizing cannot be based on external anatomy (the horizontal corneal diameter or white-to-white distance), because it has shown to correlate poorly with the internal dimensions.
- To accurately predict the postoperative intraocular implant-to-tissue clearances, an ICL must be customized to the individual, internal biometric measurements of the anterior segment, obtained with very high-frequency echography and calculated by accomplished software.
- After surgery, the implanted eyes should be monitored at least yearly with very high-frequency echography or anterior chamber OCT.

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Retinal Detachment

33

Marta S. Figueroa and Andrea Govetto

Core Messages

- This chapter discusses retinal complications, in particular retinal detachment after lens surgery in high myopic patients.
- The incidence of retinal detachment in high myopic patients corrected by intraocular surgery is reported based on the experience of the authors and on a review of published reports.
- The cumulative risk of retinal detachment development in high myopic patients after intraocular refractive surgical procedures (whether lens exchange or phakic intraocular lenses) is reported.
- Various options for the treatment of retinal detachment in high myopic patients after ocular refractive surgery are outlined.

33.1 Introduction

Anterior segment specialists constantly look for techniques to improve safety and efficiency of refractive procedures.

However, although infrequent, refractive surgery is not free of potentially serious complications which may significantly compromise the patient's vision. Particularly, rhegmatogenous retinal detachment (RD) may complicate refractive surgery procedures like clear lens extraction (CLE) with posterior chamber intraocular lens (PCIOL) implantation, phakic intraocular lens implantation (PIOL), or excimer laser procedures (laser in situ keratomileusis, LASIK; laser-assisted subepithelial keratomileusis, LASEK; photorefractive keratectomy, PRK) [1–7].

It is well known that high myopic eyes are strongly predisposed to RD due to a combination of increased vitreous liquefaction, earlier posterior vitreous detachment, and higher incidence of vitreoretinal degeneration such as lattice degeneration. This fact becomes particularly important if we think that myopic patients are precisely the ones who often seek treatment for their refractive defect [8–11].

Along with a natural predisposition to RD in high myopia, other factors may contribute to the development of this complication after refractive surgery. For instance, the pressure induced by the microkeratome suction ring may create vitreous traction, resulting in RD [6]. The impact of laser pulses during PRK, LASIK, or LASEK may also play a role. Clear lens extraction, even without complications such posterior capsule rupture, may also favor vitreous traction [4].

The main focus of this chapter is determining whether the incidence of retinal detachment in high myopic patients increases after excimer laser surgery, CLE with PCIOL implantation, or uneventful cataract surgery.

33.2 Retinal Detachment in Highly Myopic Eyes

Previous studies reported a higher risk of RD in high myopic eyes without history of ocular surgery, compared to non-myopic eyes (whether emmetropic or hypermetropic). Annual incidence of RD was reported between 0.71% and 3.2% in eyes with a spherical equivalent (SE) greater than −6.0 D [12, 13].

In other studies, the annual incidence of RD was 0.015%, 0.07%, and 0.075% in eyes with a refractive error less than 4.75D, between −5.0 D and −9.75 D, and more than 10 D, respectively [14]. In high myopic patients with a refractive

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error superior to –15 D, the risk of developing RD increased dramatically compared to the general population.

Such findings are confirmed by Burton who reported that, in presence of lattice degeneration, high myopic patients with a refractive error greater than −5.0 D have an extraordinarily high risk of RD during their lifetime [8].

33.3 Incidence of Retinal Detachment in High Myopic Patients Corrected by Laser Excimer (LASIK, LASEK, PRK)

Although rare, there are several studies and cases reported in the literature regarding RD after LASIK. Reviglio et al. reported a case of acute RD after LASIK surgery in a highly myopic patient, diagnosed barely 14 h after the procedure [15]. Other authors reported 4 RD (0.25%) out of 1,554 myopic eyes after LASIK [16].

In a retrospective cohort study, Shu-Yen Lee et al. reported 10 patients out of 12,760 eyes (myopes and hyperopes) with RD after laser refractive surgery [17]. These patients had a mean preoperative measurement of −8.82 ± 2.94 D (range −5.25 to −14.50 D).

In a more recent report, Arevalo et al. confirmed a very low risk of RD in myopic patients with a refractive error less than –10 D, with frequencies of rhegmatogenous RD after LASIK of 0.05% (11/22,296) at 1 year, 0.15% (18/11,371) at 5 years, and 0.19% (22/11,594) at 10 years [6].

Some authors postulated that the risk of RD may be less in LASEK procedures compared to LASIK, as the former does not require a suction ring, which may cause vitreous traction and, as a consequence, may favor the development of an RD.

In this regard, Kang et al. studied the characteristics of rhegmatogenous RD in patients with previous LASIK and compared them to both rhegmatogenous RD in myopic patients with no previous refractive surgeries and to rhegmatogenous RD in patients with previous LASEK [18]. They found that the characteristics of retinal breaks and rhegmatogenous RD in patients with prior LASIK were not significantly different from those with prior LASEK or myopic patients without prior refractive surgery, suggesting that myopia itself, rather than refractive surgery, may have a greater impact on the development of rhegmatogenous RD in myopic patients with previous refractive surgery.

Finally, the incidence of RD after PRK was investigated by O'Connor et al. who reported only one case of RD out of 120 myopic eyes operated by PRK, demonstrating the safety this procedure [19].

33.4 Incidence of Retinal Detachment in High Myopic Patients Corrected by PIOL

Surgical correction of high myopia can also be achieved by PIOL either in the anterior or posterior chamber.

RD after PIOL implantation has been reported by several authors [1, 20–23]. Specifically, in 1993, Alio et al. were the first to report retinal detachment after PIOL implantation for correcting high myopia [1]. Later, Fechner reported RD in one case out of 125 myopic patients corrected with PIOLs [24]. Subsequently, other studies reported incidence rates ranging from 0.8 to 5.26% [20–23]. Other authors reported the cumulative risk of RD after PIOL implantation in high myopic patients with a refractive error greater than –18 D, as 1.36% at 5 months, 2.6% at 17 months, 3.61% at 27 months, and 5.63% at 52 months [25], frequencies which were later confirmed in a similar report [21].

The time interval between PIOL implantation and the development of RD ranged between 1 and 52 months in the first study [25], (4 eyes with time interval less than 6 months) compared to a range of 1–92 months in the second study [21]. Therefore, the relationship between PIOL implantation and RD development is not clear. A large case-control study with the same degree of myopia and with longer follow-up is needed to validate such relationship.

In a recent study, Alio et al. reported 4 cases of RD out of 97 eyes which underwent PIOL implantation, over a follow-up of 15 years [26]. Finally, Al-Abdullah et al. compared the incidence and characteristics of retinal complications following implantation of anterior versus posterior chamber PIOL in patients with myopia, finding no significant differences and concluding that implantation of either types of PIOL leads to comparable rates of retinal complications [27]. Anterior chamber PIOL does not increase the risk of retinal detachment or choroidal neovascularization in patients with myopia [27].

33.5 Incidence of Retinal Detachment in High Myopic Patients Corrected by Phacoemulsification and PCIOL Implantation

Phacoemulsification has rapidly become the preferred technique in cataract surgery in the developed world. It is considered to be safe, with relatively few complications during and after surgery.

The indications for performing cataract surgery have changed within recent years, with clear lens extraction for correction of refractive errors and multifocal lens implants for presbyopia gaining popularity [28]. However, although safe, phacoemulsification is not free of complications.

RD has been reported to occur more frequently in pseudophakic than in phakic eyes [4] and may be favored by some risk factors including high myopia and lattice retinal degeneration [4, 8]. In those cases, the risk of RD is maintained over several years, possibly due to vitreous alterations caused by the cataract surgery itself.

Generally, the cumulative incidence of RD after cataract surgery has been reported to range between 0% and 3.6%

with a follow-up period of up to 10 years [29] and can occur early or late during the postoperative period [30]. Because cataract surgery is such a common procedure, the absolute number of RD in pseudophakic patients is large.

Various large population-based studies have extensively investigated the issue of RD after cataract surgery, and high myopia has been reported as the main risk factor for this serious complication. For example, Daien et al. in a nationwide survey in France, estimated a hazard ratio for RD in myopic patients of 6.12 (95% CI, 5.84–6.41) [4].

The principal risk factors (other than high myopia) for RD after cataract surgery include young age, capsular rupture, history of eye trauma, extracapsular extraction technique, male gender, and diabetes [4].

Several different pathophysiological mechanisms have been suggested. For instance, the volume occupied by a cataract is higher when compared to that of a standard IOL. Therefore, the vitreous may move anteriorly, causing incomplete PVD, traction, and, eventually, RD. Furthermore, some authors have also suggested that the increased risk of pseudophakic RD could be caused by alterations in the vitreous proteome after surgery [31].

33.6 Treatment of Retinal Detachment After Ocular Refractive Surgery

In cases of uncomplicated rhegmatogenous RD without proliferative vitreoretinopathy (PVR), the use of scleral buckling alone may be an excellent and effective choice, especially in cases of young patients with phakic eyes and inferior breaks. However, such classic approaches may lead to significant changes in axial length and, in addition, may cause a reduction in anterior chamber depth [32, 33]. Such variables need to be taken into account, as both axial length and anterior chamber depth variations may cause significant refractive changes, especially in a patient who underwent previous refractive surgery, either with excimer laser or PIOL and PCIOL implantation.

More recently, there has been a transformative shift in the surgical approach for rhegmatogenous retinal detachment. In fact, 23-, 25-, or 27-gauge micro-incisional pars plana vitrectomy (PPV) has gained popularity and allows the retinal surgeon to remove intraocular media opacities and vitreous traction and to internally locate and treat retinal breaks [34]. When compared with older 20-gauge systems, micro-incisional PPV decreases operating time and patient discomfort and, in many cases, spares the use of sutures as the sclerotomies are self-sealing [34].

Figueroa et al. reported a primary anatomic success rate of 96.2% in eyes with RD treated with 23-G PPV without scleral buckle, a result comparable to previously published data with 20-G PPV and scleral buckling [35]. Similarly, in a recent meta-analysis of the literature comparing PPV versus PPV with scleral buckling in the treatment of rhegmatogenous retinal detachment, no significant differences in the final reattachment rate were found. Moreover, the rate of complications like postoperative development of macular edema, proliferative vitreoretinopathy, or elevation of intraocular pressure was similar in both groups [36]. Another recent paper investigating surgical outcomes of rhegmatogenous RD repair with different techniques confirmed comparable anatomical results with both PPV and scleral buckle [37]. Therefore, in case of uncomplicated RRD in a refractive patient, PPV should be the treatment of choice.

Take-Home Pearls

- Avoid intraoperative posterior capsular tears with vitreous loss, as they increase the incidence of retinal complications.
- Remove all cortexes in order to decrease the incidence of posterior capsule opacification and to provide more detailed future fundus examination.
- Perform large capsulorhexis to avoid the risk of capsular phimosis and guarantee good view of the retina during fundus examination and eventual posterior segment surgeries.
- PPV should be considered as the best therapeutic alternative especially for high myopic pseudophakic rhegmatogenous RD.

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Refractive Lens Exchange and Choroidal Neovascularisation

34

Emanuel Rosen

34.1 Introduction

Refractive lens exchange (RLE) entails exchange of the clear or relatively clear crystalline lens for a lens implant for the purpose of refractive relief, i.e. adjustment of the refraction of the eye to any desired end point. As its name implies, this is a process applicable to a younger cohort of patients than those patients undergoing lens exchange for removal of a visually disabling cataract. The surgical process is the same; the age range is different. In the older group of cataract patients (with geographic and racial variants), age-related central retinal (macular) pathology is prevalent. On the other hand, RLE is applicable to highly myopic eyes. The effects of retinal stretching include a larger eye globe of the high myopic eye as well as posterior staphyloma.

Cataract surgery is much more prevalent than RLE, and though it is intended for a different age-related cohort, lessons can be learned from the data provided in relation to the risks to macular function through subretinal pathology. Studies of pathological specimens provide a better understanding of the relationship between clinical ophthalmoscopic signs and subretinal pathology. The role of light in the development of macular pathology is also relevant for RLE, as it involves the exchange of a yellowing (but optically well-functioning) lens for a lens implant (IOL), which in general does not have the light filtration qualities of the natural lens.

There is a clear distinction between RLE in myopic eyes and in hyperopic eyes, as the latter are not subject to the effects of retinal stretching which can lead to premature macular subretinal neovascularisation and macular degeneration.

34.2 Pathology

Age-related macular degeneration (AMD) is clinically less common in India compared to Caucasian eyes, where cataract surgery is applicable in general to a younger age group. Potential lessons may be learned from post-mortem eyes which can be related to clinical signs in eyes of patients being considered for RLE (1). Forty-eight percent had some form of age-related macular change. These included basal laminar deposits, hard drusen, soft drusen, extensive retinal pigment epithelium atrophy of the macula, and disciform degeneration of macula, with a combination of changes often seen. See illustrations of clinical aspects of these pathological changes (Figs. 34.1, 34.2, 34.3, 34.4, 34.5, 34.6, 34.7, 34.8, 34.9, 34.10).

Spraul et al. (2) performed a histopathologic study to compare eyes with different stages of AMD with age-matched eyes to identify characteristics associated with exudative vs nonexudative AMD. They showed that in the macular area, a statistically significant difference was observed for the degree of calcification ($P = 0.02$) and fragmentation ($P = 0.03$) of Bruch's membrane in eyes with exudative AMD (1.6 and 5 per eye, respectively) compared with eyes with nonexudative AMD (0.8 and 1 per eye, respectively) and control eyes (0.8 and 0 per eye, respectively). Eyes with AMD displayed notably softer, more confluent, and larger drusen and basal laminar (linear) deposit in the macular area compared with control eyes. Calcification and fragmentation of Bruch's membrane, soft, confluent, and large drusen, and basal laminar (linear) deposit, but not hard drusen, are associated with the histological presence of AMD. The degree of calcification and fragmentation of Bruch's membrane is greater in eyes with exudative compared with nonexudative AMD.

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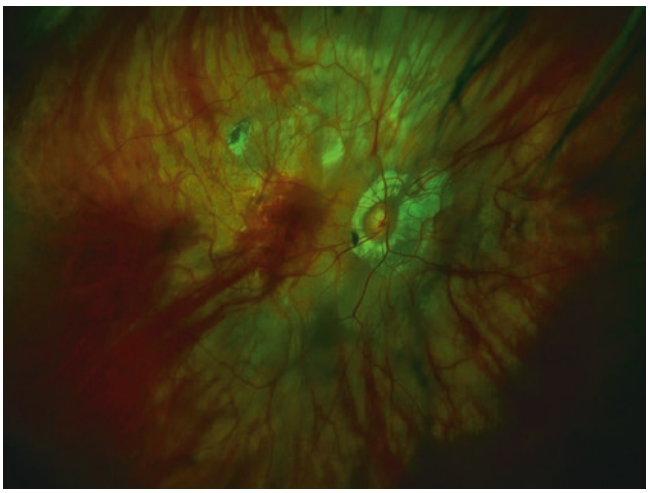

Fig. 34.1 Myopic RLE myopic retinal thinning and central RPE atrophy precursor of choroidal neovascularisation

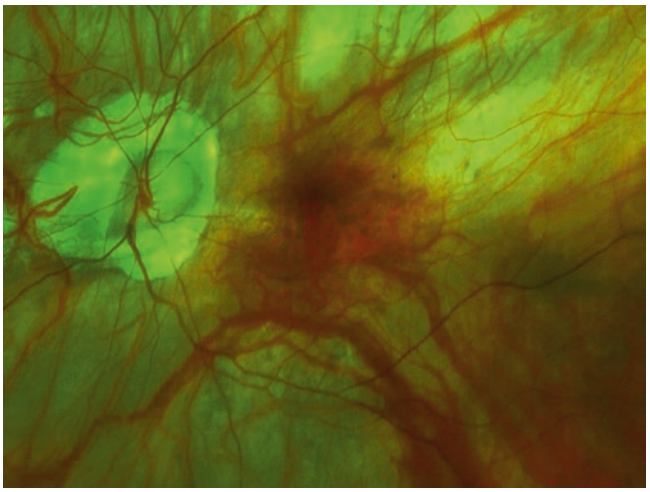

Fig. 34.2 Myopic RLE myopic retinal thinning and central RPE atrophy precursor of choroidal neovascularisation

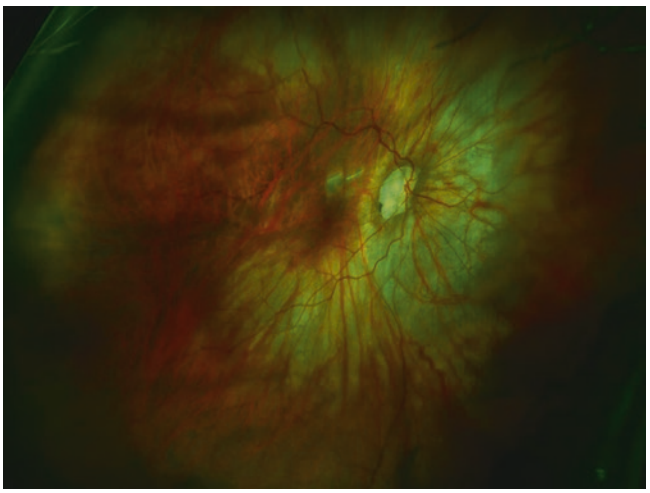

Fig. 34.3 Myopic RLE myopic retinal thinning and central RPE atrophy precursor of choroidal neovascularisation

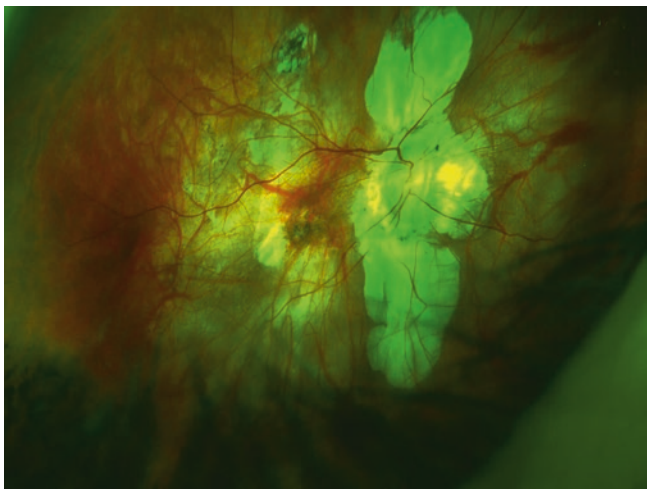

Fig. 34.4 Myopic RLE myopic retinal thinning and central RPE atrophy plus early choroidal neovascularisation

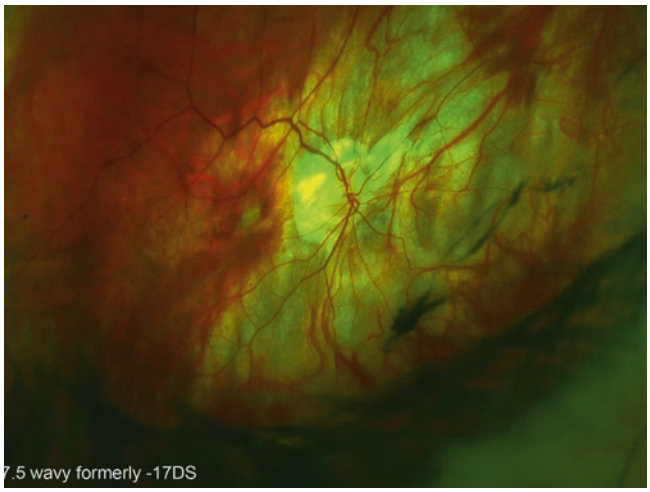

Fig. 34.5 Myopic RLE myopic retinal thinning and central RPE atrophy with early choroidal neovascularisation and distorted vision

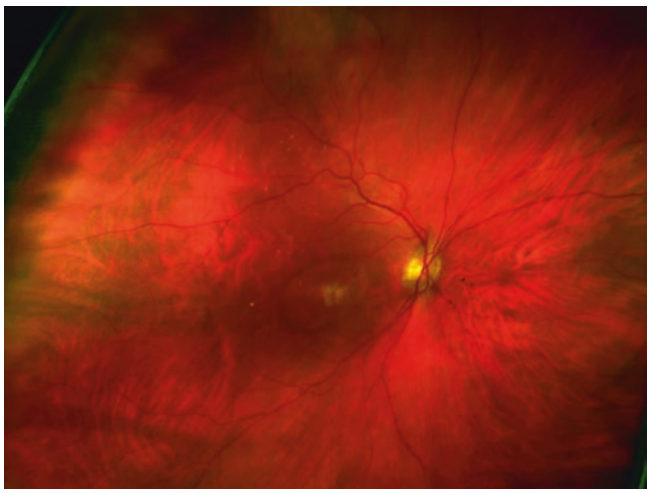

Fig. 34.6 Hyperopic RLE subretinal neovascular membrane with retinal pigment epithelium detachment

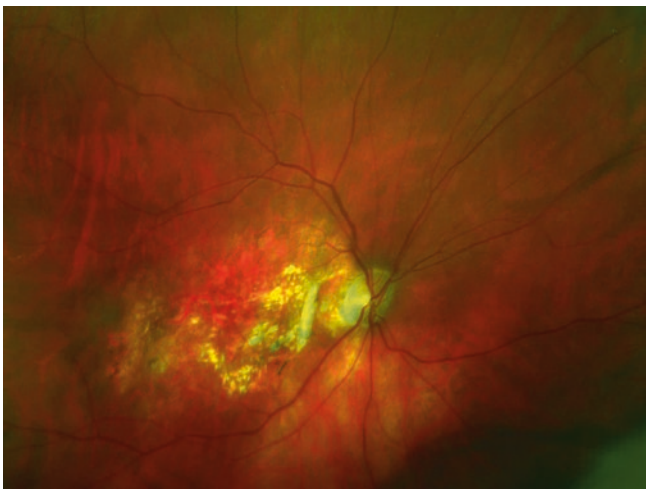

Fig. 34.7 Hyperopic RLE subretinal neovascular membrane with lipid exudate

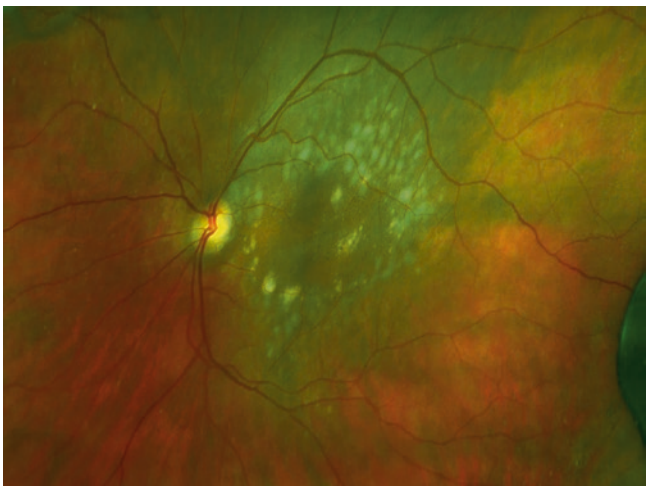

Fig. 34.9 Pseudophakia soft drusen and good vison 6/6

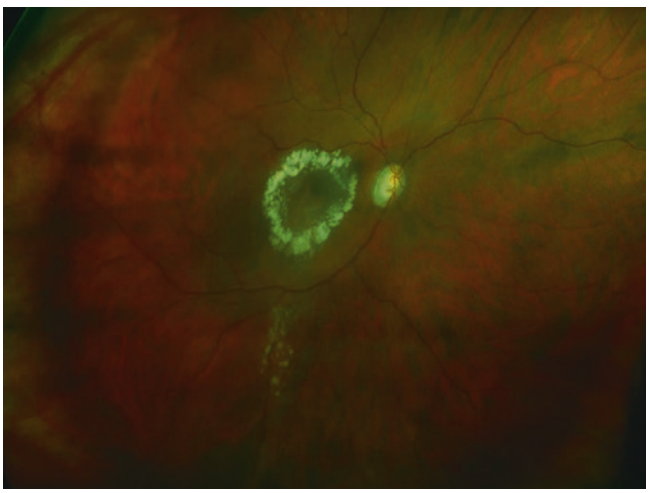

Fig. 34.8 Pseudophakia subretinal neovascular membrane with lipid circinate exudate

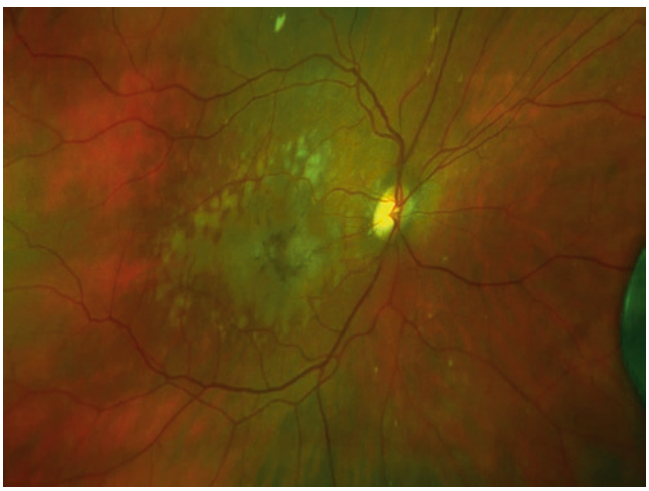

Fig. 34.10 Pseudophakia soft drusen and SRNVM

34.3 Retina in High Myopia

Pruett (3) notes that macular choroidal neovascularization occurs more often in those with moderate staphyloma than in those with advanced atrophy in the posterior pole. Indocyanine green angiography has improved our knowledge of this complication, which has been correlated with an increased number of posterior choroidal drainage systems. Clinicians must understand that while RLE offers refractive relief to severely myopic patients, the natural progression of retinal stretching can result in diminished long-term benefit of this surgery.

34.4 Prevalence

Choroidal neovascularization (CNV) is an uncommon cause of vision loss in patients <50 years of age. In these patients, CNV is often the result of pathologic myopia, but other pathologies such as angioid streaks may be coexistent in myopic eyes being considered for refractive relief through RLE. Of course, untreated CNV may cause rapid deterioration of central vision with a poor prognosis (4).

Lessons related to RLE may be derived from studies of characteristics of choroidal neovascularization in highly myopic patients corrected by the implantation of phakic

intraocular lenses (PIOLs). In one study, choroidal neovascularization occurred in 5 eyes (1.70%), 3 in women and 2 in men (Ruiz-Moreno et al. 2003) (5). The interval between phakic anterior chamber lens implant (PACL) implantation and CNV was 63.2 +/− 27.3 months (range, 18 to 87 months). The CNV was sub-foveal in 4 eyes and juxtafoveal in 1 case. The mean best spectacle-corrected visual acuity (BSCVA) after PACL implantation and before the appearance of CNV was 0.53 +/− 0.18 (range, 0.4 [20/50] to 0.8 [20/25]); after CNV appeared, it was 0.26 +/− 0.18 (range, 0.05 [20/400] to 0.5 [20/40]), a statistically significant difference (P = 0.001, paired student t-test). The cumulative risk for CNV (Kaplan-Meier survival analysis) in highly myopic patients corrected by PACL implantation was 0.43% at 18 months and 5.4% at 87 months.

In 2006, Ruiz et al. (6) studied 522 consecutive highly myopic eyes (spherical equivalent refraction > − 6.00 diopters [D] and/or axial length > 26 mm) (323 patients) corrected by the implantation of PIOLs, before and after treatment of choroidal neovascularization. Choroidal neovascularization developed after PIOL implantation at a mean interval time of 33.7 +/− 29.6 months (range, 1 to 87 months). Using Kaplan-Meier analysis, the risk of choroidal neovascularization in patients with high myopia corrected by PIOL implantation was 0.57% at 5 months, 0.81% at 18 months, 1.31% at 24 months, and 3.72% at 87 to 145 months. While phakic intraocular lens implantation for the correction of high myopia seemingly does not play a role in the development of choroidal neovascularization, the study reflects the potential natural incidence of CNV in a population similar to one which would undergo RLE, albeit for higher degrees of myopia than in this study cohort.

On the other hand, Fernandez et al. (7) evaluated the postoperative outcomes and intraoperative and postoperative complications of RLE with posterior chamber intraocular lens implantation in highly myopic eyes in a retrospective case series. Of 107 patients (190 eyes) who had been observed for at least 3 years after surgery, high myopic eyes were reviewed over 7 years (January 1990 to December 1996). Sub-foveal choroidal neovascularization (CNV) developed in 4 eyes (2.10%) of 3 patients; all of these eyes presented with a macular lacquer crack. Hayashi K et al. (8) considered the incidence and characteristics of (CNV) in patients with high myopia more than 8 diopters who underwent cataract surgery between September 1991 and March 2000. CNV was found in six eyes (12.5%) of six patients. The mean interval between cataract surgery and the development of CNV was 34 +/− 17 months (range, 12–48 months). The CNV was sub-foveal in all cases. Sub-foveal CNV developed more frequently in eyes when the fellow eye showed evidence of CNV preoperatively (40.0%) than in eyes when the fellow eye exhibited no evidence of CNV (9.3%). Implantation of a PACL to correct high myopia was followed by a small incidence of CNV (cumulative risk of 5.4% at 87 months). The appearance of CNV was followed by a significant decrease in BSCVA.

Cataract surgery is undertaken in an older age group than RLE patients, and the underlying age-related phenomena in cataractous eyes are undoubtedly different from the younger eyes undergoing RLE. Early clinical case series reports suggested a link between cataract surgery and late AMD (9–11). A report from post-mortem eyes also suggested that neovascular AMD was more frequently observed in pseudophakic than phakic eyes. Pollack et al. (10, 11), in a small number of cases, carefully documented that the risk of AMD increased within 6 to 12 months after surgery in patients with bilateral, symmetric early AMD. In contrast, Armbrecht et al. (12) could not confirm such an observation between surgical and non-surgical patients.

Myopic eyes undergoing RLE already have degenerative elements specific to myopia. Therefore, as the relationship between pseudophakia and AMD remains unclear but positive in the sense that there does appear to be a relationship, we can only speculate on the potential mechanisms that may cause RLE eyes to be more susceptible to earlier-onset AMD with or without choroidal neovascularisation. This could be mediated via inflammatory reactions associated with the surgery, postoperative biochemical environmental changes within the eye (increased free radicals or growth factors) (13–15), or increased light exposure either during or after surgery (16, 17). The question of whether or not blue light filtering intraocular lenses are helpful in this regard remains unresolved (18–21).

34.5 Light Toxicity and Potential Macular Effects

RLE patients may be in their sixth or seventh decade, and as they age, retinal health if not an immediate issue-may be compromised by retinal light exposure. Therefore, there is at least a hypothetical risk that RLE could lead to premature AMD. Photoxicity is one possible mechanism that could disturb central retinal balance.

There are at least two forms of retinal phototoxicity: blue-green and UV-blue. Blue-green phototoxicity is mediated by rhodopsin, the same photopigment involved in scotopic vision. The second type of retinal phototoxicity, UV-blue, increases with decreasing wavelength. In other words, UV radiation (100–400 nm) is more hazardous than violet light (400–440 nm), which in turn is more hazardous than blue light (440–500 nm). UV radiation is responsible for 67% of acute UV-blue phototoxicity in the part of the spectrum that

can reach the retina through an IOL, while violet light accounts for 18% and blue light for 14%.

The potentially harmful effects of UV radiation eventually led to the inclusion of UV-blocking chromophores in nearly all IOLs on the market today. It has been suggested that violet- and blue-blocking lenses (AcrySof Natural, Alcon Laboratories; AF-1, Hoya Corporation) may help prevent AMD as they mimic the color degradation of the ageing crystalline lens to some degree.

Blue light is much more important for mesopic and scotopic vision than it is for photopic vision because of rod as opposed to cone photoreceptor sensitivities. This is due to the photopigment rhodopsin, which has a peak sensitivity near 500 nm, the border between blue and green light.

Age-related pupillary miosis and crystalline lens yellowing threaten to reduce older adults' effective blue light exposure to one-tenth that of younger people.

The pathogenesis of AMD, the most common cause of visual loss after the age of 60 years, is indeed a complicated scenario that involves a variety of hereditary and environmental factors. For many years, there has been concern that light exposure might play a role, but this relationship remains unproven. The availability of visible light-blocking intraocular lenses emphasizes the importance of continuing research in this area. There may be a trade-off between blocking blue light and maintaining optimum mesopic vision (20, 21).

Cumulative sunlight exposure and cataract surgery are reported risk factors for AMD (21). Laboratory studies suggest that accumulation and photochemical reactions of A2E (N-retinylidene-N-retinylethanolamine) and its epoxides, components of lipofuscin, are important in AMD. To relate this data to the clinical setting, Meyers et al. (22) modelled the effects of macular irradiance and spectral filtering on production of A2E and reactive oxygen intermediates (ROIs) in pseudophakic eyes with a clear or "yellow" intraocular lens (IOL) and in phakic eyes. They calculated the relative changes in macular irradiance as a function of light (390 to 700 nm) intensity, pupil size, age, and lens status and modelled resulting all-trans-retinal concentration and rates of production of A2E-related photochemicals and photon-induced ROIs in rods and retinal pigment epithelium (RPE). They compared these photo-products following cataract surgery and IOL implantation with and without spectral sunglasses to normal age-related nuclear sclerotic lens changes. Following cataract and IOL surgery, all-trans-retinal and lipofuscin photochemistry would theoretically increase average generation of (1) A2E-related photochemicals, (2) ROI in rods, and (3) ROI in RPE, respectively, 2.6-fold, 15-fold, and 6.6-fold with a clear IOL and 2.1-fold, 4.1-fold, and 2.6-fold with a yellow IOL, but decrease approximately 30-fold, approximately 20-fold and 4-fold with a vermillion filter sunglass and clear IOL compared to an average 70-year-old phakic eye.

Sunglasses that strongly decrease both deep blue light and rod photobleaching, while preserving photopic sensitivity and colour perception, could provide upstream protection from potential photochemical damage in subjects at risk for AMD progression after cataract (and RLE) surgery. If this is relevant for cataract surgery, then it should be more so for RLE where life expectancy after RLE may be up to 60 years.

Take-Home Pearls

- RLE is applicable to younger patients than those who generally undergo cataract surgery.
- There is a clear distinction between RLE in myopic eyes than hyperopic eyes, which are not subject to the effects of the retinal stretching that can lead to premature macular subretinal neovascularization and macular degeneration.

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Complications of Multifocal Intraocular Lenses

35

Roberto Fernández Buenaga and Jorge L. Alio

Core Messages

- Patient satisfaction after multifocal IOL implantation is reviewed in this chapter.
- The main reasons leading to patient complaint and dissatisfaction are analyzed. The best treatment options for all these clinical situations are described, as well.
- IOL explantation, although rare, is the worst scenario possible after cataract surgery with multifocal IOL implantation. Its incidence and the outcomes after explantation surgery are discussed.
- Finally, several IOL explantation techniques reported in the literature are also discussed.

35.1 Introduction

Implantation of multifocal IOLs that offer full refractive correction at all distances is the ideal goal for cataract and lens-based refractive surgery. Overall, multifocal IOLs achieve high patient satisfaction [1, 2]. Other studies also show a high patient satisfaction after multifocal IOL surgery with scores of 8.3 ± 1.6 (out of 10) and 8.5 ± 1.2 (out of 9), respectively [3, 4].

We found correlations between some clinical parameters and quality of life parameters, such as driving (especially at night) and contrast sensitivity or eyesight quality and uncorrected distance visual acuity [5].

An interesting correlation between positive dysphotopsia complaint and personality type has been reported. In this study, 82.2% of patients would opt for a multifocal IOL again, 3.7% would not, and 14.1% were uncertain. Overall satisfaction with the procedure was correlated to low astigmatism, good visual performance, low halos and glare perception, and low spectacle dependence. The personality characteristics of compulsive checking, orderliness, competence, and dutifulness were statistically significantly associated to subjective disturbance by glare and halos [6].

Multifocal IOL explantation represents the main failure of the intended surgery. It is always disappointing for both the patient and the surgeon. Furthermore, IOL explantation surgery is not always easy to be performed, and it is not exempt of new complications. Because of all these reasons, multifocal IOL explantation should only be performed when there is no other alternative, with all the causes leading to patient dissatisfaction properly ruled out.

Thus, it is essential for the multifocal IOL surgeon to know and to investigate the main causes leading to patient dissatisfaction after cataract surgery because, in most of the cases, the situation can be successfully managed with no need for new intraocular surgeries.

In this chapter, we will review the main reasons for patient dissatisfaction after multifocal implantation surgery, and we will show the strategies to manage each situation. We will also describe the incidence and recommendations for multifocal IOL explantation. Instructions for IOL explantation surgery will be also given.

35.2 Reasons for Patient Dissatisfaction

35.2.1 Blurred Vision

Blurred vision is the leading cause of dissatisfaction among patients with multifocal IOLs [7]. Woodward, Randleman, and Stulting reported that blurred vision was the main complaint in 30 patients (41 eyes), out of 32 patients (43 eyes). Fifteen patients (18 eyes) reported photic phenomena, and 13 patients (16 eyes) reported both blurred vision and photic phenomena. The etiology of blurred vision was attributed to ametropia and posterior capsule opacification (PCO) in the majority of cases. Despite overall success with less invasive interventions, 7% of eyes required IOL exchange to resolve symptoms [7].

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In another study, blurred vision (with or without photic phenomenon) was reported in 72 eyes (94.7%) and photic phenomena (with or without blurred vision) in 29 eyes (38.2%). Both symptoms were present in 25 eyes (32.9%). Residual ametropia and astigmatism, posterior capsule opacification, and a large pupil were the three most significant etiologies. Intraocular lens exchange was performed in three cases (4.0%) [8].

Dissatisfaction after multifocal IOL implantation is reported by patients who do not achieve the desired visual goals, have limited sharpness of vision, or have new visual aberrations. A Cochrane review about multifocal IOLs found that photic phenomena are 3.5 times more likely with multifocal IOLs than with monofocal IOLs [9].

Most of the times, there is an identifiable reason. Woodward MA et al., showed that causes of blurred vision included ametropia (29% of cases), dry eye (15%), PCO (54%), and unexplained etiology (2%). Regarding the photic phenomena, its causes included IOL decentration (12%), retained lens fragment (6%), PCO (66%), dry eye (2%), and unknown etiology (2%). In this paper, the authors achieved an improvement in 81% of eyes with conservative treatment [7]. In a similar study, 84.2% of eyes were amenable to therapy, with refractive surgery, spectacles, and laser capsulotomy as the most frequent treatment modalities [8].

Venter JA et al., showed that in more than 9300 eyes implanted with a multifocal IOL, patient satisfaction was very high: 93.8% of the patients reported to be satisfied or very satisfied, while only 1.7% of the patients were dissatisfied or very dissatisfied [10].

35.2.2 IOL Decentration

Several clinical studies have determined the decentration of IOLs after cataract surgery [11–21]. In general, the mean decentration (after uneventful cataract surgery) in studies is 0.30 ± 0.16 mm (range 0–1.09 mm). When a multifocal IOL is displaced from its center, it may lose its ability to achieve optimal optical properties, thus decreasing the visual function (Fig. 35.1). There are three main factors that determine how visual function is affected by IOL decentration:

- The degree of decentration
- The IOL design
- Pupil size

Soda M et al., studied the performance of four different multifocal IOL models (two diffractive and two refractive) at increasing degrees of decentration in an eye model with a 3 mm pupil. For the ReSTOR (+4), the near MTF (modulation transfer function) deteriorates with increasing degrees of decentration, while the far MTF tends to improve. This is explained by the specific design of this IOL with a monofocal design in its peripheral part. In other IOL models like the ZM900, the entire optical surface has a diffraction structure; therefore, a slight decrease in both far and near MTF starting at decentrations of 0.75 mm was observed. For the refractive models (ReZoom and SFX-MV1), even when the decentration was 1 mm, the near MTF did not change. However, the far MTF decreased starting at decentrations of 0.75 and 1 mm, respectively. In conclusion, the MTFs and near images are affected, but clinical relevant effects are not to be expected up to a decentration of 0.75 mm using this eye model with a 3 mm pupil and the previously mentioned IOLs [22].

In a different study comparing refractive multifocal and monofocal IOL performance depending on the pupil size and decentration, it was found that in the multifocal group smaller pupils correlated with worse near visual acuity, while decentration was significantly correlated with worse distance and intermediate visual acuity. However, in the monofocal group, pupil size and IOL decentration did not affect the final visual acuity [23].

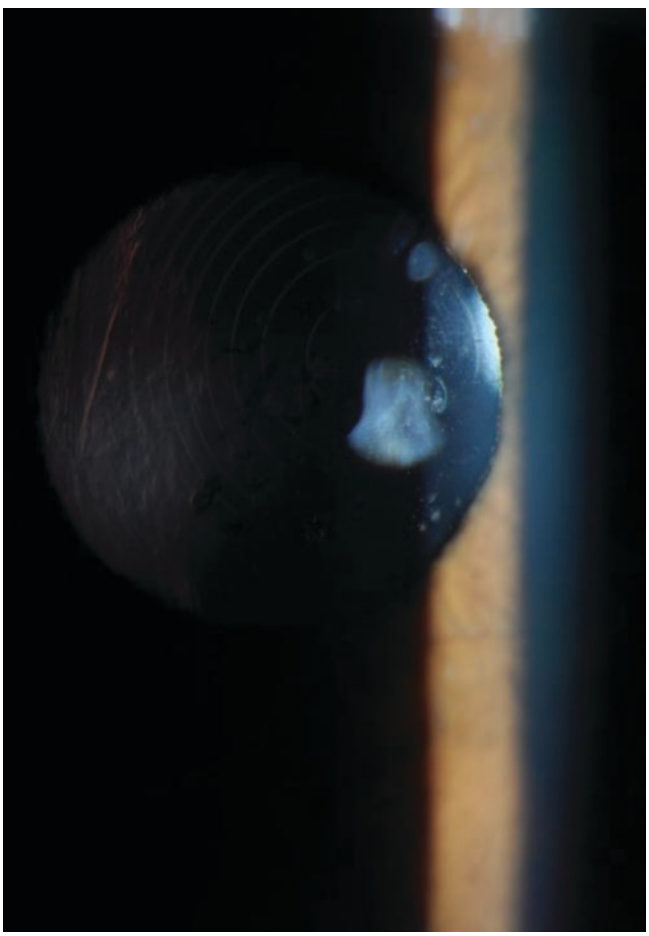

Fig. 35.1 This picture shows a diffractive IOL decentered nasally

It has also been shown by other authors that the more sophisticated the IOL is, the more sensitive to decentration it is. In a paper comparing aberration-correcting, aberration-free, and spherical IOLs, after decentration, the performance of the IOL was more affected in the aberration-correcting group followed by the aberration-free IOLs, while the spherical IOLs were not affected by decentration at all [24].

Another interesting consideration is the kappa angle. Although it is not very common, some patients may have a large kappa angle. It should be suspected and checked in every patient with a perfectly pupil-centered multifocal IOL but with poor vision complaint [25].

The main symptoms when multifocal IOL decentration occurs are the photic phenomena including glare and halo. A suboptimal visual acuity is also detected in these cases.

Management:

The first important message is that multifocal IOL decentration, that occurs after an uneventful cataract surgery, can be managed without IOL explantation in the majority of cases. We advocate performing argon laser iridoplasty as the treatment of choice, with the argon laser settings for iridoplasty as 0.5 s, 500 mW, and 500 μm.

35.2.3 IOL Tilt

The material and biocompatibility of the haptics have been shown to play a role in IOL centration [26, 27]. Hydrophilic IOLs have several advantages because of their pliable and scratch resistance nature that allow us to implant these IOLs through small corneal incisions. However, this malleable material may be a major drawback if capsular bag contraction develops. The combination of hydrophilic material with soft C-loop haptics may facilitate IOL decentration and tilt when capsule bag contraction starts to develop. Rotationally, asymmetric refractive IOLs are sensitive to decentration and tilt because of their inherent design characteristics [28–30].

As a research group, we have several recent publications on this issue especially regarding our experience with the Oculentis Mplus IOL [29–31]. To date, there are two different versions of the Lentis Mplus, the LS-312 and the LS-313. The former one was the first to be marketed, and it has a C-loop design), while the latter one has a plate-haptic design (Fig. 35.2).

We evaluated this IOL performance "in vivo" and compared it with a monofocal spherical IOL [29]. We found that the Lentis Mplus LS-312 effectively restored near visual acuity with also very good levels of intermediate vision showing a very good defocus curve (Fig. 35.3). It is intrinsic to this IOL design to induce primary vertical coma, and this could be related with the increased depth of focus found in this group of eyes. However, primary coma, especially in larger amounts, has a very negative impact on visual acuity because it induces optical blur. Furthermore, in this study, the multifocal IOL group had larger amounts of intraocular tilt (Fig. 35.4). This suggested that the Lentis Mplus LS-312 might be tilted and perhaps decentered in the capsular bag in a significant number of cases. We found a strong and significant correlation between IOL tilt and increased primary

Fig. 35.2 C-loop design (LS-312) on the left and plate-haptic design (LS-313) on the right

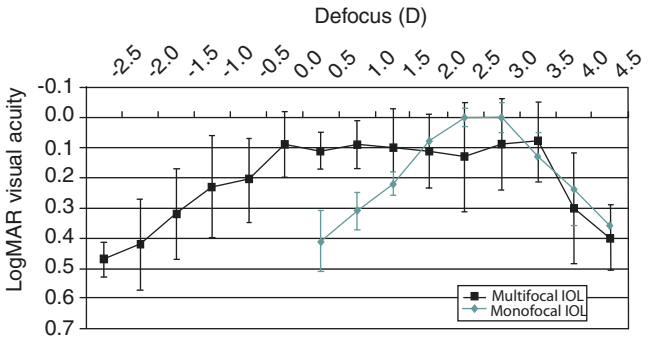

Fig. 35.3 Mean defocus curves (*IOL* intraocular lens)

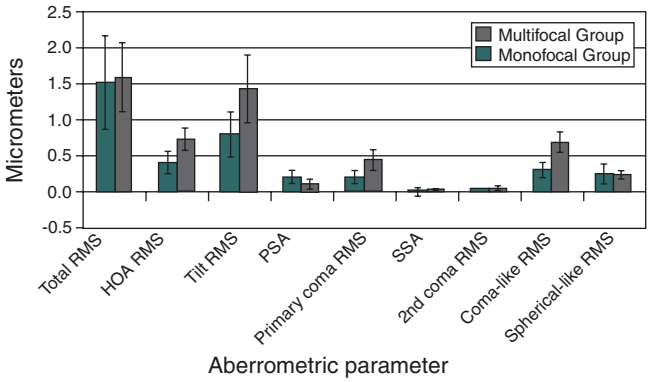

Fig. 35.4 Mean (±SD) postoperative intraocular aberrations with a 5.0 mm pupil (*2nd coma* secondary coma, *HOA* higher-order aberration, *IOL* intraocular lens, *PSA* primary spherical aberration, *RMS* root mean square, *SSA* secondary spherical aberration)

coma. Although, as previously commented, primary coma could have a positive effect on the depth of focus, large amounts of this aberration are due to the IOL tilting causing significant degradation of the retinal image. Therefore, near vision outcomes seemed to be significantly limited by the increase of primary coma in cases of IOL tilt.

Capsular tension rings (CTR) have been shown to inhibit posterior capsule opacification [32], play a role in the stability and positioning of IOLs [33], and prevent IOL movements caused by capsular bag contraction [34–36].

Based on outcomes shown, we decided to conduct another study to ascertain whether the use of a capsular tension ring positively affects the refractive and visual outcomes as well as the intraocular optical quality of eyes implanted with the rotationally asymmetric multifocal Lentis Mplus LS-312 IOL (Oculentis GmbH, Berlin, Germany). We compared two different groups of patients, one group with the Mplus LS-312 plus CTR and the second group implanted without CTR. It was found that refractive predictability and intermediate visual outcomes with the Lentis Mplus LS-312 IOL improved significantly when implanted in combination with a capsular tension ring. However, no significant differences were observed in the optical quality analysis between groups [31].

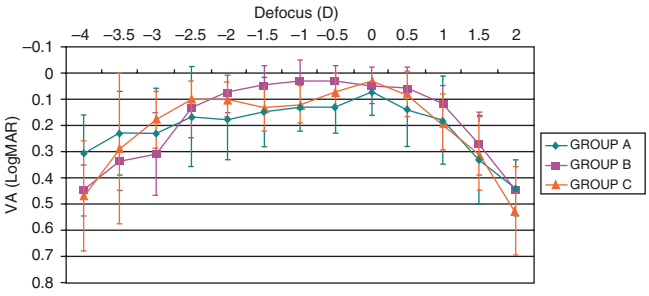

Fig. 35.5 Mean defocus curve in the three groups of eyes analyzed: group A = eyes implanted with the C-Loop haptic design of the refractive rotationally asymmetric multifocal intraocular lens (MIOL) without using a capsular tension ring (CTR) (*green line*); group B = eyes implanted with the C-Loop haptic design of the refractive rotationally asymmetric MIOL using a CTR (*pink line*); and group C = eyes implanted with the plate-haptic design of the refractive rotationally asymmetric MIOL (*orange line*)

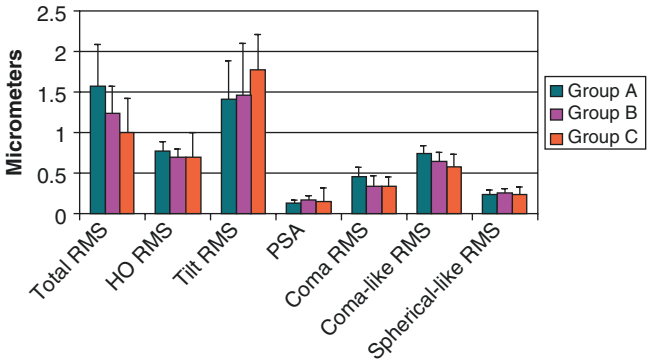

Fig. 35.6 Postoperative intraocular aberrations in the three groups of eyes analyzed: group A = eyes implanted with the C-Loop haptic design of the refractive rotationally asymmetric multifocal intraocular lens (MIOL) without using a capsular tension ring (CTR) (*green bars*); group B = eyes implanted with the C-Loop haptic design of the refractive rotationally asymmetric MIOL using a CTR (*pink bars*); group C eyes implanted with the plate-haptic design of the refractive rotationally asymmetric MIOL (*orange bars*). RMS values (in micrometers) and standard deviation of total, higher-order, tilt, spherical-like, and coma-like aberrations. In addition, the primary spherical aberration is also reported with its sign. *RMS* root mean square, *HO* higher order, *PSA* primary spherical aberration, *SSA* secondary spherical aberration

Due to all these inconveniences, Oculentis GmbH, Berlin, Germany, decided to introduce a new plate-haptic design for the Mplus IOL, the LS-313, in an attempt to achieve a greater IOL stability when the capsular bag contracts. We conducted another study to check whether that purpose was achieved with the new design [30]. Significantly better visual acuities were present in the C-Loop haptic with the CTR group for defocus levels of −2.0, −1.5, −1.0, and −0.50 D ($P = 0.03$) (Fig. 35.5). Statistically significant differences among groups were found in total intraocular root mean square (RMS), high-order intraocular RMS, and intraocular coma-like RMS aberrations ($P = 0.04$), with lower values from the plate-haptic group (Fig. 35.6). However, it

is interesting to notice that when we analyzed the intraocular tilt aberrations, no significant differences between groups were detected. Thus, our findings indicate that it is unclear which IOL haptic design allows more effective control of IOL tilting.

To summarize, IOL tilt due to capsular bag contraction is more prone to occur in lenses made of soft materials especially in combination with C-loop haptics. IOL tilt determines increased high-order optical aberrations; thus poorer optical quality and limited performance are also related to a worse refractive predictability. IOL tilt should be prevented using robust IOL designs resistant to the normally occurring capsular bag scarring.

35.2.4 Inadequate Pupil Size

Postsurgical pupil size is a very important parameter that definitely determines the IOL performance. The main challenge regarding this issue is that it is very difficult to predict the pupil size that will be found after the surgery because it usually changes in comparison with the preoperative measurements. Thus a very small pupil after the surgery will limit near vision performance of most of the multifocal lenses. On the other hand, large postoperative pupils are associated with an increased photic phenomena referred by the patients.

Visual acuity correlates with pupil size, where a larger pupil permits greater use of the multifocal IOL optic with zonal models and improved contrast sensitivity with diffractive models [23, 37].

Management:

- In patients with poor near vision outcomes due to very small pupils, we advocate to use cyclopentolate to enlarge the pupil. If a clear improvement is noticed, the patient may keep using the cyclopentolate as described by other authors [7], or a 360°-argon iridoplasty (0.5 s, 500 mW, and 500 μm) can be planned.
- The other side of the spectrum is comprised by patients with very large pupils who complain of increased photic phenomena. In these cases, brimonidine tartrate 0.2% to decrease mydriasis at night is a classical solution in refractive surgery that has been also recommended by other authors [7, 38, 39]. It decreases the pupil size, thus improving the photic phenomena at night.

35.2.5 Residual Refractive Error

As multifocal IOLs are more sophisticated lenses, they are also more sensitive to any residual refractive error.

Despite new advances in cataract surgery, unsatisfactory visual outcomes as a result of residual refractive errors occasionally occur. In a recent report analyzing refractive data from more than 17,000 eyes after cataract surgery, it was shown that emmetropia was only reached in 55% of eyes planned for that goal [40]. These outcomes highlight that refractive error after cataract surgery is an important issue.

Postoperative refractive errors may be due to different causes, such as inaccuracies in the biometric analysis [41–43], inadequate selection of the IOL power, limitations of the calculation formulas especially in extreme ametropia, or IOL positional errors [44].

Previous studies have shown good efficacy, predictability, and safety for myopic and hyperopic laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) enhancements after cataract surgery [45–51]. Lens-based procedures are also useful alternatives to consider [52, 53]. It should be noticed that some surgeons do not have excimer laser in their centers. Thus, lens procedures become the only possible option in these cases. We have conducted a study aims to present and compare the results assessing the efficacy, predictability, and safety of three different procedures to correct residual refractive error after cataract surgery: LASIK, IOL exchange, and piggyback lens implantation. Although this study only included monofocal IOLs, the outcomes could be extrapolated to multifocal IOLs. The results of this study showed that the three procedures were effective, but LASIK achieved the highest efficacy index, the best predictability with 100% of the eyes within ±1 diopters of final spherical equivalent, and 92.85% of eyes showed a final SE within ±0.50 D (Figs. 35.7 and 35.8). LASIK also showed lower risk of losing lines of corrected vision compared with the other two procedures [54].

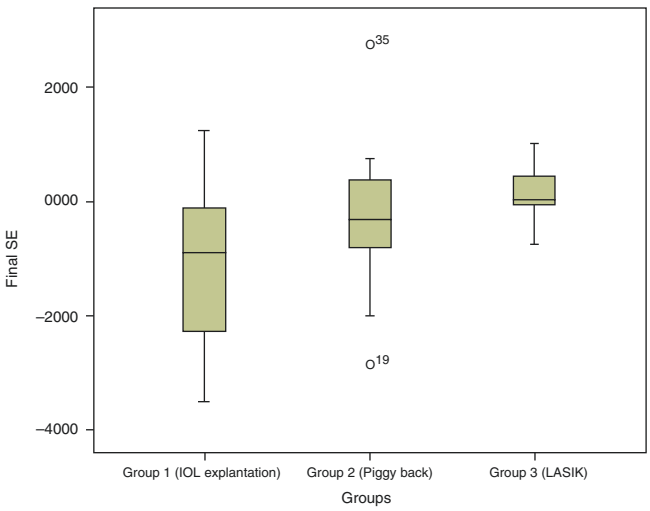

Fig. 35.7 Comparison of the final spherical equivalent (SE) among the three groups. Group 3 (LASIK) achieved the best outcome with the smallest result dispersion

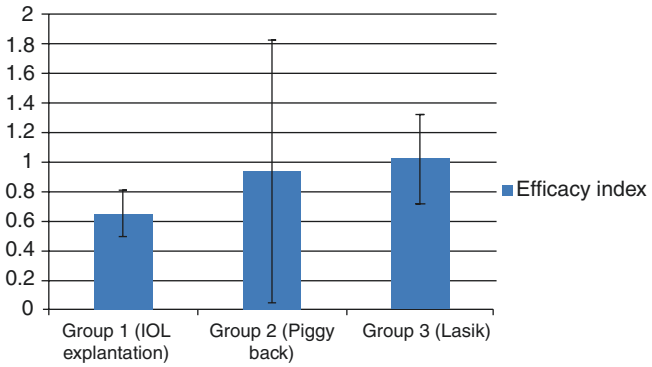

Fig. 35.8 The efficacy index mean and distribution among groups. The highest value was achieved by group 3 (LASIK)

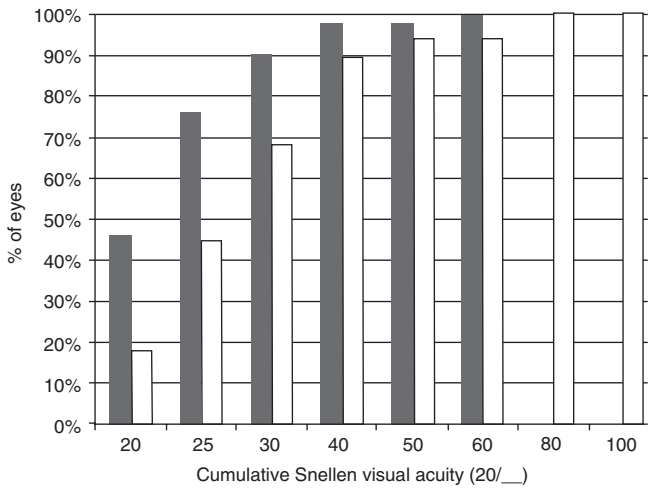

Fig. 35.9 Distribution of postoperative uncorrected distance visual acuity outcomes (UDVA) (*white bars*) compared to preoperative distribution of corrected distance visual acuity (CDVA) (*gray bars*) in the multifocal group (50 eyes). Uncorrected distance visual acuity was 20/40 or better in 90% of eyes and 20/25 or better in 44% of eyes

Regarding laser enhancement after multifocal IOL implantation, some authors have reported improvement in distance vision with limited effect on photic phenomena after PRK re-treatments in patients implanted with refractive multifocal IOLs [46], while others have reported excellent predictability in patients implanted with apodized diffractive/refractive and diffractive IOLs [45, 55].

In another study, we evaluated efficacy, predictability, and safety of LASIK to correct residual refractive errors following cataract surgery, comparing the outcomes of patients implanted with multifocal and monofocal IOLs. We found that laser in situ keratomileusis refinement after cataract surgery with monofocal IOL implantation provides a more accurate refractive outcome than after multifocal IOL implantation. Predictability of LASIK correction is limited in hyperopic eyes implanted with multifocal IOLs (Figs. 35.9, 35.10, 35.11, and 35.12) [51].

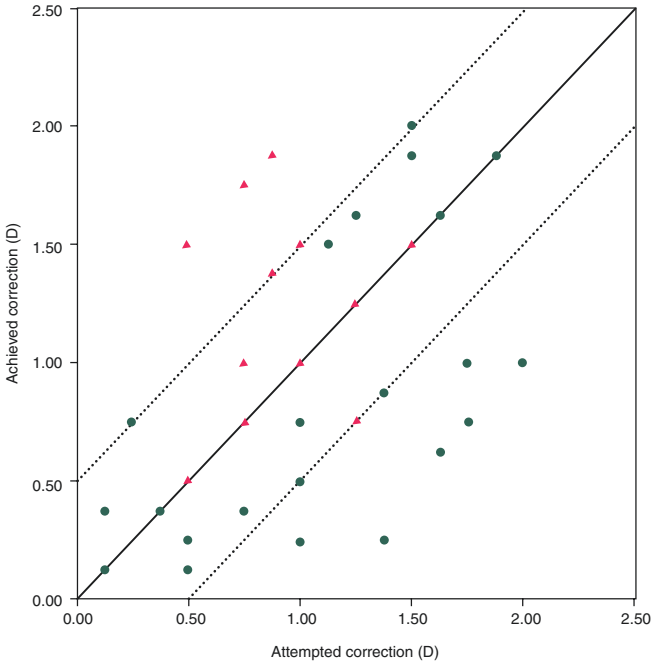

Fig. 35.10 Scattergram of attempted versus achieved correction for the multifocal group (50 eyes). *Green circles* represent hyperopic cases, whereas *red triangles* represent myopic cases. A tendency for undercorrection was noted in eyes that underwent hyperopic LASIK after multifocal IOL implantation. *Dashed lines* represent ±0.50 D from the 1:1 line

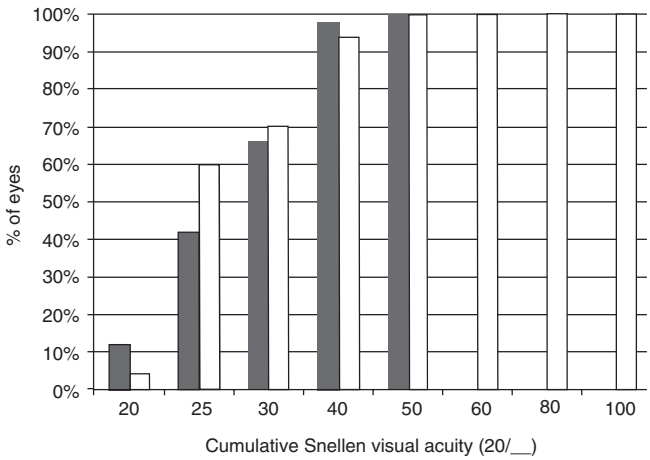

Fig. 35.11 Distribution of postoperative UDVA outcomes (*white bars*) compared to preoperative distribution of CDVA (*gray bars*) in the monofocal group (50 eyes). Uncorrected distance visual acuity was 20/40 or better in 94% of eyes and 20/25 or better in 60% of eyes

In summary, residual refractive error is one of the most common reasons of patient complaints after cataract surgery with multifocal IOL implantation. Hence, it is extremely important to make sure prior to the cataract surgery with multifocal IOL implantation that the patient has normal topography and pachymetry that will permit a laser enhancement in case we need it.

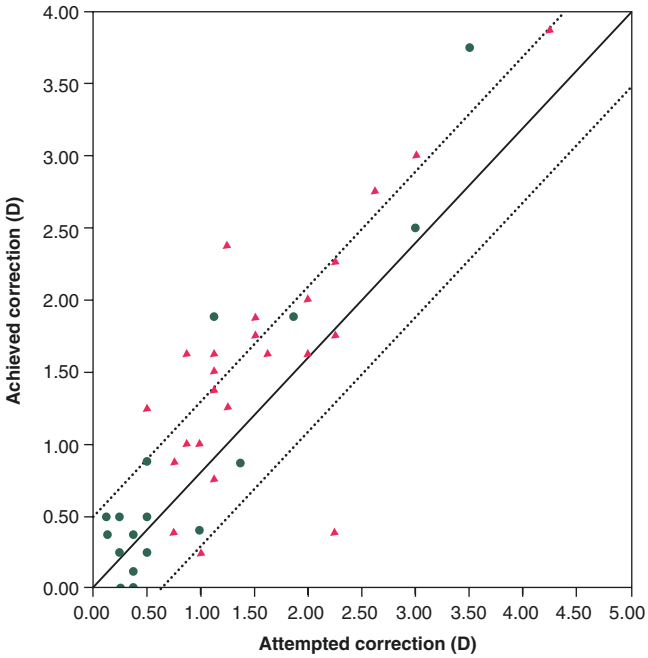

Fig. 35.12 Scattergram of attempted versus achieved correction for eyes from the monofocal group (50 eyes). *Green circles* represent hyperopic cases, whereas *red triangles* represent myopic cases. Predictability was good with almost all the eyes within ±1.00 D of spherical equivalent refraction. The *dashed lines* represent the ±0.50 D range from the 1:1 line

35.2.6 Posterior Capsule Opacification

The most common long-term complication of implanted IOLs is posterior capsule opacification (PCO) [56–58]. Patients with PCO complain of decreased visual acuity, contrast sensitivity, and increased photic phenomena like glare. The treatment is fast and safe using the Nd:YAG laser. However, although rarely, there may be some associated complications like optic IOL damage, intraocular pressure rise, cystoid macular edema, and retinal detachment [59]. Furthermore the procedure has a noticeable economical impact (250 millions of dollars per year in the USA).

A Cochrane Review [60] showed significantly higher PCO rates after hydrogel IOL implantation than after implantation of IOLs of other materials, significantly lower PCO rates with sharp posterior optic edge IOLs than with round-edged IOLs, no difference between 1-piece and 3-piece IOLs, lower PCO rates with IOLs placed in the capsular bag than in the sulcus, and lower PCO rates in eyes with a small capsulorhexis than with a large capsulorhexis.

PCO is especially important in multifocal IOLs because due to more sophisticated designs and higher visual demands, these lenses might be more sensitive to PCO than the monofocal ones. Indeed, in a study comparing the frequency of posterior capsulotomies in patients receiving a multifocal or monofocal intraocular lens (IOL) of a similar design, it was shown that the use of multifocal IOLs in clinical practice may result in more frequent Nd:YAG laser capsulotomies. After the average 22-month postoperative follow-up (range: 2–41 months), 15.49% of eyes in the multifocal group underwent posterior capsulotomies compared to 5.82% of eyes in the monofocal group [61].

The main complaints in patients with multifocal IOLs implanted and PCO are blurred vision and increased photic phenomena [7]. In fact, in this study, blurred vision and photic phenomena were attributed to PCO in 54% and 66% of eyes, respectively.

Other authors have studied the capsulotomy rate after the implantation of different multifocal IOL models to see if there is a difference in this rate related to the IOL material or design. Gauthier L et al., compared a hydrophobic lens (AcrySof ReSTOR) with a hydrophilic IOL (Acri.LISA), and they found that 24 months after surgery the capsulotomy rates were 8.8% in the hydrophobic group and 37.2% in the hydrophilic group ($P < 0.0001$). Eyes in the hydrophilic group had a 4.50-fold (2.28 versus 8.91) higher risk for Nd:YAG laser capsulotomy ($P < 0.0001$) [62].

Management:

It is evident that the best treatment to resolve a PCO is Nd:YAG laser capsulotomy. However, we encourage surgeons to reserve Nd:YAG capsulotomy until all other causes of patient complaints are treated or ruled out. Although IOL exchange is necessary in rare cases, it is significantly more challenging and associated with higher risk of complications when the posterior capsule has been previously opened. Surgeons should be especially aware of patient complaints arising from elements intrinsic to IOL design, which should generate complaints in the immediate postoperative period before PCO formation.

35.2.7 Photic Phenomena and Contrast Sensitivity

In a literature review about multifocal IOL benefits and side effects, photic phenomena were detected as one of the most important drawbacks after multifocal IOL implantation [63]. Halos and glare (Fig. 35.13) are more often reported by patients with a multifocal IOL than with a monofocal IOL [64, 65]. Refractive multifocal IOLs appear to be associated with more photic phenomena than diffractive multifocal IOLs [2]. Photic phenomena are among the most frequent reasons for dissatisfaction after multifocal IOL implantation [7, 8].

Multifocal IOLs are associated with lower contrast sensitivity than monofocal IOLs [2], especially in mesopic conditions [66]. It has been demonstrated that patients with a diffractive multifocal IOL have a relevant reduction in contrast sensitivity as assessed with standard automated

Fig. 35.13 (**a**) Normal image is shown up on the left. (**b**) Image with glare is shown up on the right. (**c**) Down on the left: halos. (**d**) Down on the right: contrast sensitivity loss

perimetry for size III and size V stimuli in comparison with phakic patients and with monofocal implanted patients [67].

An explanation for lower contrast sensitivity could be that multifocal IOLs result in coexisting images, because the light is shared between two (or more) different foci. Therefore, there are two images, one sharp and one out of focus, with the light from the latter reducing the detectability of the former image. Diffractive multifocal IOLs appear to be equal or superior to refractive multifocal IOLs with respect to contrast sensitivity [68–70]. Although contrast sensitivity in individuals with multifocal IOLs is diminished compared with individuals with monofocal IOLs, it is generally within the normal range of contrast in age-matched phakic individuals [37, 66].

Management:

In our opinion, the photic phenomena management starts before the cataract surgery when the multifocal IOL implantation is performed. Preoperative patient education is very important, and patients should be told that they will notice glare and halos after the surgery (because they are inherent to the IOL design), although in most of the cases, the photic phenomena are mild to moderate, and most of the patients get used to it with time (neural adaption process). However, we do not recommend to implant multifocal IOLs in night professional drivers, even more if the patient has a large scotopic pupil size which will increase the perception of halos and glare at night.

When the photic phenomena complaint is very prominent, all the causes that may exacerbate it (previously discussed in this chapter) have to be ruled out.

35.2.8 Dry Eye

Dry eye is a multifactorial disease of the tear film and the ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability.

Dry eye and cataract formation are very common in the elderly population. In addition, cataract surgery can induce dry eye or exacerbate pre-existing disease. The incisions

created during surgery may damage the cornea's neuroarchitecture, reduce corneal sensation, and induce dry eye disease [71]. A study found a significant increase in the incidence of dry eye in patients having cataract surgery [72]. In another study, patients with pre-existing dry eye had decreased tear production and tear breakup time (TBUT) after cataract extraction, leading to ocular discomfort and irritation [73]. Given the inherent importance of the ocular surface and tear film to the quality of vision, dry eye may significantly degrade visual outcomes after multifocal IOL implantation [71].

Postoperative cataract surgery treatment may also play a role in triggering a dry eye or exacerbating a pre-existing one. Therefore, in our opinion, it is mandatory to use preservative-free drops and to avoid very long and unnecessary antibiotic prescriptions.

Management:

Dry eye treatment is not the purpose of this chapter, but as general guidelines we start the treatment by improving the eyelid hygiene and using artificial tears. In more resistant cases, cyclosporine has proven to be a very useful treatment in improving patient symptoms and tear breakup time and decreasing conjunctival staining [71]. Another alternative to consider is to implant punctal plugs, especially in those patients with aqueous deficiency and lack of associated inflammation. We have a very positive experience with the use of PRP (platelet-rich plasma) drops in patients presenting with severe dry eye. We have conducted several studies which show that platelet-rich plasma has very good outcomes in treating dry eye, dry eye after LASIK surgery, corneal ulcer, and even perforated corneas in its solid form [74–78].

35.3 Multifocal IOL Explantation

As previously discussed, IOL explantation is the worst scenario possible after cataract surgery with multifocal IOL implantation, because it may be associated with new complications. Fortunately, it is only needed in very few patients. Several studies show that the rate of multifocal IOL exchange among dissatisfied patients is 0.85% [10], 4% [8], and 7% [7].

In a study analyzing the main reasons for pseudophakic IOL explantation, the failure to neuroadapt in patients with multifocal lenses implanted was the fourth main cause of explantation after IOL dislocation (first cause), refractive error (second cause), and IOL opacification (third cause) [79]. Explantation surgery is always challenging; however, explantation of a multifocal lens is usually easier (especially with a capsular tension ring) than explantation due to other causes. First, because the decision of explantation is made only few months after the cataract surgery, the scarring process has not occurred yet. Second, because the ocular structures are undamaged, therefore, the surgery is less risky. In contrast, when performing IOL explantation due to other causes as dislocation or IOL opacification, the surgery is associated with more complications due to ocular structure damage in the former and the presence of fibrotic tissue in the latter, especially, because in these cases the IOL explantation is performed long time after the original cataract surgery [80, 81].

The main issue about multifocal IOL explantation is if it is worth to do it. Will the satisfaction rate increase after the explantation surgery? Is it associated with a high complication rate? Surprisingly, to date, there are only two papers [82, 83] answering these questions.

In the first publication, Galor et al. [82] retrospectively studied the outcomes after refractive IOL explantation in 12 eyes of 10 dissatisfied patients. The study comprised of refractive IOLs: ReZoom (5 eyes), ReSTOR (4), Crystalens 4.5 (2) and Crystalens 5.0 (1). The main symptoms before surgery were blurry vision, glare/halos, and contrast sensitivity loss. The corrected and uncorrected distance visual acuity (CDVA and UDVA) was 20/30 or better in all the dissatisfied patients. The median time to IOL exchange after the initial cataract surgery was 13.6 months, and the median follow-up after the explantation surgery was 8.9 months. The surgical outcomes were the following: at 6 months UDVA was 20/30 or better in 4 eyes and 20/60 or better in 8 eyes. Meanwhile, the CDVA at 6 months was 20/20 or better in 8 eyes and 20/25 or better in 9 eyes. Regarding the surgical complications, 1 eye had corneal decompensation, 1 eye had IOL dislocation needing another surgery to perform IOL sclera fixation, and 1 eye had steroid response with elevated IOP. The aim of the surgery was achieved in 8 patients as they noticed an improvement of their symptoms, while the other 2 patients did not experience any change.

We can extract some conclusions from this paper. First, the symptoms leading to the explantation surgery were improved in most of the patients (8 of 10). Second, there was a refractive worsening after the exchange surgery: prior to the surgery, all the eyes had UDVA of 20/30 or better, while in contrast, only 4 eyes achieved this result after the IOL exchange surgery. Third, in 2 eyes there were severe complications such as corneal decompensation and IOL dislocation, requiring scleral suturing, having steroid response with elevated IOP, and cystoid macular edema in the postoperative course.

The other publication is a more larger one. Kamiya et al. [83] is included 50 eyes that required multifocal IOL explantation. Of the explanted multifocal IOLs, 84% were diffractive and 16% were refractive. Monofocal IOLs accounted for 90% of the new implanted IOLs. The most common

complaints before the explantation surgery were waxy vision (58%), followed by glare and halos (30%), blurred vision at far (24%), dysphotopsia (20%), blurred vision at near (18%), and blurred vision at intermediate (6%).

The main objective reasons for explantation were decreased contrast sensitivity (36%), photic phenomena (34%), unknown origin including neuroadaption failure (32%), and incorrect lens power (20%).

Patient satisfaction for overall quality of vision was graded on a scale of 1 (very dissatisfied) to 5 (very satisfied). After the IOL exchange surgery, patient satisfaction was significantly increased from 1.22 ± 0.55 preoperatively to 3.78 ± 0.98.

The LogMAR mean preoperative UDVA and CDVA were 0.23 ± 0.27 and −0.01 ± 0.16, respectively. Before the explantation surgery, 30% and 68% of the patients had a UDVA and CDVA of 20/20 or better, respectively. The visual outcomes after the explantation surgery showed that 42% and 86% of eyes achieved UDVA and CDVA of 20/20 or better.

Contrast sensitivity function also significantly improved after the IOL exchange surgery. The authors state that CDVA is not always a good measure of patient symptoms. In this study, despite of visual complaints, CDVA was 20/20 or better in almost 70% of the eyes. Therefore, more specific tests, such as contrast sensitivity measurement, are needed especially in those cases with excellent CDVA.

Regarding complications, anterior vitrectomy was necessary in three cases (6%). The IOL was placed in the bag in 38 eyes (76%), out of the bag in the sulcus in 11 eyes (22%), and sulcus placement with scleral suture in 1 more eye (2%).

In conclusion, this paper shows that multifocal IOL explantation in dissatisfied patients is a feasible option that significantly improved patient satisfaction. It emphasizes the importance of performing specific tests for the accurate assessment of the visual function especially in patients with good visual acuity who complain of poor vision. Decreased contrast sensitivity was found in most of these cases.

However, it is important to keep in mind that IOL exchange is not exempted from complications. In this series, the IOL had to be placed in the ciliary sulcus in 24% of the cases, and anterior vitrectomy was performed in 6% of the eyes.

IOL explantation techniques:

There are many explantation techniques described in the literature [84–92]. In recent years, the interest has focused explanting IOLs through small incisions (2.2–2.65 mm) in order to avoid astigmatism induction, thus improving the predictability associated to the exchange procedure.

Explantation techniques can be divided into four different types:

1. Whole lens removal. It is not currently used because wound enlargement is needed. It is only used in marginal cases of rigid PMMA pseudophakic IOL. However, there is a publication about a surgical technique of explanting a single-piece acrylic hydrophobic lens through a 2.75 mm incision without cutting or folding, just pulling the lens out with toothed forceps [93].
2. Intraocular lens cutting. Intraocular lens cuts are performed inside the eye in order to remove the lens through a small corneal incision. This can be done in many different ways: by bisecting the lens [84], partial bisection [85, 86], trisecting it [91], sectorial bisection [92], or by multiple cuts [90].
3. Intraocular lens haptic cutting. The haptics may be cut prior to the surgery with a YAG laser [89] or at the time of surgery with scissors [88], thus facilitating the removal of the optic. When the degree of fibrosis is so high that it is not possible to release the haptics without taking risks, it is preferable to leave the haptics in place.
4. Intraocular lens refolding. The IOL is folded in the anterior chamber and afterward explanted through a minimally enlarged incision [87]. However, this technique involves extensive manipulation and may cause more damage to clear corneal incisions and a 25% reduction in the endothelial cell count.

In summary, the implantation of multifocal intraocular lenses (MfIOLs) has increased in the last few years as a treatment of pseudophakic presbyopia [94]. After MfIOLs implantation, the vast majority of patients are happy and satisfied and do not need spectacles or contact lenses as visual aids after the operation. However, complications sometimes happen that influence the quality of life and the level of patient's satisfaction. The common symptoms of dissatisfaction with multifocal lenses are blurred vision and photic phenomena associated with residual ametropia, posterior capsule opacification (PCO), large pupil size, wavefront anomalies, dry eye, and IOL decentration. The main reasons for pseudophakic IOL explantation are the failure to neuroadapt, IOL dislocation, residual refractive error, and IOL opacification. To avoid patient dissatisfaction after MfIOLs implantation, it is important to consider the following recommendations in the preoperative visit: patient characteristics, styles, exhaustive preoperative examination, and biometry, topography, and pupil reactivity. It is very important to explain to the patient the visual expectation and possible postoperative complications and solutions.

Take-Home Pearls

- Overall, patient satisfaction after multifocal IOL implantation is higher than that achieved with monofocal IOLs.
- Adequate patient selection is essential in order to have a satisfied patient after the surgery.
- The most common complaints of dissatisfied patients are blurred vision and photic phenomena.

- Most of the times, these complaint are due to residual refractive error, posterior capsule opacification, and dry eye. Therefore, these unwanted situations may be easily managed avoiding IOL explantation.
- Some other causes such as IOL tilting or IOL decentration are less common.
- Posterior YAG capsulotomy should only be performed when the posterior capsule opacification is evident. In the case of IOL explantation, the rate of complications is higher in those patients with previous capsulotomy.
- With modern multifocal IOLs, explantation is only needed in very few patients.

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Refractive Surprise After Cataract Following Corneal Refractive Surgery

36

Béatrice Cochener and Jean Louis Arne

Core Messages

Refractive surprises after cataract post-corneal surgeries:

- Refractive surprises after cataract post-corneal surgeries are mostly related to curvature changes induced by corneal refractive surgeries.
- Refractive surprises after cataract post-corneal surgeries appear as hyperopic shifts
- <3 D may be resolved in 1–3 months; >3 D suggests an IOL calculation error, exchange.
- Progressive myopia or astigmatism can show a secondary ectasia.
- The quality of vision can be altered by an increase in spherical aberrations (addition of asphericity loss after photoablation + spherical lens implantation).

Population ageing and increase in visual needs will lead to increased surgical cataracts. This evolution will undoubtedly be observed in patients who have undergone refractive surgery in the past. Indeed, those patients used to emmetropia and satisfied by the removal of glasses could very early detect visual changes induced by the beginning of lenticular opacification. Furthermore, they will require cataract surgery to avoid a return to glasses. In other words, we will have to manage more demanding patients by less predictable surgery.

However, difficulties in intraocular lens (IOL) power calculations represent one major limitation of cataract surgery following previous corneal refractive surgery, essentially related to corneal curvature and asphericity changes. This could lead to postoperative refractive and visual surprises that require delicate enhancement procedures for inadequate outcomes [1–4].

These complications justify an adjustment of calculation formulas, integrating keratometry and refractive changes induced by the initial corneal surgery [5–8]. This chapter will focus on photoablative surgeries.

A review of these unexpected results after pseudophakic IOL implantation following corneal refractive surgery will be described as well as the therapeutic solutions that have been proposed for their correction. Various modified methods for IOL calculations, their principles, interests and limitations will be discussed.

36.1 Surprises After Cataract Surgery Following Corneal Refractive Surgeries

They can be essentially summarized to an inadequate calculation of the IOL, especially if this were based on keratometry data secondary to photoablation. Note that after phakic implantation, measurements such as axial length can be modified by the intraocular lens. It is recommended to archive preoperative information of the virgin eyes in order to facilitate IOL calculation.

36.1.1 Hyperopic Shift

A hyperopic shift commonly complicates incisional corneal surgery (cf. chapter on radial keratotomy) and photoablation for myopia. Concerning RK, surgery causes oedema surrounding the incisions that regularly induce a transitory hyperopia (around +3 dioptres) spontaneously resolved in 1–3 months. This potential favourable evolution suggests not surgically correcting this secondary ametropia.

Adversely, when hyperopia is superior to a + 3 dioptre level, an IOL calculation error can be suspected that could be associated with this corneal response. The same assumption

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of an inadequate implant calculation can be made when a hyperopic shift is noted after a cataract surgery following excimer surface photoablation or a LASIK.

This ametropia is particularly difficult to tolerate in an initially myopic patient who became hyperopic with discomfort in far and near vision. Therefore, such patients will ask for an improvement and will be reluctant to glasses, especially multifocal, which they were not used to before the surgery.

36.1.2 Myopic Shift

Its occurrence is rare, but it would be easier to manage myopia than hyperopia. Theoretically it could appear after a surgery for hyperopia with an overestimation of keratometry.

A secondary ectasia should be eliminated in case of progressive myopia that would be often associated to a loss in the best corrected visual acuity and irregular induced astigmatism.

36.1.3 Induced Astigmatism

This complication can be reported after any cataract surgery and can result from the incision procedure. The risk of postoperative astigmatism was considerably reduced by the advent of mini- and micro-incisions. Nevertheless, it may potentially increase the size of the preoperative cylinder if the size and the site of incision had not been correctly adapted.

However, because mechanical integrity is better preserved in photoablation compared to corneal incisions, the occurrence of irregular astigmatism is very uncommon.

In long-term corneal surgery, the occurrence of a progressive astigmatism should be suspected to announce a secondary ectasia, even more specifically than a progressive postoperative myopia.

36.1.4 Decentration

Photoablation, whatever the profile (including the use of scanning beam and wavefront custom treatment), is responsible for edging effects. However, this effect has been decreased by the creation of progressive transitional edges, enlargement in the optical zone and introduction of the transition zone.

The crucial role of good laser centration on visual results is perfectly demonstrated and has justified the development of options such as cyclotorsion and pupil shift compensation.

At the intraocular implantation stage, the adequate positioning of the lens in terms of centration and tilt admittedly plays a major role in the quality of vision. If positioning/centration are not perfect, a conflict appears between the ablation area and the IOL, inducing a degradation in qualitative vision with halos, glare, diplopia and an increase in high-order aberrations.

36.1.5 Alteration of Vision Quality

Alteration of the quality of vision can be induced by all the complications previously described. The addition of an intraocular lens behind a cornea whose physiologic curvatures have been surgically modified systematically causes changes in optical properties. These degradations are sources of functional symptoms and increases in high-order aberrations.

Before the advent of wavefront sensors, many inadequate outcomes were unexplained because of limitations of available measurement concepts. First, geometrical optics provide only the pure spherocylindrical refraction and are based on the Gaussian assumption that the eye can be simplified to a convergent dioptre. This concept appears too approximate in cases of a non-perfect optical system, such as in an eye modified by surgery. Furthermore, the measurement is paraxial, centrated and static (does not integrate the effects of pupil dilation). Videotopography is considered (whichever Placido or elevation system), if it can assess toricity and symmetry and more recently quantify asphericity; none of the available devices can access the periphery of the cornea for a true three-dimensional evaluation and a real-time measurement. However the topography will confirm the corneal origin of the astigmatism that is the key criteria for its surgical correction. The value of the cylinder should be correlated to other measurements of astigmatism in axis and amplitude to allow surgery.

Elaboration of aspherical ablation profiles would help to preserve natural characteristics of the cornea. These adjustments should contribute to minimize the impact on the quality of vision. The new design of aspherical IOLs has the same goal and is based on two concepts: a lens with negative spherical aberrations (in order to compensate positive spherical aberrations of the cornea) and a lens free of aberration. The choice of an aspherical IOL after corneal refractive surgery would be, at that date, the second model, since the photoablation has changed the corneal profile resulting in an increase in positive spherical aberration in case of hyperopic correction and in the adverse event for myopic treatment. Therefore, we would first try not to increase high-order aberrations in using an implant with neutral effects on spherical aberrations.

36.2 Management of Refractive Complications Following Cataract Surgery After Corneal Surgery

36.2.1 Optical Equipment

Adaptation of glasses represents the most common and safe solution to correct imperfect visual results after cataract extraction. When we consider that visual recovery in that specific surgical condition takes time (1–3 months), the option of glasses offers the advantages of safety and

adjustability. However, if the residual ametropia is responsible for anisometropia, glasses may not be tolerated by the patient. In the case of irregular astigmatism, an adjustment of contact lenses could be recommended in order to optimize visual performances. This contact lens adaptation is easier to conduct after photoablation than after radial keratectomy but requires specific experience from the physician. Scleral contact lenses represent the last evolution and offer the chance to compensate high irregularities with an optimized tolerance for the patient.

36.2.2 Lens Exchange

This option is the most commonly discussed since the most frequent complication is hyperopic shift resulting from an IOL calculation error. Patience is required from the patient for at least 2 weeks in order to control the stability of induced ametropia, despite an unusual regression compared to radial keratectomy. Over three dioptres can be discussed for a high-power lens exchange (based on the addition of the residual hyperopic value to the initial IOL power).

The need for an IOL exchange became very rare thanks to a better approach of intraocular lens calculation issued from refined formulas, and an increase in surgical experience. Nevertheless it appears crucial to inform the patient of this eventuality. Furthermore, preoperative keratometry and refractive data should be provided to patients who underwent corneal refractive surgery in order to facilitate IOL calculations and to decrease the occurrence of this complication.

Care and caution are required for the selection of the IOL which should be easy to manipulate and remove. Moreover, when an exchange is required, it should be performed early for safer mobilization in the capsular bag.

36.2.3 Photoablation

A complementary photoablation can be justified in the case of low spherical and/or cylindrical refractive error. That could consist of excimer correction by PRK or under a LASIK flap (newly created or relifted). The choice of the technique will depend on the initial method, on the type of ametropia and on the surgeons conviction.

A particular vigilance is required for the eye-tracker connection because it may be disturbed by the reflect others lens. The presence of an intraocular lens may also make the aberrometry measurement difficult (even impossible in cases of high irregular astigmatism after radial keratectomy). However, when this one is accessible, it is interesting to perform a custom ablation to improve quality of vision. But the best option for management of irregular astigmatism nowadays is represented by the topography-guided photoablation that will reshape and smoothen the cornea based on an elevation map.

In all cases, especially secondary hyperopia, it is necessary to maintain an optical zone as large as possible in order to minimize functional symptoms resulting from the superposition of different successive surgeries.

36.2.4 Incisions

For surgeons experienced in incisional surgical techniques, it is common to perform incisions at the same stage of phacoemulsification; arcuate incisions on the axis of the meridian flatten it for the correction of preoperative astigmatism.

The efficacy of this one single-step technique depends on the surgical expertise and is limited by the unpredictability of the postoperative refraction, as has already been underlined. It could appear logical to discuss a two-step correction, with the adjustment of incisions according to the refraction after cataract surgery. But, as we know that persistent refractive errors are mostly hyperopic, incisions will be rarely indicated. The introduction of the femtosecond laser increased interest for incisional surgery, whether it is femtocataract or corneal femtosecond laser.

36.2.5 Piggyback

This method corresponds to a secondary implantation of an IOL in the sulcus in front of an intraocular lens previously placed in the bag. The initial lens provides an incomplete correction, resulting in residual ametropia that defines the value of the secondary IOL (with an addition of around 20%) [9, 10].

The second lens will be chosen with the same biomaterial as the first one. Its design has to be compatible with positioning in the sulcus, which means associating rigid haptics in a three-piece model to correct centration and stability. Particular care will be brought to the interface between the two intraocular lenses, in order to prevent cell ingrowth that would be the source of transparency and vision alteration.

Different concepts have been developed with a specific design adjusted to the sulcus positioning (enlarged diameter of 14 mm, round edges, concave posterior surface and convex anterior surface). These piggyback IOLs (Sulcoflex©, AddOn©, Reverso©) are available in monofocal version with or without toricity and even in multifocal version with or without toricity. All of them are foldable and can be implanted through an incision of 2.8–3.2 mm. They can correct a remaining refractive error after cataract surgery to decrease anisometropia or even to compensate the loss of accommodation using the multifocal model. In that case the key issue is the unguarantee of a perfect centration because of the lack

of accuracy for the measurement from sulcus to sulcus space. Special indications such as traumatic or congenital unilateral surgery can be underlined.

36.2.6 Perspectives: Multifocal Intraocular Lenses? Toric?

High difficulties in IOL calculation in cataract extraction after corneal refractive surgery make the use of multifocal lenses very delicate. Despite convincing results achieved with the new generation of diffractive IOLs, they could result, in that specific context, in under- or overcorrections. But first of all, in induced optical aberrations related to the conflict between traces of the previous surgery (limit of a LASIK, ablation PRK bed, corneal incision, etc.) and multiple zones of the lens, they can be very difficult to tolerate. This may lead to a major alteration in the quality of vision untenable for the operated patient suffering from halos, glare, dysphotopsia, poor visual performances, and loss in contrast sensitivity, etc. However, the option for multifocal IOLs after refractive surgery has been demonstrated to be valuable in well-selected patients in terms of corneal regularity, normal retina and reasonable level of expectations.

Among currently available concepts, the elective choice should consider the new aspherical profile in order not to add to these multioperated eyes and high-order aberrations which are difficult to quantify and neutralize. It has been demonstrated that corneas that had a photoablation have increased (in case of myopic correction) or reversed (in case of hyperopic correction) preoperative positive spherical aberrations. Whatever the ablation profile, these induced changes presume that aspherical IOLs with negative spherical aberrations would partially compensate or in the adverse event increase initial corneal spherical aberrations.

We can guess that the ideal IOL could one day be customized to the eye. This would be an interesting method to compensate for corneal aberrations, especially for those corneas which have received refractive surgery in the past [11–21].

36.3 Prevention of Surprises: An Adjusted Implant Calculation

In an eye that underwent refractive surgery, miscalculation of intraocular lens (IOL) power frequently occurs, leading to hyperopia after myopic surgery and to myopia after hyperopic surgery [22, 23]. In addition, we have learned that emmetropia is the target to achieve for multifocal implantation.

A significant hyperopic result after cataract surgery in eyes that had previous radial keratotomy (RK) has been reported when the IOL power was calculated using corneal power obtained by manual keratometry [24, 25].

IOL lens power calculation depends on the axial lens (AL), anterior chamber depth (ACD) and keratometry readings:

- Studies of axial length changes after corneal refractive surgeries have shown no significant changes [26]. With few exceptions (corneal rings) ACD is not changed after corneal refractive surgery.

Factors leading to errors are:

- Inaccurate estimation of corneal power
- Use of an inappropriate IOL power calculation formula [27]

Corneal refractive surgery produces an abnormally shaped cornea. The centre of the cornea becomes flatter than the peripheral cornea after refractive surgery for myopia. Manual keratometry measures 2 points approximately 3.0 mm apart. If these points are measured outside the flatter central area, the manual keratometer reads values that are steeper [28, 29].

Current instruments measure the anterior corneal radius of curvature (Ra) by measuring the reflected images of the projected mires. The posterior radius of curvature is not assessed but is compensated for by the use of a modified (effective) index of refraction. The keratometric dioptres are derived from the anterior radius of curvature using an effective refractive index (n) in the paraxial formula:

Keratometric power $(D) = (n - 1)/Ra$

However, this effective refractive index is valid only if the proportion between the radius of the anterior and posterior surfaces of the cornea resembles that of a model eye.

Following RK, both the anterior and posterior corneal surfaces undergo a relatively proportional flattening, and the relationship between them is not changed. The central cornea flattens more than the paracentral transition (knee) zone, which leads to an overestimate of the curvature of the central flat optical zone.

Following PRK or LASIK, if the treatment zone is large, the anterior radius of curvature measurement can still be accurate because the transition area is far outside the 2.6–3 mm measured zone. In this instance, the lack of accuracy in K readings results from disruption between the anterior and posterior corneal surface curvature, where the anterior corneal surface flattens, while the posterior surface curvature remains unchanged. Therefore, the use of an effective index of refraction, which was generated in normal corneas, does not compensate correctly for the posterior corneal surface power, which results in inaccurate K readings [23, 30].

Another problem is that it is impossible to accurately quantify the discrepancy between measured corneal power

change and refractive change to determine a correction factor that could derive true evaluations from the measured corneal power.

There are two ways of correcting the variance when calculating the IOL power. The first involves the development of a method that accurately estimates corneal power and the second the development of a more appropriate formula.

36.4 Estimation of Corneal Power After Corneal Refractive Surgery [31]

- Standard office keratometers estimate central corneal power. The problem is that the reflected ring of the keratometer measures the cornea at approximately the 3 mm diameter zone which is often a steeper area after myopic surgery than the flatter optical centre (vice versa after hyperopic surgery).
- Another method is measuring the corneal power within 3.0 mm of the centre of the cornea using a videokeratometer. Corneal topography measures more than 1000 points in the central 3.0 mm zone, while conventional keratometry only measures 2 points located 3.2 mm and 2.6 mm from the corneal centre. Simulated keratotopographic reading (Sim-K) values seem the most accurate among measured keratometric power [32]. However it is often admitted that the central corneal power should be used with topography as it gives a more reliable central power measurement than the stimulated keratometry value after refractive surgery.

  It has often been noted that videokeratography-derived keratometry values are inaccurate in the eyes with abnormal or surgically altered corneal surfaces.

  Sonego-Krone et al. [33] think that Orbscan II total mean and total optical power maps accurately assess the corneal power after myopic LASIK, independent of preoperative data or correcting factors improving IOL calculation.
- As a general rule, with all the techniques, it is safer to use a smaller value to prevent a hyperopic shift after surgery for myopia and a larger value after hyperopic surgery. To avoid underestimation of intraocular lens power after surgery for myopia, the measured corneal power must be corrected. There are no universal and absolutely reliable methods, but many surgeons subtract 1 dioptre from the measured value.

  After surgery for hyperopia, the measured value must be increased.
- The hard contact lens method, introduced by Holladay [34], is based on determining the difference between the manifest refraction with and without a rigid "plane" contact trial lens of a known base curve. An unchanged refraction indicates that the tear lens between the cornea and contact lens has zero power and that the effective anterior corneal radius is equal to the posterior radius (base curve) of the trial lens. If a myopic shift in refraction occurs with the contact lens, the base curve is steeper (i.e. the tear lens forms a plus lens) and vice versa. The idea is to determine the corneal radius by finding the trial lens that does not change the refraction with and without contact lenses and then read the power from the contact lens.

  This method takes a relatively long time. It cannot be used if visual acuity is too low because of the lens opacity. It is widely used after RK but has not been validated for use after PRK or LASIK. Dense cataracts may give rise to a false refraction.

  Case example, hard contact lens method:

- Plane hard contact lens curvature 40.5 D
- S.E. (corneal plane vertex 12.5 mm) without contact lens: 0.5 D
- S.E. with contact lens

  → Unchanged refraction:

  Mean corneal power = [40.5 + 0 (−0.5) − (0.5)] = 40.5

  →S.E. = − 1 D:

  Mean corneal power = [40.5 + 0 + (−1) − (0.5)] = 40

  → S.E. = + 1 D:

  Mean corneal power = [40.5 + 0 + (+1) − (−0.5)] = 42
- Clinical history method [34, 35]: postoperative corneal power is obtained by subtracting the refractive change (calculated at the corneal plane using a standard vertex distance of 12.0 mm) induced by surgery from the preoperative keratometry readings in myopic eyes. The refractive change must be determined once refraction has been stabilized after corneal surgery by subtracting the postoperative from the preoperative spherical equivalent refraction, but both must be corrected by the vertex distance to the plane of the cornea. These values can be calculated with the following formula: Rc= Rs + (1-vRs) where Rc = power (D) at the corneal plane, Rs = power (D) at vertex (v) distance, and V = vertex distance (metres); a vertex distance of 0.012 m is often assumed. However myopia induced by the opacification of the crystalline lens is an important factor of error.

  Case example, clinical history method:

* Preoperative keratotomy	44 D
* Preoperative refraction	−7 D
* Postoperative refraction	−2 D
* Change in S.E.	(−7)–(−2) = −5 D
– Calculated keratometry for determination of IOL power	44–5 = 39 D

- Refraction-derived corrected keratometric value (Kc-rd): according to this method, which Shammas [15] derived from the clinical history method, the corneal power is the result of the formula Kc-rd = Kpost (−0.25 × CRc), where Kpost is the actual keratometry reading and CRc is the amount of myopia corrected at the corneal plane.
- Clinically derived corrected keratometric value (Kc-cd): this method (also developed by Shammas from the historical method) calculates the corneal power by means of the following equation, Kc-cd = 1.14 Kpost–6.8, where Kpost is the actual keratometry reading [36].
- Correction factor method by ROSA et al. [37]: the postoperative radius, as measured by videokeratography, is multiplied by a correcting factor that varies between 1.01 and 1.22 according to the axial length of the eye.
- Theoretical variable refractive index (TRI) as proposed by Ferrara et al. [38]: the change in the corneal refractive index after excimer laser surgery is correlated to the axial length. Such correlation is expressed by the formula: TRI = −0.0006 × (AL × AL) + 0.0213 × AL + 1.1572 where AL is axial length. Corneal power (P) can be calculated using the formula:

$$P = (TRI - 1)/r$$

where r is the corneal curvature in metres.

- Separate consideration of anterior and posterior corneal curvature: this method is based on the assumption that the total corneal refractive power of the cornea (P) can be calculated by adding the power of the anterior (Pa) and posterior (Pp) corneal surfaces [39]:

$$P = Pa + Pp = (n2 - n1)/r1 + (n3 - n2)/r2$$

where n1 is the refractive index of air (−1)
n2 is the refractive index of the cornea (1.376)
n3 is the refractive index of the aqueous humour (1.336)

Both preoperatively and postoperatively, the power of the anterior corneal surface (Pa) can be obtained by multiplying the videokeratographic corneal power by 1.114 (corresponding to 376/337.5) [40].

Hence, $Pp = Pa - P = (Sim - K \times 1.114) - Sim - K$

To measure the total corneal power after excimer laser surgery, there are two options:

- If the preoperative videokeratographic power is available and thus the posterior corneal surface can be calculated, the postoperative power of the anterior corneal surface may be added to the power of the posterior corneal surface (which is assumed not to be significantly altered by surgery) as expressed by the formula P = postop Pa + Pp = postop Sim-K × 1.114 + (preop Sim-K × 1.114–preop Sim-K).
- If the preoperative videokeratographic power is not available, thus precluding calculation of the posterior corneal surface power, the latter is substituted by a mean value 4.98. The resulting formula is P = postop Pa + Pp = postop Sim-K × 1.114–4.98 [41].

36.5 Methods to Calculate IOL Power

The list of methods for IOL calculations after refractive surgery is long and growing (Table 36.1).

- The Feiz-Mannis vertex IOL power method [42]: the IOL power for emmetropia is based on pre-LASIK keratometry values. The SE change resulting from LASIK is then used to modify the IOL power, assuming 1.0 D of change in IOL produces only 0.7 D change in refraction at the spectacle plane. This is based on the IOL position behind the iris and a vertex distance of 12.0–13.0 mm. This method produces higher IOL powers after myopic LASIK and lower IOL powers after hyperopic LASIK. Furthermore, the higher the amount of treatment, the more inaccurate the traditional keratometry readings. Based on these results, the authors created a nomogram using linear regression analysis as a basis.
- Errors often occur when calculating IOL powers using the SRK/T formula.
  The reason for residual hyperopia is incorrect effective lens position (ELP) estimation calculated by third-generation theoretical formulas in which the postrefractive surgery K value is used. This usually short value

Table 36.1 Methods for lens power calculation

Methods requiring prerefractive surgery data
Double-K VKG
Double-K clinical history
Single-K refraction-derived method
Feiz-Mannis formula
Double-K based on separate consideration of anterior and posterior corneal curvatures (with preoperative data)
Latkany's regression formula
Feiz-Mannis monogram
Walter method
Masket formula
Methods not requiring prerefractive surgery data
Single-K clinically derived method
Rosa's single-K method
Ferrara's single-K method
Double-K based on separate consideration of anterior and posterior corneal curvatures (without preoperative data)
Mackool method
Ianchulev method

underestimates the ELP and IOL power after surgery for myopia resulting in a hyperopia.
  - Aramberri [43] modified the SRK/T formula to use the prerefractive surgery K value (Kpre) for the ELP calculation and the postrefractive surgery K value for IOL power calculation by the vergence formula.
  - The Kpre value is obtained by keratometry or topography and the Kpost by the clinical history method, once the refraction stabilized. This value is converted to the corneal plane and substrated from Kpre.
  - Rosa [37] et al. tried to calculate IOL power in cases where prerefractive surgery data are not available by adjusting the corneal radius based on the axial eye length.
  - Latkany et al. [44] described regression formulas based on both the average and flattest postrefractive surgery keratometric readings when prerefractive surgery data are not available.

They describe two methods:

1. Calculation of IOL power using mean keratometry readings obtained using the Javal keratometer and modifying it by –0.46× + 0.21, where x equals the surgically induced change in refraction.
2. Calculation of IOL power using the flat K modified by –0.47× + 0.85.
   - Presented at the ASCRS convention of March 2006, the BEESt formula developed by Borasio and Stevens is based on an improved version of the Gaussian optics formula for paraxial imagery. This method requires measurement of the anterior and posterior corneal radii and central corneal thickness, which are taken from the Oculus Pentacam [45].

Methods were described to calculate IOL power after refractive surgery without using the inaccuracies of the post-LASIK corneal power.

- Walter et al. [46] assumed the patient never had myopic LASIK to calculate IOL power and then targeted the IOL at the pre-LASIK amount of myopia. The pre-LASIK keratometry values, pre-LASIK manifest refraction and the current axial length are placed in the Holladay formula by passing the post-LASIK corneal power.
- In Masket's formula [17], one calculates IOL power in a standard fashion and simply modifies the final value of the IOL as a function of the LASIK-induced refractive change. An advantage of this method is that there is less reliance on historical data as the LASIK-induced change is multiplied by 0.323. Therefore, if there is a 1 dioptre error in the historical data regarding the refractive change, this translates to only a 0.32 dioptre error in IOL selection.
- Ianchulev et al. [47] used an intraoperative autorefractive retinoscopy to obtain aphakic autorefraction and measured the aphakic spherical equivalent before lens implantation.
- Mackool et al. [48] described a technique in which the cataract is removed without IOL implantation. Approximately 30 min later, manifest aphakic refraction is performed. The calculation of the IOL power is obtained using a specific algorithm. The patient then returns to the operating room for lens implantation.

36.6 Specific Problems

In case of cataract surgery after radial keratotomy, all eyes experience an initial hyperopic shift caused by early postoperative corneal flattening due to stromal oedema [49].

Corneal oedema normally resolves within a few weeks after cataract surgery. A significant amount of hyperopic error will also regress, and it is suggested to wait at least 3 months before performing IOL exchange. However, a larger hyperopic error does not totally regress, and the IOL exchange must be done earlier. The benefit of performing secondary surgery earlier is that the same incision can be used, and lens replacement is easier. The disadvantage is that accurate IOL power selection is difficult because the corneal curvature and power are still unstable [50].

What should the clinician do when faced with the daunting problem of postrefractive surgery IOL power calculation after excimer corneal refractive surgery [51]?

To evaluate the corneal power, it is recommended to choose the lowest value after myopic surgery and the highest after hyperopic surgery.

For the IOL power calculation, the surgeon must use several approaches and look for values that are consistent with at least one other reading [52–55].

Patients should be informed that the accuracy of these methods to calculate the IOL power after refractive surgery has not yet been validated and that an exchange of the IOL or other interventions may be necessary.

Take-Home Pearls

Management of refractive surprises after cataract post-corneal surgeries:

- Optical equipment: the safest method but partial and/or transitory solution
- Lens exchange: preoperative patient information ++ (not too early, >3 D)
- Photoablation (surface or LASIK): for low residual refractive error post cataract

- Incision: rarely indicated at the day of surgery for residual cylinder
- Piggyback implantation: in sulcus or in the bag, 2° IOL brings residual error
  (New designs under evaluation)

Perspectives of cataract surgery after corneal surgeries:

- Prevention of surprises: archiving keratometry + axial lens prerefractive surgery
- Ideal implantation
  - Multifocal IOLs (pseudophakic, piggyback)
  - Aspherical profile (aberration free, customized as a mirror of the operated cornea)

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Part IX

Other Refractive Surgical Procedures

Complications of Refractive Keratotomy

37

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Core Messages

- Radial keratotomy, initially a Russian technique, was promoted and practiced globally until the availability of the excimer laser.
- A myriad of techniques have resulted in a legacy refractive surgeons will continue seeing for decades of very challenging, incision-related, clinical problems.
- Newer measurement devices and treatment options have provided new options to improve the condition of what would otherwise be a difficult clinical prognosis.

37.1 Introduction

Refractive keratotomy (RK) was the most widely performed refractive surgery in the mid-1980s and early 1990s. Even with its encouraging refractive outcomes, RK resulted in difficult to manage or even untreatable complications and in serious side effects (Table 37.1). Even the most perfect RK procedure has irreversibly altered the cornea's natural optical behavior and its lifelong corneal stability (biomechanical homeostasis) while generating a vulnerability to blunt trauma resultant from the intrinsic and enduring weakness of the wounds [1]. With the appearance of excimer laser technologies, RK has become universally anachronistic. In Italy, we perform incisional procedures on keratoconic eyes [2, 3] (Fig. 37.1). The cessation of RK was a relief; nonetheless understanding its complications and long-term effects on the eye is important for the practicing surgeon. Therefore, this chapter will focus on management of long-term complications only, without discussion of techniques or patient selection strategies to prevent and deal with intraoperative and early postoperative complications.

On the other hand, astigmatic—transverse or curvilinear—keratotomies (AKs) continue to be useful, inexpensive, safe, effective, relatively simple procedures for treating simple astigmatism, as well as more complex cases such as post-keratoplasty eyes [4]. Arcuate incisions, in particular, fully respect the width of the optic pupillary zone and in most cases improve the physiological corneal profile. Limbal relaxing incisions are a mainstay of lens-based refractive surgery dealing with even small degrees of astigmatism to optimize the outcome of multifocal, aspheric, accommodative, phakic IOLs. With a finite, element analysis-based, biomechanical model of the nonlinear anisotropic hyperelastic behavior of the human cornea [5], empirical nomograms [6] achieve high degrees of predictability and precision.

Contrary to the sequelae of intraoperative complications (e.g., incorrect number, location, depth of incisions, perforation, decentration, intersection of the visual axis and/or the limbus) or postoperative complications, either early or delayed (e.g., inflammations, infections, healing defects), *refractive complications* of RK may be approached systematically. It is easy to statistically forecast—the PERK (prospective evaluation of RK) study estimates that approximately 1.2 million patients were treated with RK only in the USA between 1980 and 1990 [7]—that a large number of patients with either residual refractive errors (overcorrection, undercorrection, induced regular or irregular astigmatism) or more or less disabling visual symptoms are or will be seeking a remedy in the near future. These problematic visual symptoms may be complex and originate from multiple negative

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Table 37.1 Complicated sequelae of RK (Modified from Waring G. Refractive Keratotomy [1])

Secondary to intraoperative complications
• Corneal perforations (micro and macro)
• Decentered procedures
• Incisions intersecting the visual axis
• Incisions across the limbus
• Incorrect number/meridian of incisions
• Incorrect depth of incisions
• Incisions intersecting with combined astigmatic cuts
Corneal scars secondary to early or delayed postoperative complications
• Bacterial/fungal/viral infections
• Healing defects
–Hypertrophic scars
–Haze of the clear optical zone
–Limbal scarring/vascularization
–Inclusion cysts
• Recurrent erosions (epithelial basement membrane changes)
• Repeated operations
• Multiple, intersecting, abnormal, irregular incisions
Refractive complications
• Overcorrection
• Undercorrection
• Induced regular astigmatism
• Induced higher-order aberrations
• Induced anisometropia
• Induced meridional aniseikonia
Biomechanical complications (iatrogenic keratectasia)
• Irregular, asymmetrical astigmatism
• Progressive hyperopic drift
• RK on unrecognized ectatic corneal disorder (forme fruste KC)
Visual symptoms
• Instability
–Diurnal
–Over time
• Glare
–Starburst
–Disability glare
• Loss of contrast sensitivity
• Monocular diplopia
• Diminished night vision
Cataract surgery
• Intraoperative opening of incisions
• Difficulties in calculation of IOL power

attributes of RK. Examples of such symptoms are diurnal or over time instability, starburst, glare, loss of contrast sensitivity, monocular diplopia, diminished night vision, induced anisometropia with imbalance of binocular vision, and meridional aniseikonia (unequal magnification of the retinal image across various meridians from induced asymmetrical astigmatism). One or more of these problems may distort the patient's spatial perception to levels that are not tolerable by the normal physiological mechanisms of neuroadaptation.

37.2 The Excimer Laser Option: Reestablishing the Physiological Corneal Shape

After an uneventful RK procedure with an uncomplicated outcome, conventional computerized videokeratography of the anterior corneal surface shows the classic central "blue lake" pattern, with a well-centered 3–4.5 mm flattened area. The width of the effective optical zone is inversely correlated to the amount of myopic correction achieved. The central flat area is surrounded by a steepened mid-peripheral red ring (Fig. 37.2a). With Placido disk ring reflection topography, it is not easy to distinguish these maps from those generated after conventional excimer laser myopic photoablations. Sometimes, the slightly irregular, squared, or octagonal shape of the mid-peripheral "knee" of the optical zone may help in differentiating RK from the perfectly round and smooth borders of excimer ablations.

In contrast, differential diagnosis becomes very easy when utilizing elevation maps and pachymetry provided by scanning slit systems such as the Orbscan™ or the various rotating Scheimpflug-based systems now on the market. With elevation or altitudinal tomography, the RK-treated eye's anterior surface pattern is similar to that of the posterior surface, both presenting a central area underlying the best fit sphere (Fig. 37.2b). The resultant difference between the two similar surfaces, the pachymetric map, displays normal thickness values across the entire cornea. Additionally, even in eyes with the most perfect radial keratotomy, the optical quality of the vision is less than desirable, due to the marginal optical performance resulting from a small optical zone, the extremely oblate aspheric shape of the cornea, and the micro- or macro-irregularities at the incisions yielding higher-order aberrations. With small pupils in photopic environments, optical quality is dominantly affected by diffraction, and aberrations have little effect, but the spatial resolution is low. In dim light conditions with large pupils, the effect of diffraction decreases, and the contribution of optical aberrations becomes significantly larger, increasing with the square of pupil size. More or less irregular patterns, with ectatic bulging of the corneal regions from complicated wounds, are frequently observed. Surface irregularities are mainly a function of intraoperative complications or problems arising in the healing phase (see Table 37.1), which induce local bulging of both corneal surfaces. Pachymetry changes are often unremarkable. Topography shows high local

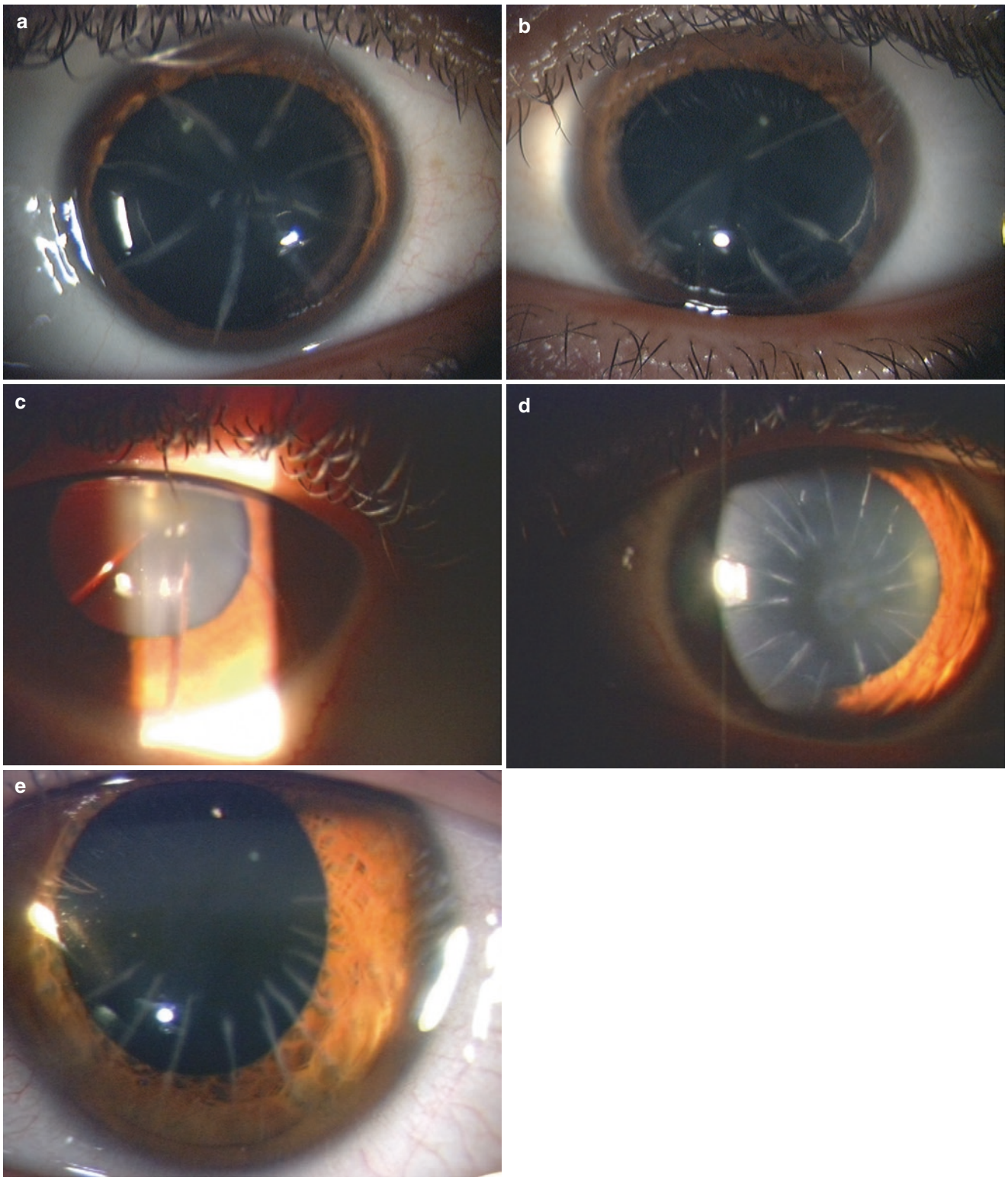

Fig. 37.1 Some typical examples contributing to the bad reputation of RK. Simultaneous "artisan" radial 8-cut (**a**) and asymmetrical 5-cut (**b**) bilaterally performed with non-calibrated steel blades. On-the-visual-axis 8-cut RK (**c**); 18-cut (four cardinal incisions, four in the supranasal and four in the infratemporal, three in the supratemporal and three in the infra-nasal quadrants) with dense central haze and an iron ring (**d**). 10-cut asymmetrical RK on the infratemporal cornea for keratoconus (**e**)

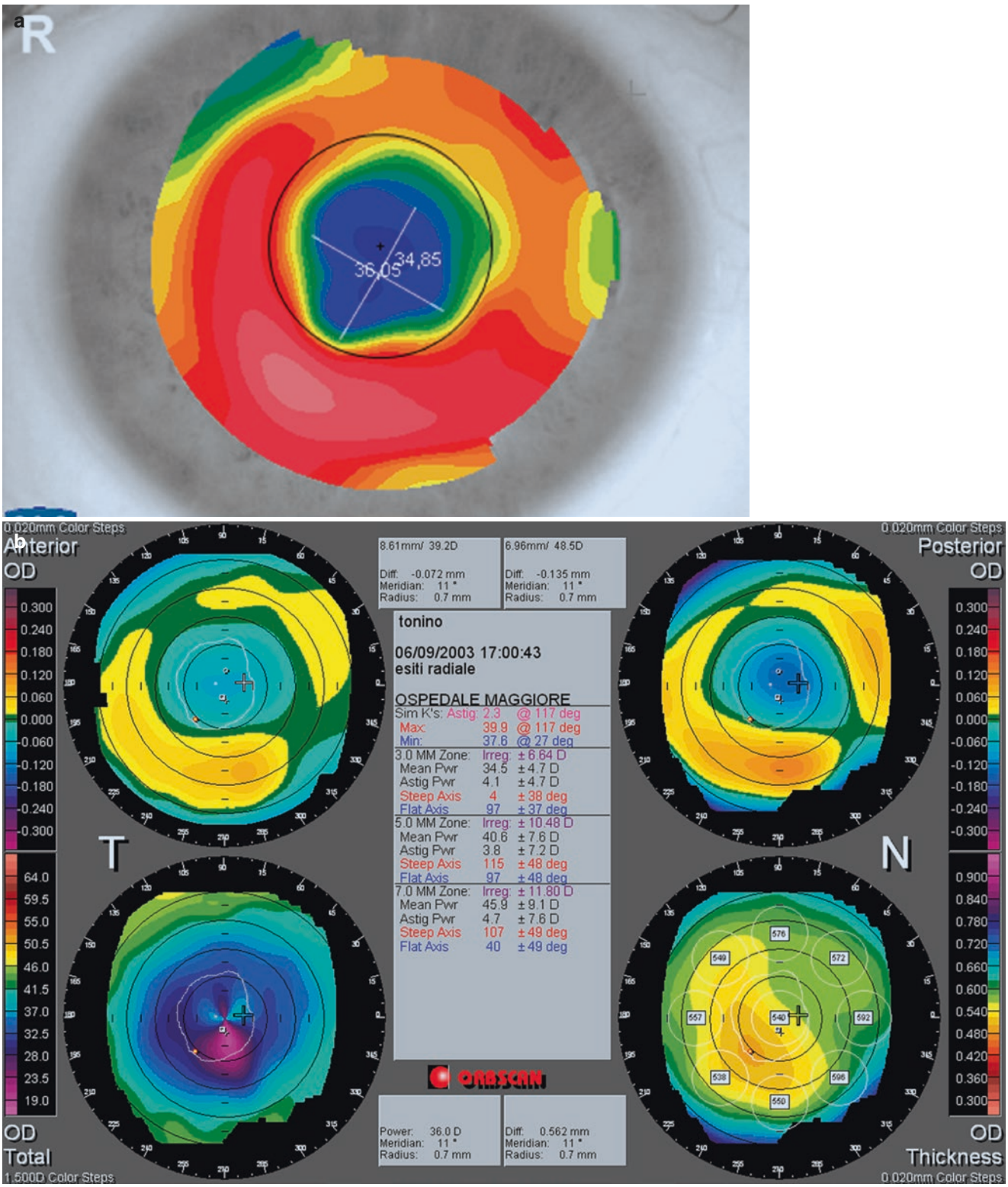

Fig. 37.2 Classic computerized videokeratography pattern (tangential or instantaneous or "true curvature" map). (**a**) Orbscan elevation maps (**b**) after uncomplicated 8-cut RK: similar anterior (**b**, *upper left*) and posterior (**b**, *upper right*) shape modifications are observed; the pachymetric values (**b**, *lower right*) are normal. *Precisio* elevation and pachymetry maps (**c**) of a decentered 8-cut RK (**c**)

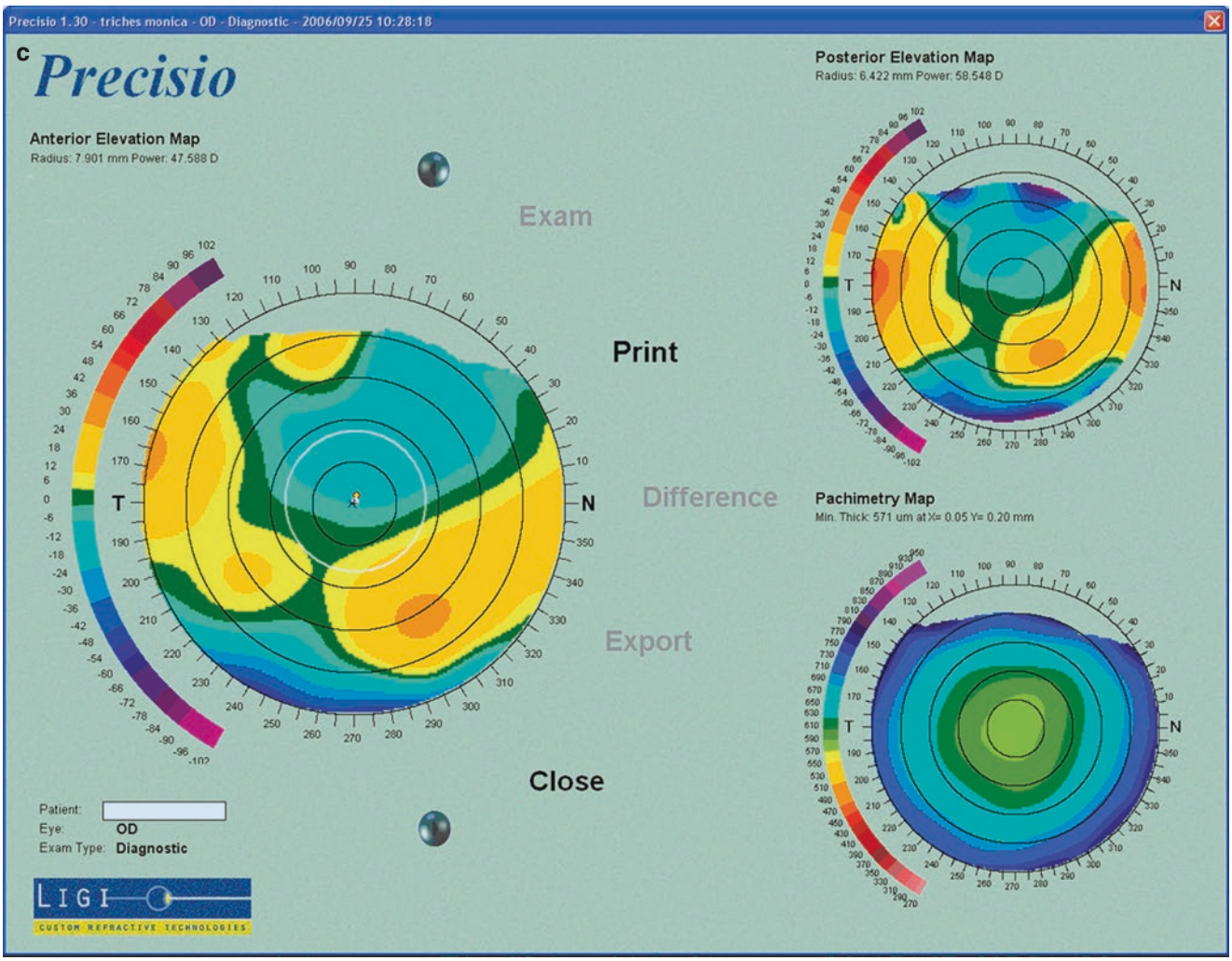

Fig. 37.2 (continued)

dioptric differences in adjacent areas. This localized irregular astigmatism reduces the effective optical zone as well as the resultant optical quality (Fig. 37.3).

As opposed to surgical or healing complications, in many cases, undiagnosed underlying corneal disorders, such as forme fruste ectatic corneal disorders (keratoconus or pellucid marginal degeneration) or epithelial basement membrane dystrophy (map-dot-fingerprint disorder), should be considered in determining the main etiology. Widespread awareness and recent improvements in identifying at-risk patients with sophisticated corneal indices will greatly help in properly screening future refractive surgery candidates [8, 9].

In the excimer laser era, the vast majority of ex-RK patients are looking for a LASIK fix. Conventional LASIK can be safely and effectively performed to correct significant amounts of residual ametropia [10–19] provided that a certain amount of time has passed (at least 2 years), there is a meticulous inspection of the apparently well-healed incisions showing no epithelial cysts or scarring (Fig. 37.4), and the refraction and biomechanics are stable (no irregular astigmatism, no major fluctuations of refraction). Hyperopic ablations for overcorrections may provide good outcomes, by restoring a more physiologically normal corneal asphericity.

The most common secondary surgical strategy consists of using a deeper than usual keratome plate (180 or 200 μm) and taking extreme care when manipulating and aligning the flap, taking advantage of the healed wounds as markers. In more than 100 procedures with this type of case, we have been fortunate to not experience any flap fragmentation and only a single button-holed flap. As opposed to LASIK

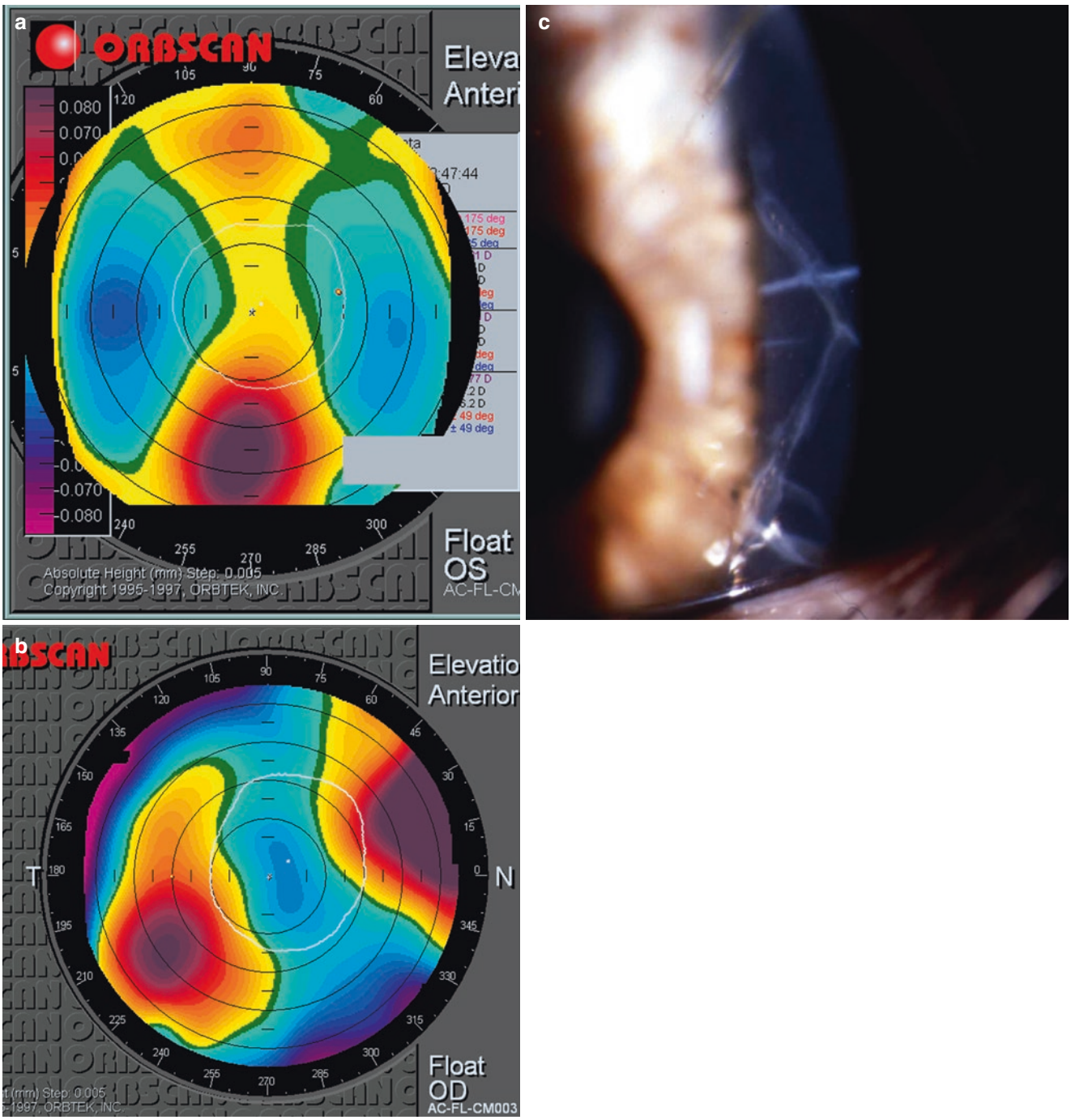

Fig. 37.3 Due to an intraoperative macroperforation of the 6 o'clock incision, an inferior ectasia has occurred (**a**); infra-nasal and supratemporal ectatic bulgings (**b**) are caused by poor healing that has occurred in the corneal regions where there are crossed radial and arcuate incisions (**c**)

enhancement for myopic overcorrection, where our nomogram plans for 30% undercorrection, we perform 100% of the hyperopic treatment, as in a virgin eye. This has been consistent across the different laser platforms we have used. In the youngest patients with an expected mean hyperopic shift of 0.15 diopter per year, we are not concerned with a small overcorrection (110–120% of the treatment) for the same reasons that we would limit the treatment of undercorrected post-RK patients to 80–90%. Patients must be advised of unrealistic expectations. Additionally a number of common problems resultant from RK, such as diurnal refractive fluctuations (cornea is flatter following sleep and becomes steeper as the day progresses), nighttime visual symptoms, and progressive hyperopic shift with age, will not be

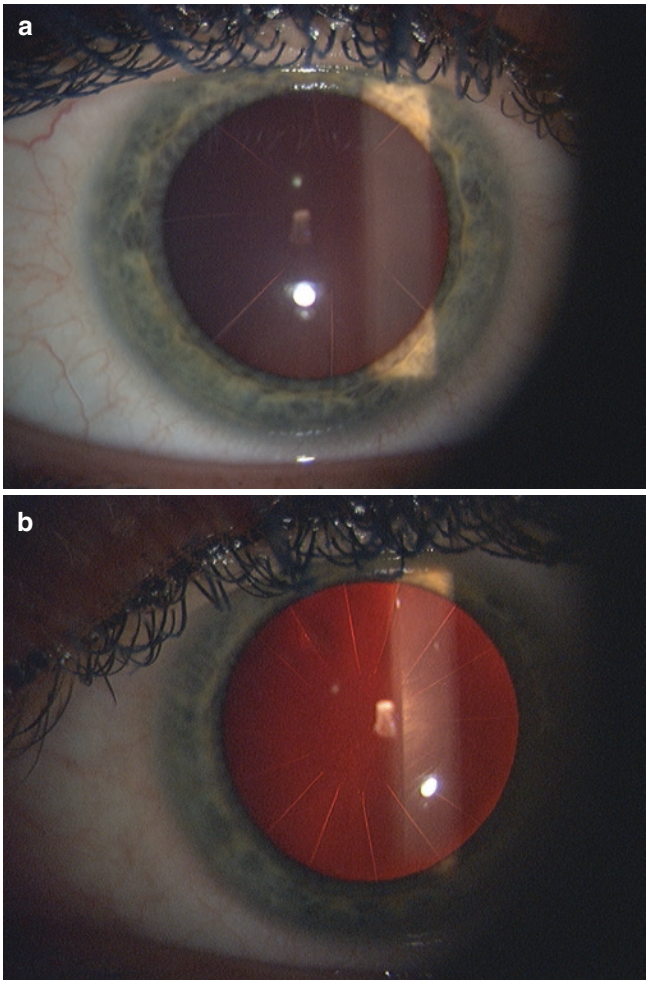

Fig. 37.4 Slit lamp retroillumination images of 8-cut (**a**) and 16-cut (**b**), well-healed RK treatments with a 3.2-mm clear zone. There is no evidence of wound gape or persistent epithelial plugs

addressed as the underlying cause; the incisions will not be removed from the eye. However, enlargement of the optical zone and the recovery of a more prolate corneal shape may improve enough of the contributory visual disturbances to make the patient happy.

Preoperatively, significant attention must be paid to the epithelial plugs in the incisions and weighed against the risk of postoperative recurrent and difficult to manage epithelial ingrowths (about 6% in our series).

The use of the laser (femtosecond) keratome may potentially offer minimized flap complications by creating homogeneous flaps at a more reproducible depth with less mechanical interaction during flap creation. Our experience is in agreement with the few reports we could find in the literature on this topic [20]. The RK incisions opened in each of these cases, when the flap was lifted and a LASIK procedure was successfully completed with no occurrences of slipped flaps, microstriae, or epithelial ingrowth. The major complications occurred in patients with more than eight RK incisions and were incisions opening and postoperative inflammatory response associated with haze requiring extensive steroidal treatment that may explain the loss of CDVA in some cases. Efficacy and predictability of the procedure were comparable to that obtained after RK with mechanical keratomes.

Even perfectly performed, less aggressive, four-incision RK typically achieved only partial improvement of uncorrected visual acuity in patients with nonprogressive, low, and moderate amounts of myopia (up to −4.50 D) [21, 22]. Undercorrection occurred more commonly than overcorrection. In the eight-incision or more group, the unpredictability of the refractive outcome becomes increasingly evident and stems from significant variability among different individual's biology, surgical "hands," and techniques, difficulty in making all incisions uniformly, and the inability to measure and control the biomechanical properties of the cornea. Improvements or enhancements with reoperation have been described with non-staged techniques [23, 24] (Fig. 37.5), with no evidence of significantly improved safety and efficacy ratios.

The following are case reports of surface treatments with modern laser platforms (topography linked, corneal aberrometry linked, and wavefront linked) currently available.

37.2.1 Case #1 (Courtesy of Dan Reinstein, M.D., F.A.C.S.)

Figure 37.6 shows an example of successful reparative treatment for decentration and irregular astigmatism following RK. A 20-year-old male patient underwent RK in the right eye for a −5.75 sphere using eight radial incisions with a 3 mm optical zone. Two further incisions were made as an enhancement at 30° 1 year later. After 2 years, the patient presented to us complaining of severe night vision disturbances (Fig. 37.7a) with no evidence of poor wound healing (Fig. 37.8). On examination, the UDVA in the right eye was 20/40 improving to 20/20 with sph +1.50 cyl −1.50 × 111. The contrast sensitivity was below the normal range in the treated right eye and two levels lower than the untreated left eye for 3, 6, and 12 cpd. Topography showed a significant decentration (top left, Fig. 37.6), and the wavefront analysis (WASCA) exam showed that the eye had significantly raised higher-order aberrations, in particular −11.81 μm of Seidel spherical aberration where a normal eye would typically be approximately −2 μm. Three-dimensional, layer-by-layer pachymetry maps based upon very high-frequency echography (Artemis 2, Ultralink) scans (Fig. 37.9) show how the epithelium responds with a compensatory behavior. The epithelium thins where the stroma steepens and thickens where the surface curvatures flatten. The patient was treated with

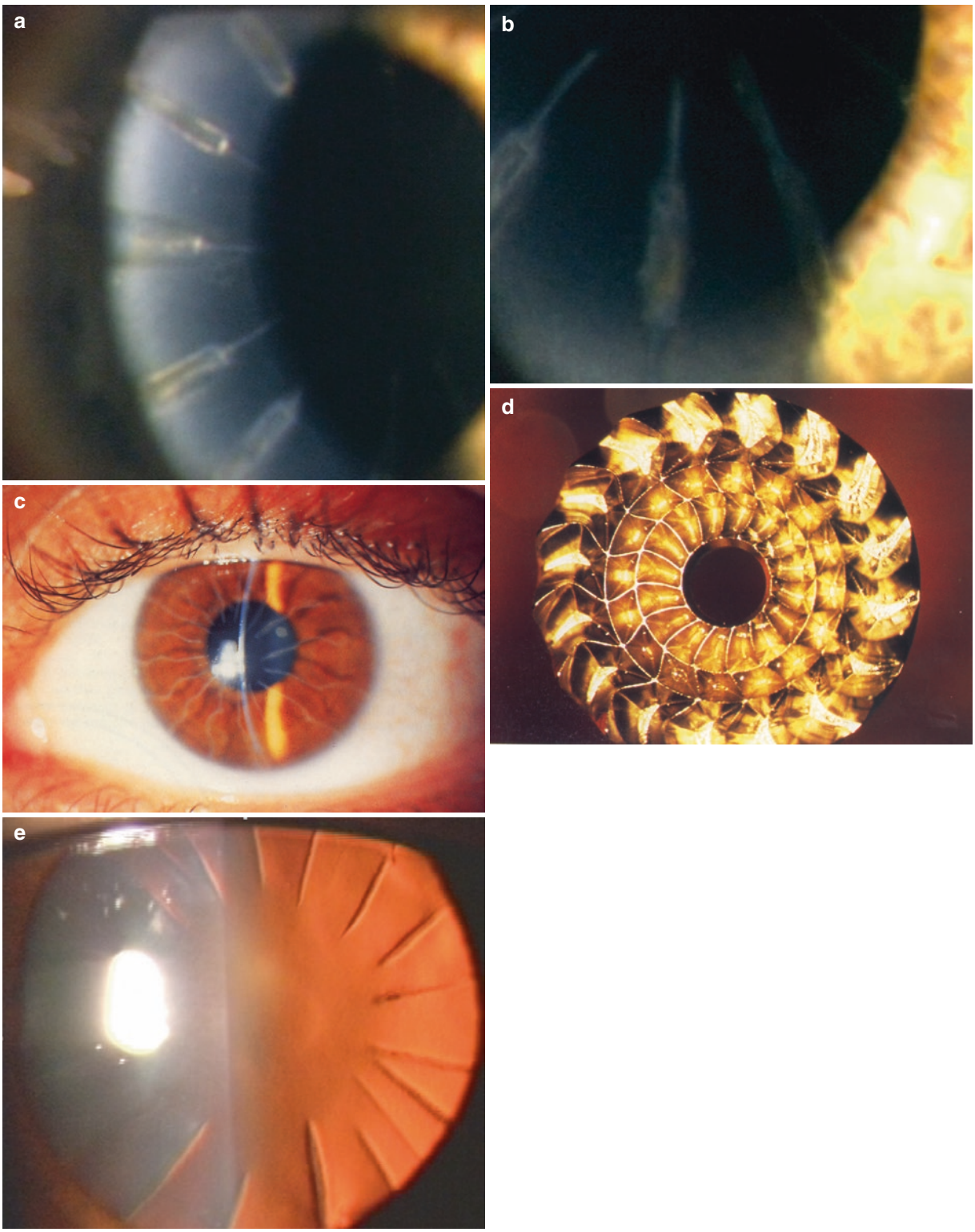

Fig. 37.5 Before the advent of the excimer laser, the management of undercorrected cases was attempted by enhancing the flattening effect on the central cornea with several nontitrated techniques, many of which do not even find citizenship in the medical literature. Examples of these are the intrastromal insertion of PMMA cylinders to keep the incisions open (**a**, **b**); the "zigzag" or "Kriss" technique, with its marker (**c**, **d**, courtesy of Fabio and Roberto Dossi, MD's); the downhill or "American technique" (cut direction from the OZ toward the limbus) or uphill; "Russian technique" (cut direction from the limbus toward the optical zone), single or double peripheral (starting from 6.0 mm) 20 μm redeepening of cuts; repeated operation (Stan Franks back-cutting technique) and the addition of incisions (**e**). Fancy or creative procedures were frequently combined despite the lack of a true rationale and adequate risk/benefit analysis

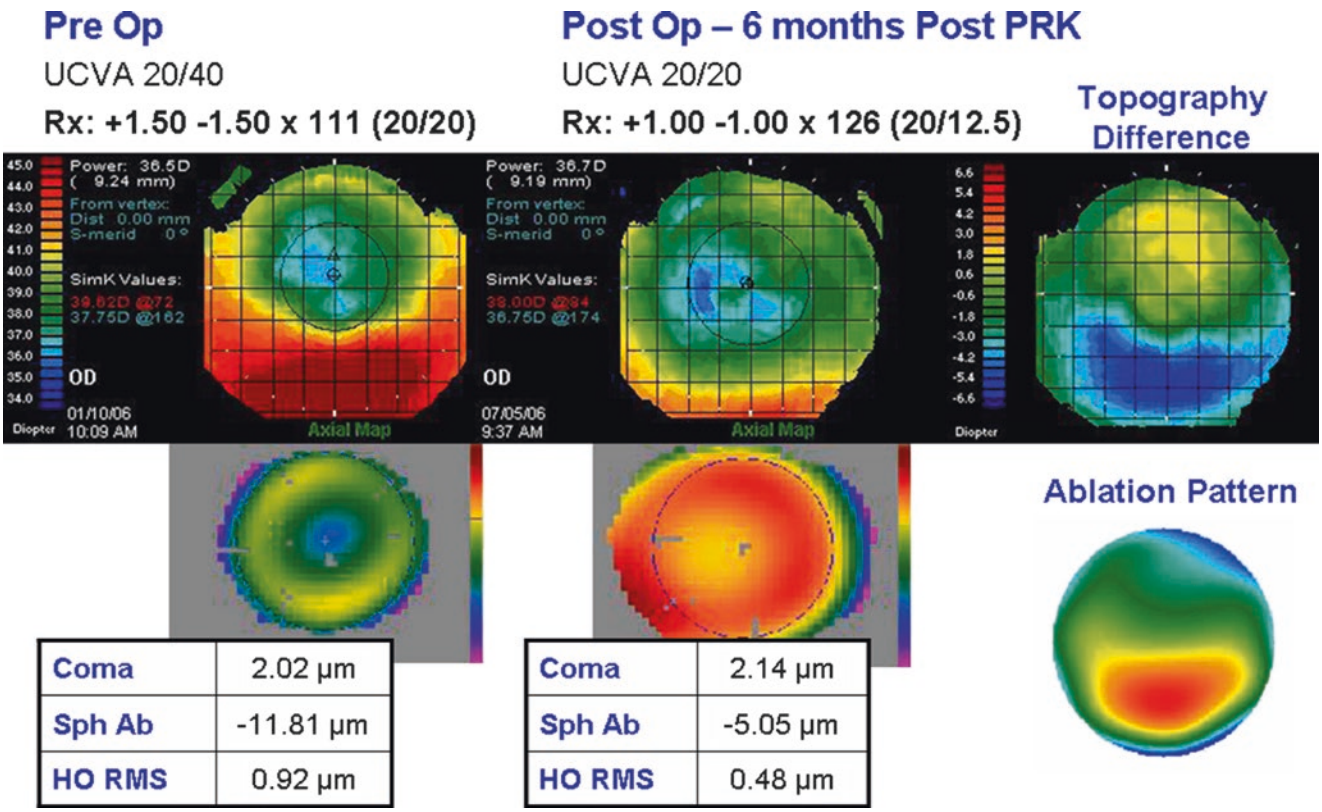

Fig. 37.6 See text for description (Courtesy of Dan Reinstein, MD)

PRK with the MEL80 excimer laser (Zeiss Meditec) using a topographically guided treatment generated by the CRS-Master II TOSCA system (ablation profile: bottom right, Fig. 37.6). The intended postoperative refraction was plano. Four months postoperatively, the UDVA was 20/20 improving to 20/12.5 with sph +1.00 cyl −1.00 × 126, a gain of 3 lines of UDVA and 2 lines of CDVA. The contrast sensitivity was unchanged. The patient reported that the haloes had disappeared (Fig. 37.7b), but the starbursts remained. The postoperative topography was well centered with a large optical zone (top middle, Fig. 37.6, plotted on the same scale as the pre-op for direct comparison). The topography difference map (top right, Fig. 37.6) shows an area of inferior flattening that was achieved corresponding to the ablation profile generated by the CRS-Master II TOSCA algorithm. The treatment had also significantly reduced the higher-order aberrations; in particular the spherical aberration was reduced by 57% (bottom middle, plotted on the same scale as the pre-op for direct comparison).

Following the outcomes reported with the original Meditec TOSCA [25] (topography-supported custom ablation) system on the MEL70, the MEL-80 CRS-Master II TOSCA algorithm incorporates both the corneal anterior surface wavefront information (derived from topography) and the intraocular optics to determine the refraction of the front surface and hence the ablation required to remove the irregularities and leave a target toric surface.

37.2.2 Case #2 (Courtesy of Massimo Camellin, M.D., and Renzo Mattioli, Ph.D.)

In this example, a 26-year-old male patient underwent bilateral RK. Preoperatively OD CDVA was 20/20 with sph −3.75 cyl −4.00 × 5°; OS CDVA was 20/20 with sph −2.75 cyl −4.00 × 160°. Four radial and four curvilinear incisions were applied (Fig. 37.10). The underlying reasons for the significant variation (intraoperative correction of an incorrect meridian of incision site) from the usual nomogram were not available.

One year after surgery, the patient presented to us complaining of a drop of vision in the left eye and severe night vision disturbances. On examination, CDVA and manifest refractions were 20/25 with sph −3.00 cyl −4.00 × 95° OD, 20/30 with sph −1.00 cyl −7.00 × 170° OS. Contrast sensitivity was well below the normal range in both eyes. Pentacam optical pachymetry (Fig. 37.10b) was considered normal (central OD: 621 µm, OS: 621 µm). Corneal topography (Keratron Scout, Optikon) showed a centered optical zone with a peculiar tetrafoil pattern in the left eye (Fig. 37.11a);

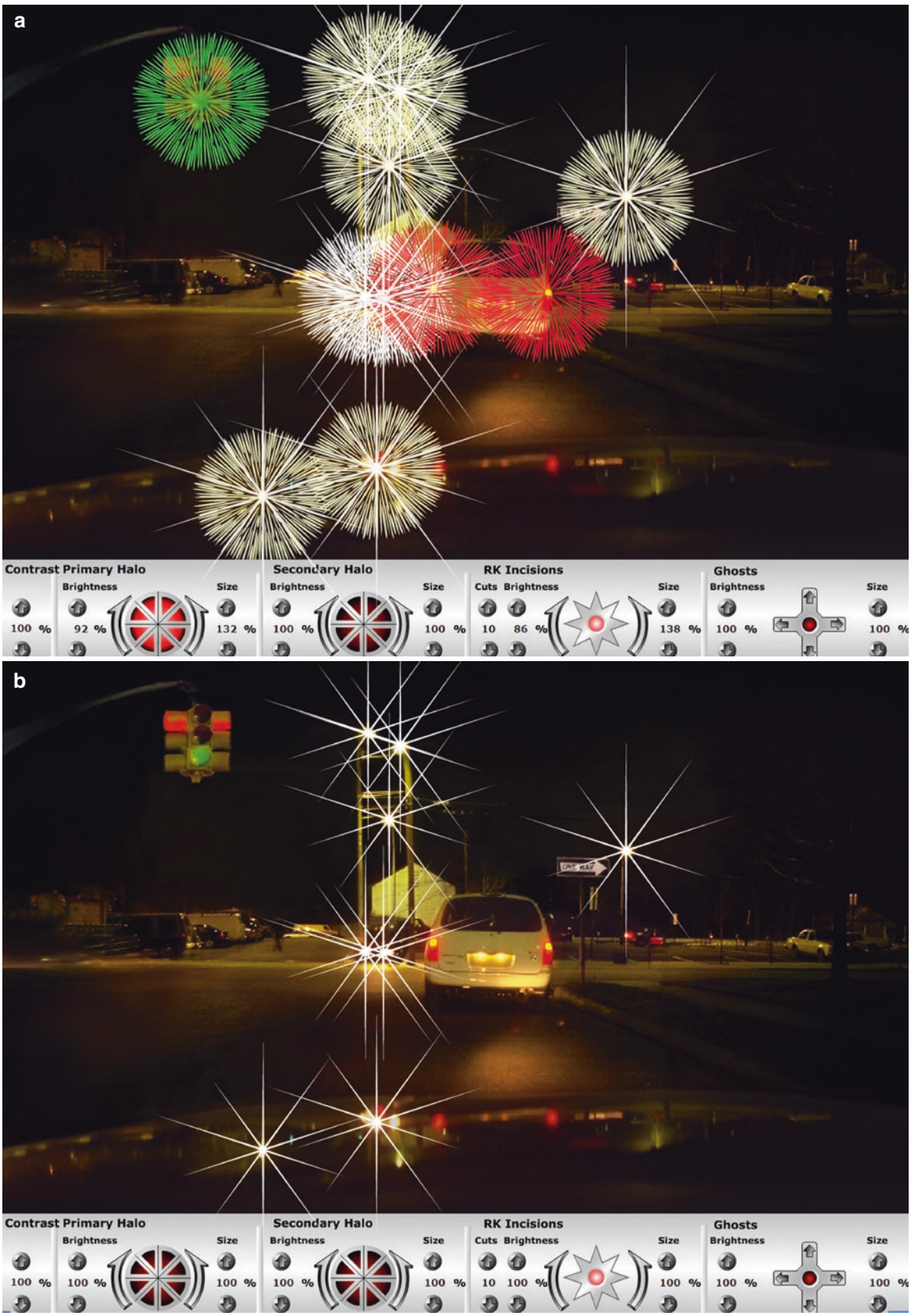

Fig. 37.7 Night-driving quality of vision simulation as based on the preoperative (**a**) and postoperative (**b**) patient's subjective impression of case #1, as discussed in text and Fig. 37.6 (Courtesy of Dan Reinstein, MD)

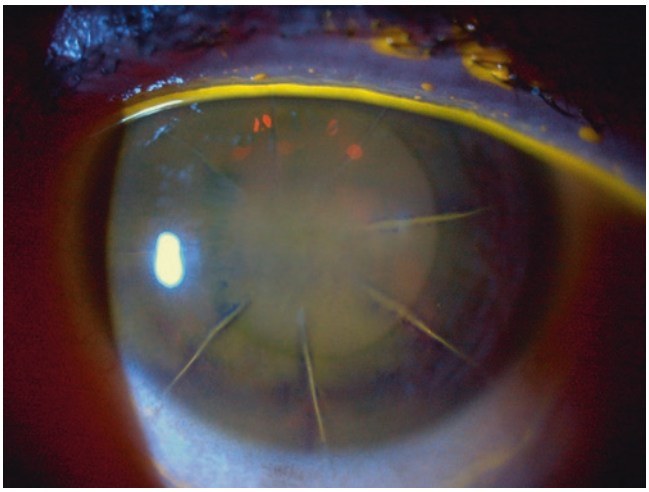

Fig. 37.8 Slit lamp appearance of case #1 (Courtesy of Dan Reinstein, MD)

corneal wavefront exam (Fig. 37.11b) showed that the eye had significantly increased higher-order aberrations. The left eye of the patient was treated as surface ablation with the ESIRIS laser (Schwind, Kleinhosteim, Germany) using a *corneal wavefront link* generated by the Keratron Scout videokeratographer (Optikon 2000, Roma, Italy) through the software *ORK-w* (*optimized refractive keratectomy—wavefront*) (ablation profile: Fig. 37.11c). Corneal wavefront, the component of the overall aberrometry that is due to the anterior corneal surface alone [26], was obtained by performing a virtual ray tracing on the corneal elevation maps from altitudinal topographies. 0.02% mitomycin C was applied for 120 s and the corneal surface carefully washed at the end of the procedure. The intended postoperative refraction was −0.50 sph. Six months postoperatively, the UDVA was 20/25, not improvable with spectacles. No haze could be detected at

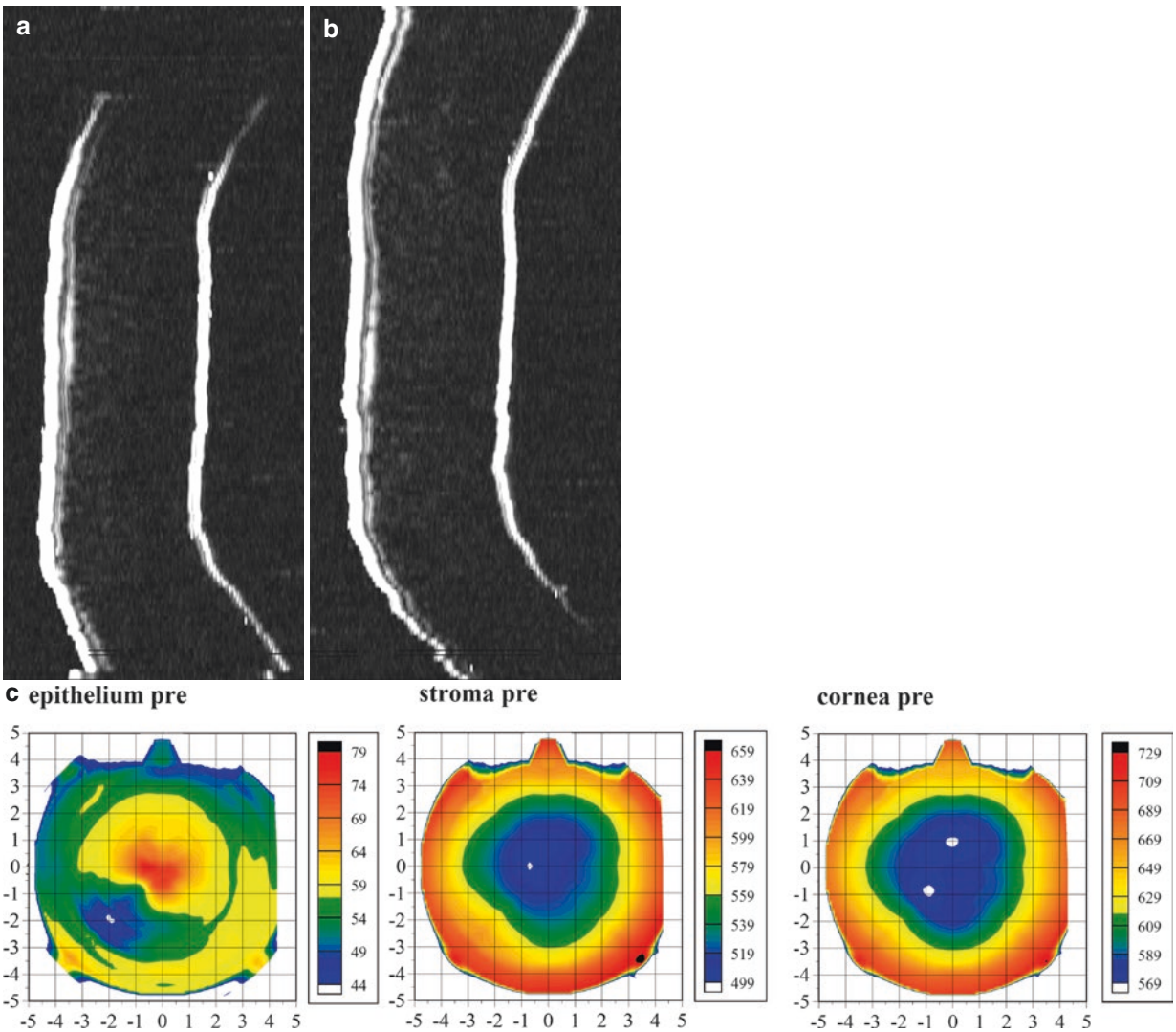

Fig. 37.9 Preoperative VHF echographic meridional scans (Artemis 2, Ultralink) (**a**, **b**) and color-coded, layer-by-layer pachymetry corneal maps (**c**) of case #1 (Courtesy of Dan Reinstein, MD)

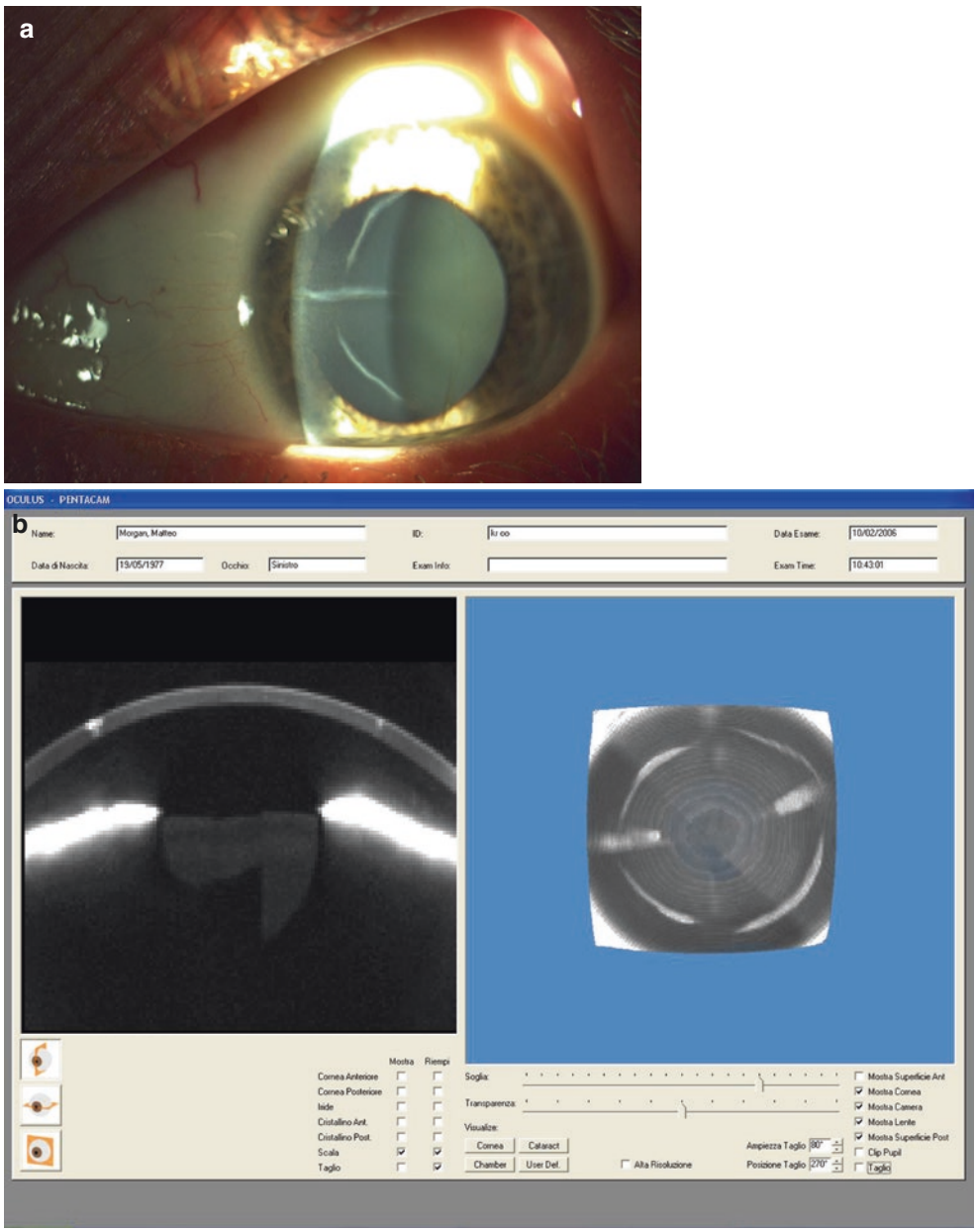

Fig. 37.10 Left eye of case #2. Slit lamp view (**a**) and Pentacam optical pachymetry (**b**) (see text) (Courtesy of Massimo Camellin)

the slit lamp. Visual symptoms and contrast sensitivity were greatly improved. The postoperative topography showed a well-centered, enlarged optical zone with a regularization of the tetrafoil pattern (Fig. 37.12a). The treatment had also significantly reduced the higher-order aberrations (Fig. 37.12b). The pachymetry differential map (Pentacam, Fig. 37.12c) gave confirmation of the precise execution of the planned ablation profile.

37.2.3 Case #3

Figure 37.13 shows an example of an undercorrected post-RK eye treated with a total eye aberrometry wavefront link (Custom Cornea Alcon Autonomous). A 27-year-old male patient underwent RK in the left eye for sph −10.00 using eight radial incisions in a 2.5 mm clear optical zone. Seven years after surgery, the patient presented to us asking for a laser retreatment. On examination, the UDVA in OS was count fingers improving to 20/30 with sph −5.50 cyl $-1.50 \times 0°$. The contrast sensitivity was far below the normal range. On topography (Fig. 37.13a), the optical zone was irregular and decentered inferiorly. Central pachymetry was 561 μm. Wavefront analysis (LadarWave, Alcon) showed that the eye had significantly raised higher-order aberrations, in particular horizontal and vertical coma, trefoil, and spherical aberration (Fig. 37.13b). A wavefront-linked custom cornea LASIK procedure was performed. The planned depth of

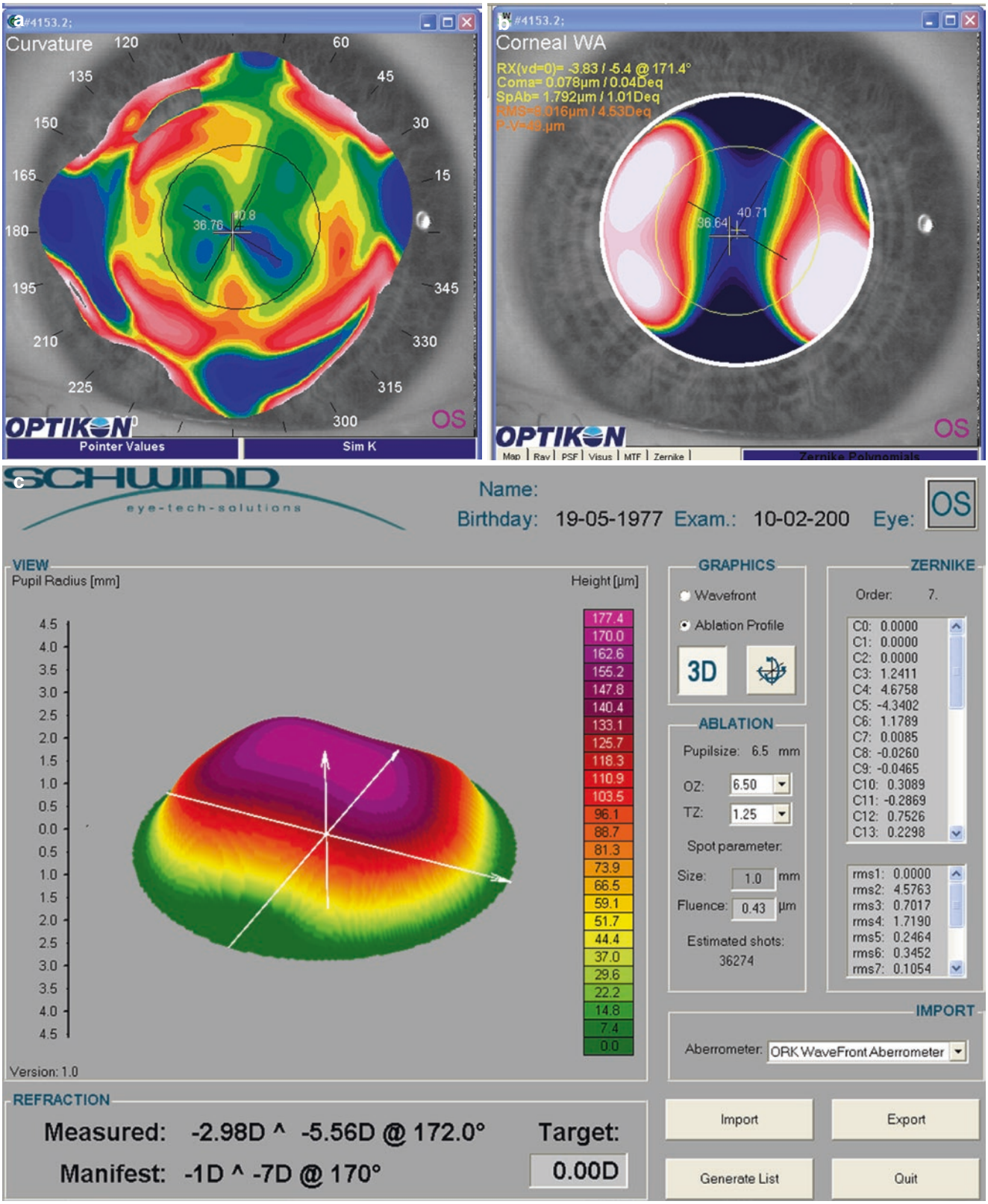

Fig. 37.11 Scout Keratron preoperative topography (**a**) and corneal wavefront (**b**) of case #2; ablation profile using a *corneal wavefront link* generated through the ORK-w software with the ESIRIS Schwind excimer laser system (**c**) (Courtesy of Massimo Camellin and Renzo Mattioli)

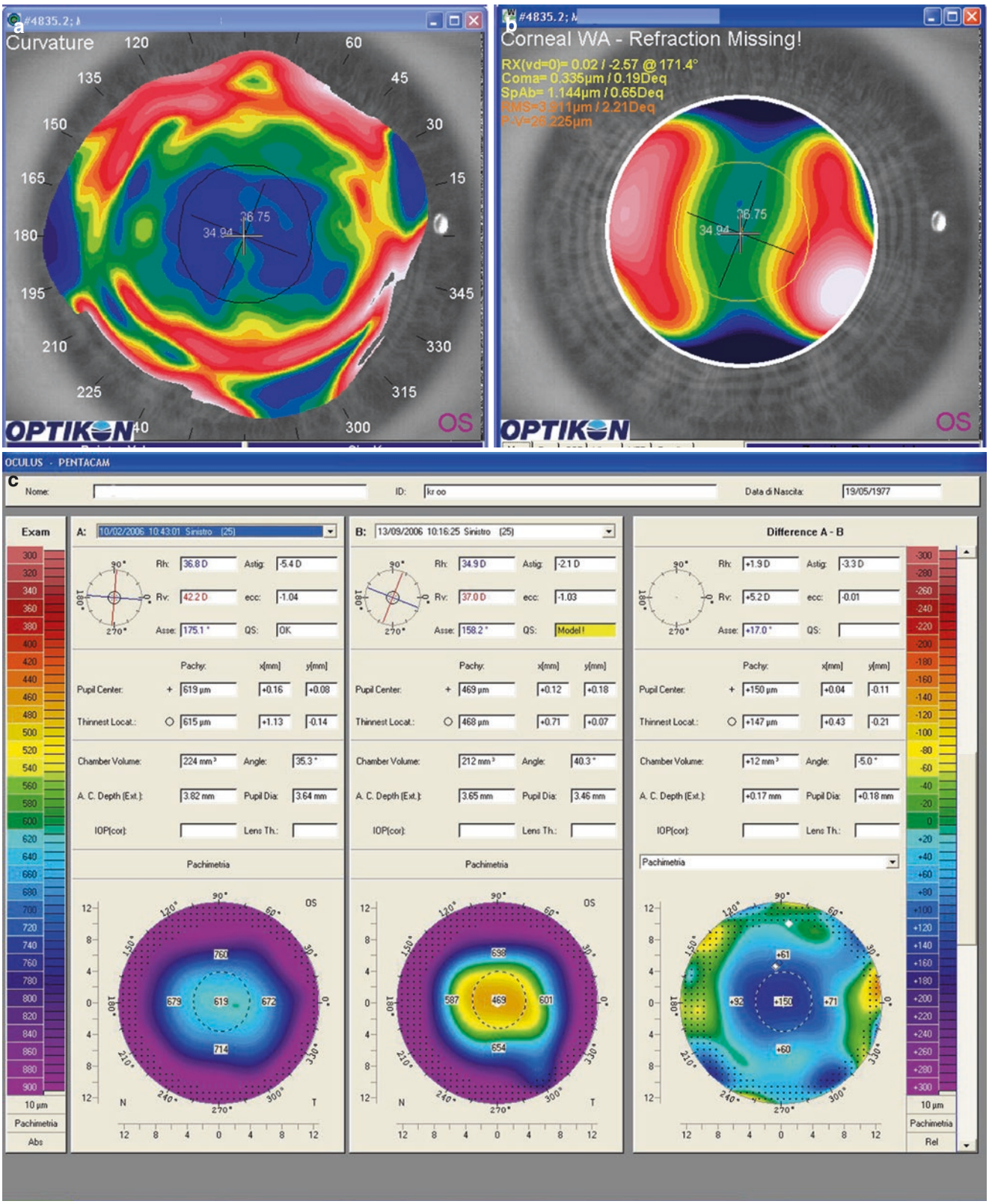

Fig. 37.12 Scout Keratron 6-month postoperative topography (**a**) and corneal wavefront (**b**) of case #2; Pentacam pachymetry differential map (**c**) allows the comparison to the planned ablation profile showed in Fig. 37.11c (Courtesy of Massimo Camellin and Renzo Mattioli)

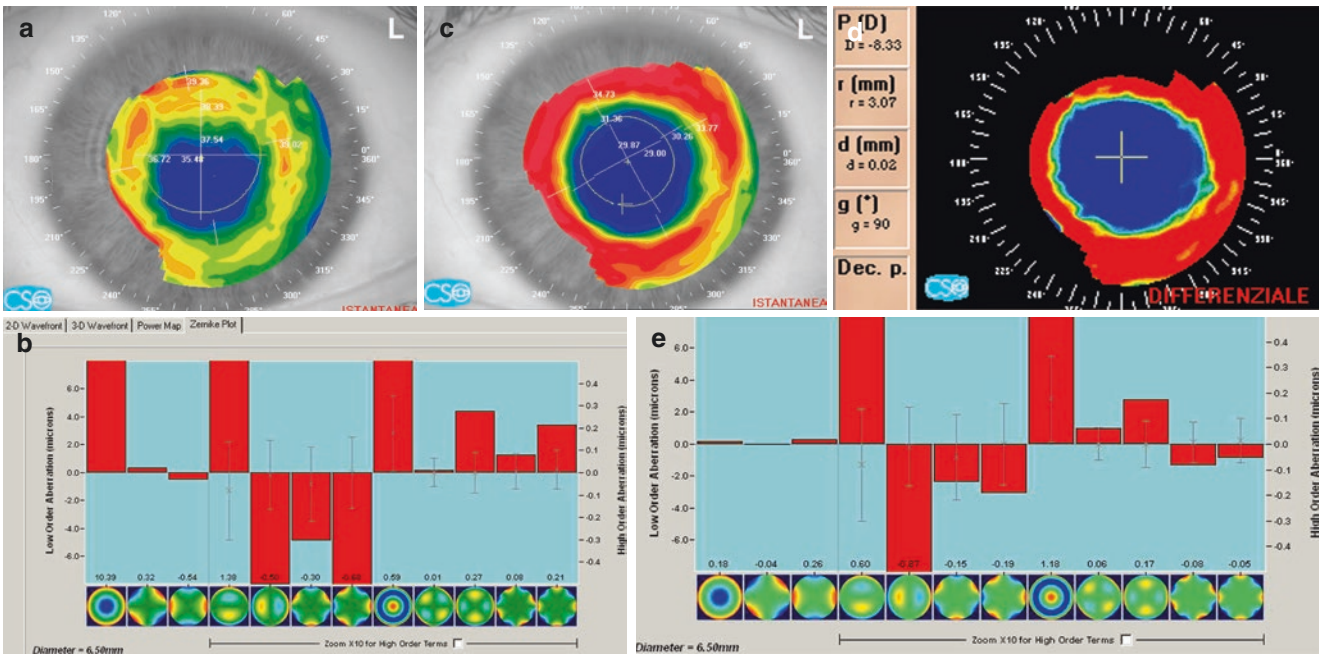

Fig. 37.13 Preoperative CSO topography (**a**), preoperative LadarWave aberrometry (**b**), 2-month postoperative CSO topography (**c**), difference map (**d**) and wavefront analysis (**e**) of case #3

the flap was 180 μm. The postoperative topography (Fig. 37.13c) and difference map (Fig. 37.13d) show a nice re-centration and a moderate enlargement of the optical zone. The treatment significantly reduced the amount of trefoil and vertical coma but did not significantly affect the spherical aberration and the horizontal coma. The patient was happy with his UDVA improving to 20/25 (CDVA was 20/25 with +3.00 sph) but with an unfortunate +4.00 sph of cycloplegic refraction.

37.2.4 Case #4

A 39-year-old male patient underwent three consecutive laser procedures (PTK), after a viral keratitis complicated the original AK procedure for a sph +0.25 cyl −4.00 × 90° in the right eye. An examination performed 15 years after the first procedure showed that the UDVA was 20/400, improving to 20/80 with sph −2.75 cyl −2.00 × 110° and to 20/25 with pinhole. A 2+ haze and a slight basement membrane dystrophy were found to be partially responsible for the irregularities in the anterior corneal surface. Corneal topography and corneal wavefront analysis (CSO) showed that the eye had significantly raised higher-order aberrations (Fig. 37.14a, b). The eye was treated using a trans-epithelial surface ablation procedure, using a topographically guided treatment designed with CIPTA software [27] (ablation profile: Fig. 37.14c) delivered with the iVIS Technologies iRES laser system. 0.02% mitomycin C was applied for 15 s at the end of the procedure. The intended postoperative refraction was plano. One month postoperatively, the UDVA was 20/20, improving to 20/15 with sph +0.75 cyl −1.00 × 102! All haloes and starbursts disappeared with impressive subjective and objective improvements. The postoperative topography was well centered with an enlarged optical zone (Fig. 37.15). The iVIS Suite™ integrates high-resolution tomography from *Precisio*™ topography system (Fig. 37.16) and detailed pupil function analysis using the pMetrics™ dynamic pupillometer. pMetrics provides a full understanding of the patient's dynamic range of pupil sizes, relative reactivities from scotopic to photopic, and a unique statistical analysis with lifestyle weighting. This *Ideal Pupil* dimension represents the diameter which will cover two standard deviations (95%) of all pupil sizes encountered with the individual's lifestyle-related conditions and activities. The iVIS Suite uses the *iRES* laser, which is controlled by a proprietary technology that produces two separate beams, each with a very regular Gaussian profile of micrometric size, 0.65 mm. Combining the dual beam technology with the laser head repetition rate, iRES delivers a frequency of 1000 Hz on the corneal plane leaving a very smooth surface without inducing any acoustic shock effect. Moreover, the iRES' high repetition rate is leveraged to use a technique in which a variable pulse rate is delivered to the cornea achieving a Constant Frequency per Area™ (CF/A) (Fig. 37.17).

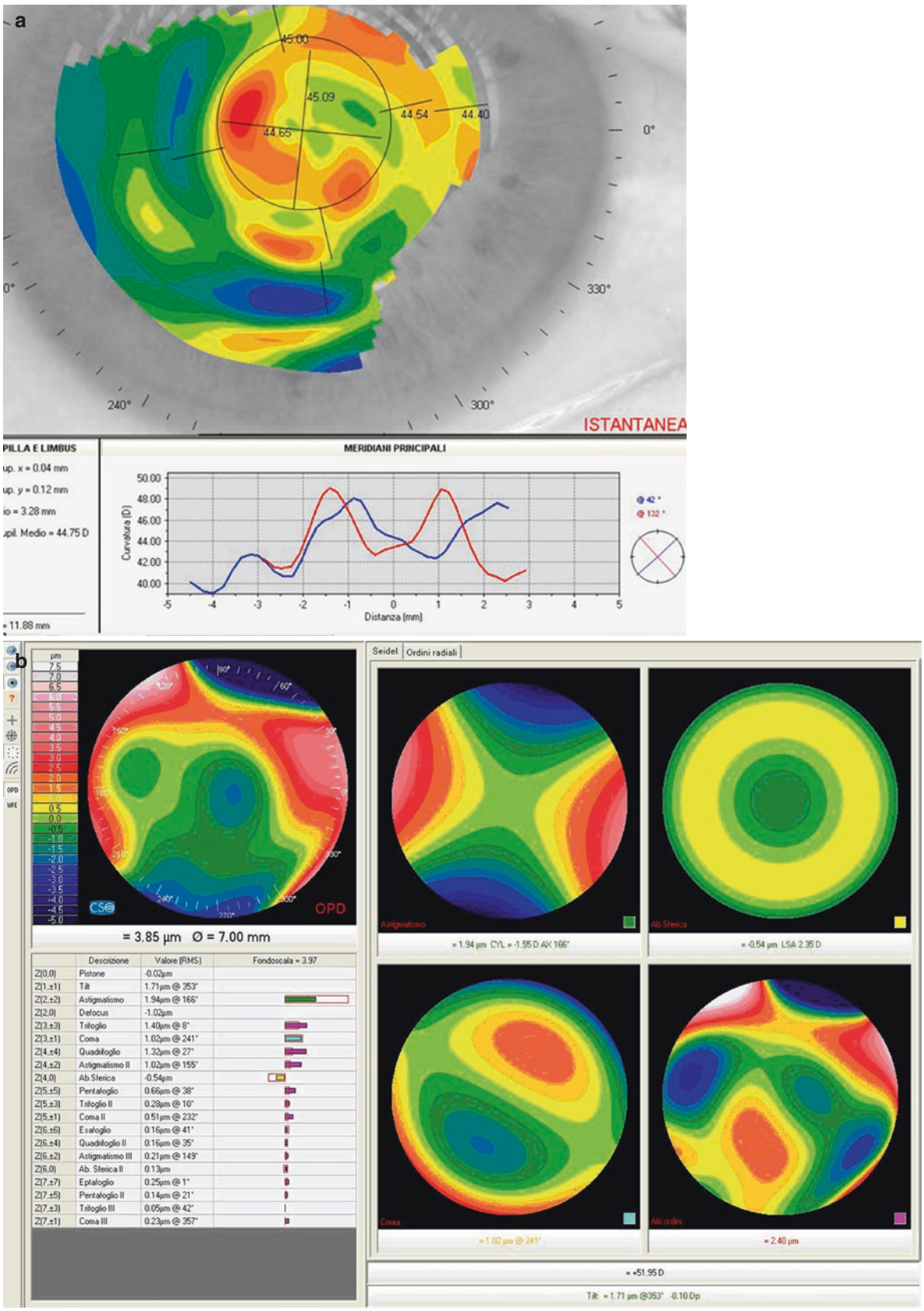

Fig. 37.14 Preoperative corneal topography (**a**), corneal wavefront analysis (**b**) (CSO), and ablation profile planned with CIPTA software (**c**) of case #4

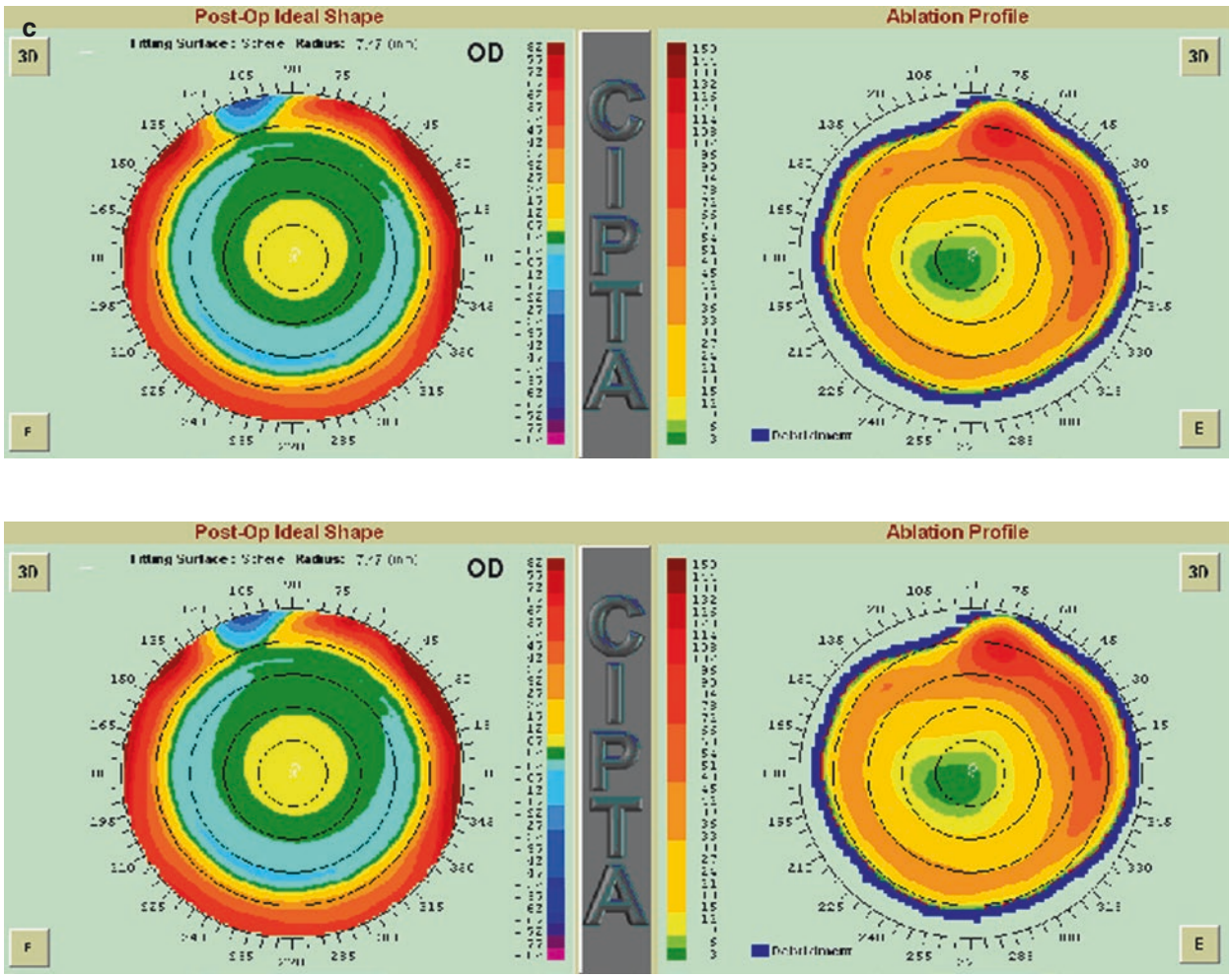

Fig. 37.14 (continued)

37.2.5 Conclusive Considerations

1. Adopting topography [28], elevation maps, or the Zernike polynomial coefficients of the *corneal wavefront* for a laser link in post-RK eyes, in which the internal components of the total amount of ocular aberrations can be considered of little relevance, seems more convenient and potentially more accurate than using a total eye wavefront analysis. Firstly, the data from total eye aberrometry is more artefactual and less reliable [29] in cases of distorted corneas; secondly, the measurements obtained by elevation topography for large pupil diameters are not influenced by additional factors, such as accommodative or cycloplegic state [30] and environmental light conditions.
2. As with other custom treatments, post-RK topography planned surgeries include higher-order aberrations and are unforgiving for any misalignment between ablation plan and the proper position on the cornea. Perfect registration (calibration of the topographer, elimination of artifacts, good repeatability of consecutive maps, and proper placement of the planned ablation on the corresponding corneal tissue) and proper tracking of the entrance pupil are requirements. The laser eye tracker centers the ablation pattern on the pupil or the geometric center of the cornea and relies on the patient's cooperation to maintain fixation, since it cannot distinguish between a lateral movement of the head and a fixation loss that would unavoidably introduce a parallax error.
3. The correct choice of the corneal asphericity is crucial. The correction of the topographic peripheral knee from RK that causes high degrees of spherical aberration is critical to restore a more prolate physiological profile, to influence the lower orders (sphero-cylinder) and is often responsible for the overcorrection (such as reported above in case #3). The exact amount of change in corneal asphericity (Q or e) to plan is open to debate [31–33], is

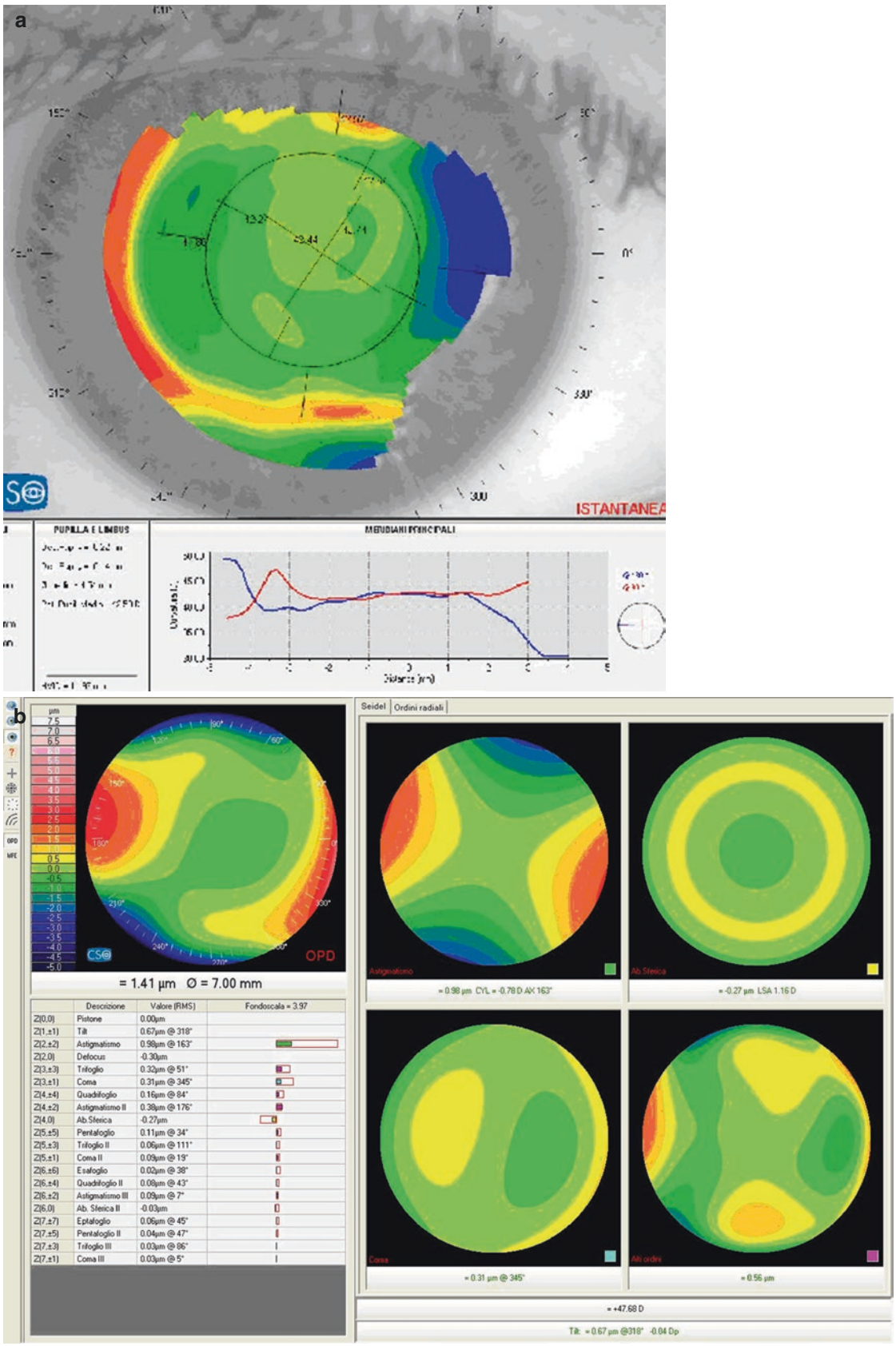

Fig. 37.15 Postoperative topography (**a**), corneal wavefront (**b**), and differential map (**c**) of case #4

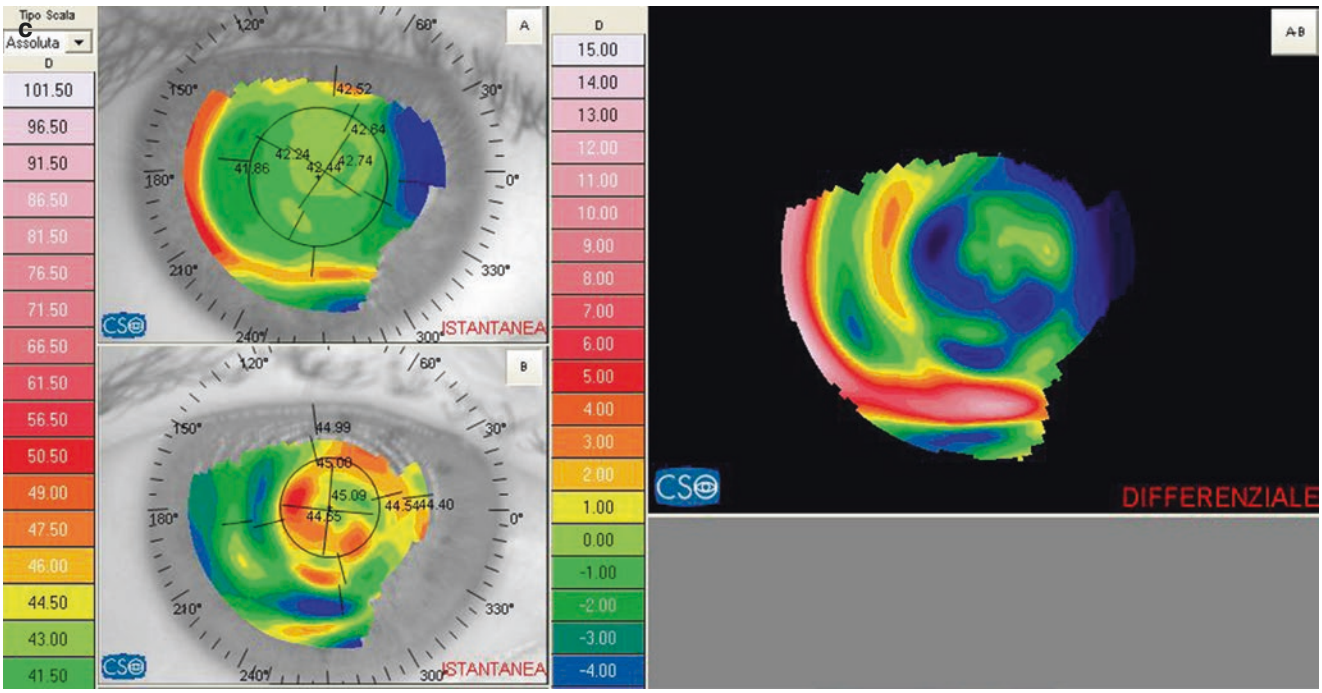

Fig. 37.15 (continued)

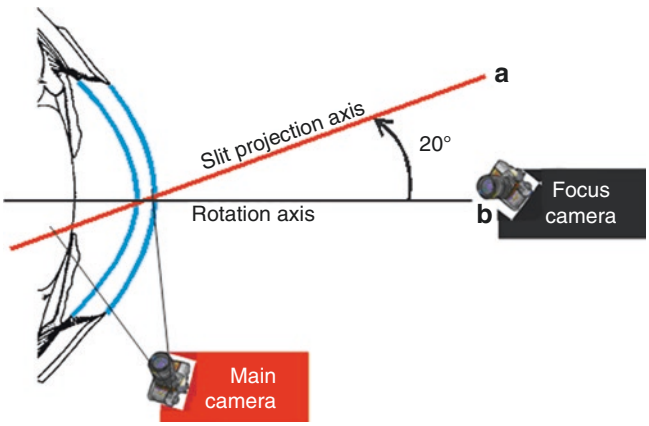

Fig. 37.16 Based on triangulation combined with the rotation of a white light slit that is detected using a Scheimpflug optical system, the *Precisio*™ provides high-resolution measurements across a wide viewing angle which includes both the anterior and posterior surfaces' morphology of the cornea while calculating point-by-point pachymetry. Its slit is projected onto the cornea with an incidence angle of 20° with respect to the axis of rotation of the system (**a**). A dedicated fixation target allows the patient to align his visual axis with the rotation axis (**b**). During the acquisition, the slit is imaged serially and recorded through an integrated system composed of two different CCD cameras (MAIN and FOCUS) working in sync. An intelligent eye-tracker system, whose references are the corneal reflections of four infrared LEDs, allows the correct location of acquired points in three-dimensional spaces. All points collected by the MAIN and FOCUS cameras are stored in conjunction with the position of the limbus vessels which are visible through the proprietary illumination system

uniquely dependent on the diameter referenced, and depends on several factors, such as:

(a) The preoperative asphericity
(b) the sign (positive or negative) and dioptric amount of lower-order aberrations to be corrected
(c) The patient's age, taking into account the internal aberrations
(d) the corneal biomechanics

4. A typical postoperative finding in the eyes, in which a secondary, standard PRK was performed over prior to refractive keratotomy without the application of mitomycin C, was haze associated with a lack of predictability [34, 35]. Anecdotally, we have also observed two cases of moderate haze with difficult explanation. With the first case, +2 haze spontaneously appeared bilaterally 7 years after an 8-cut procedure. Subjective and objective vision was OD UDVA, 20/40; CDVA, sph −0.50 cyl −1.25 × 90° 20/20⁻; OS UDVA, 20/25; and CDVA, plano, cyl-1.00 × 90° 20/20 (Fig. 37.18). In the second case, haze showed up 3 months after RK was performed as an enhancement on an undercorrected PRK performed 12 months prior [36]. The lack of predictability of cutting flaps in post-RK eyes [37] (no post-RK eye is similar to another from the biomechanical standpoint) and, above all, the great outcomes obtained with modern topography [25, 27, 28, 38] or wavefront-linked surface ablations plus

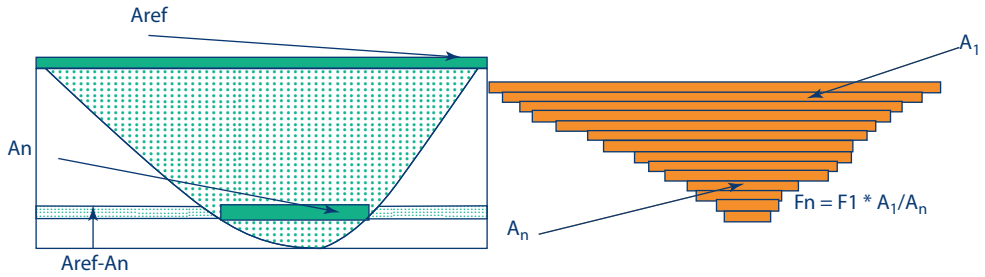

Fig. 37.17 An ablation volume is composed of a fixed number of layers. In the standard method's randomization, the repetition rate varies per area in each ablation layer based upon the layer's total area; spot delivery is specifically designed to avoid firing subsequent shots in the same or adjacent areas. This is effective only for large areas where a sufficient time passes between adjacent shots, but as the layer area becomes smaller, randomization does not allow enough time to pass to avoid firing through plume. This can significantly affect various aspects of the ablation: the amount of energy delivered due to the plume's absorption, thermal effects, predictability of the resultant treatment, and the completeness of the total desired surface affecting smoothness of the pattern. Surgeons or manufactures attempt to partially mitigate these issues by using nomograms or algorithms, which cannot be specific to the nature of these unknown variables. By varying the frequency "layer by layer" and planning equal ablation time for each reference area (Aref), the iRES technology delivers a constant frequency per square millimeter for all layers. A_1 first layer area, A_n last layer area, F_1 frequency per mm^2 at the first layer, F_n frequency per mm^2 at the last layer

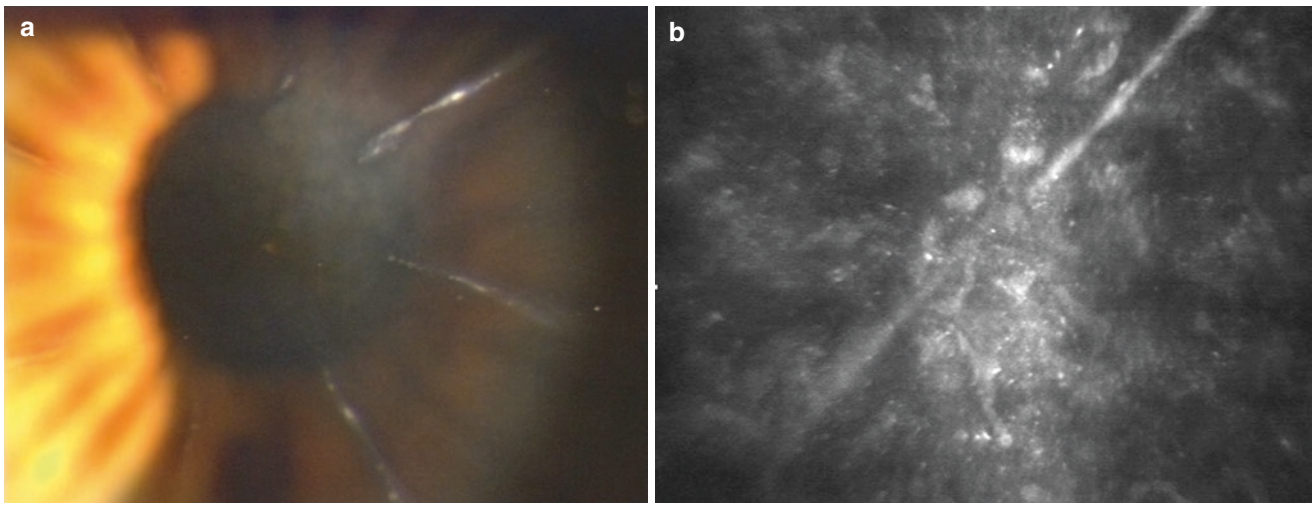

Fig. 37.18 Central haze +2 and iron line (hemosiderin deposition) (**a**) developed 7 years after uneventful RK surgery and unremarkable course. Confocal microscopy (**b**) showed the typical pattern of haze after excimer laser ablation, i.e., high reflectivity of subepithelial dense matrix and activated keratocytes around the healed RK wound

mitomycin C (MMC) applications [34, 39–41] have recently converted our practices to the exclusive use of surface ablations [42]. At present, all post-RK eyes in our practice that are enrolled for excimer laser surgery receive a customized surface ablation plus 15 s application of a sponge imbibed with 0.02% MMC, with protection of the limbal stem cells by means of a specifically cut, ring-shaped standard soft contact lens.

5. When RK incisions are found to be gaped, they are usually filled with pearl-like, persistent clusters of keratin plugs [43] (Fig. 37.19). Despite a moderate number of adjacent activated keratocytes observed in confocal microscopy [44], these epithelial inclusions prevent formation, remodeling, and cross-linking of new collagen fibers. The continuity of anterior stromal lamellae never repairs completely, thus causing an intrinsic weakness of the wound integrity (Fig. 37.20). Significant vulnerability of the incised cornea to blunt trauma [45], intraocular surgery like phacoemulsification [46, 47] or penetrating keratoplasty [48] or even external treatment like conductive keratoplasty [49], has been reported even decades after surgery [50]. The wounds are also prone to develop delayed or recurrent eye surface erosion defects and infections [51, 52]. In our experience, epithelial plugs do

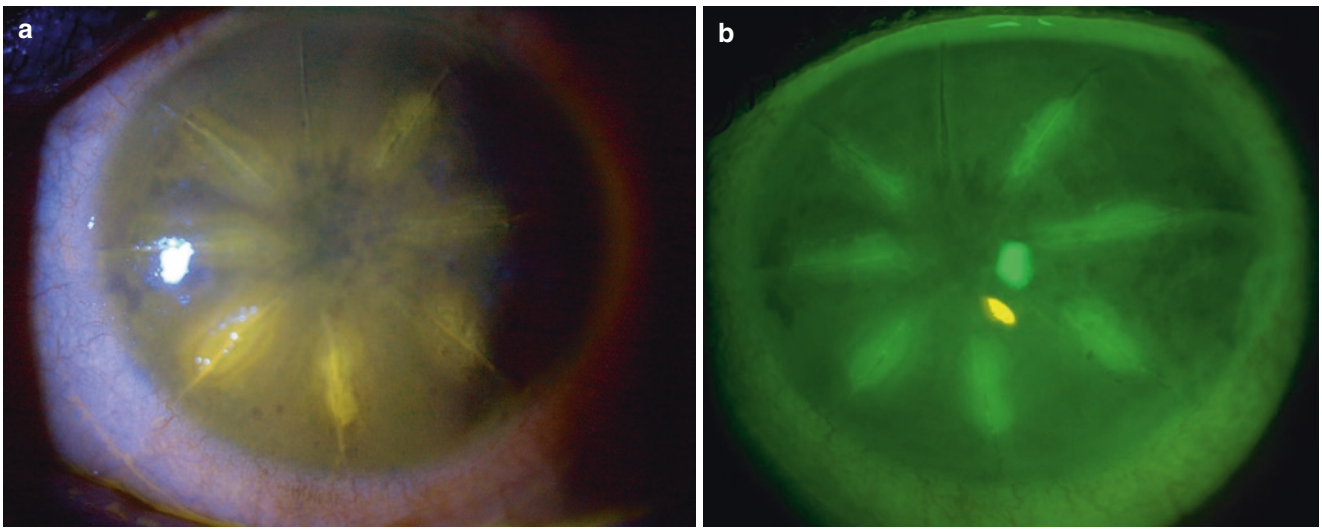

Fig. 37.19 Slit lamp evidence of epithelial plugs in seven out of eight radial keratotomies after fluorescein staining (**a**) and under *blue cobalt filter* (**b**) (Courtesy of Dan Reinstein)

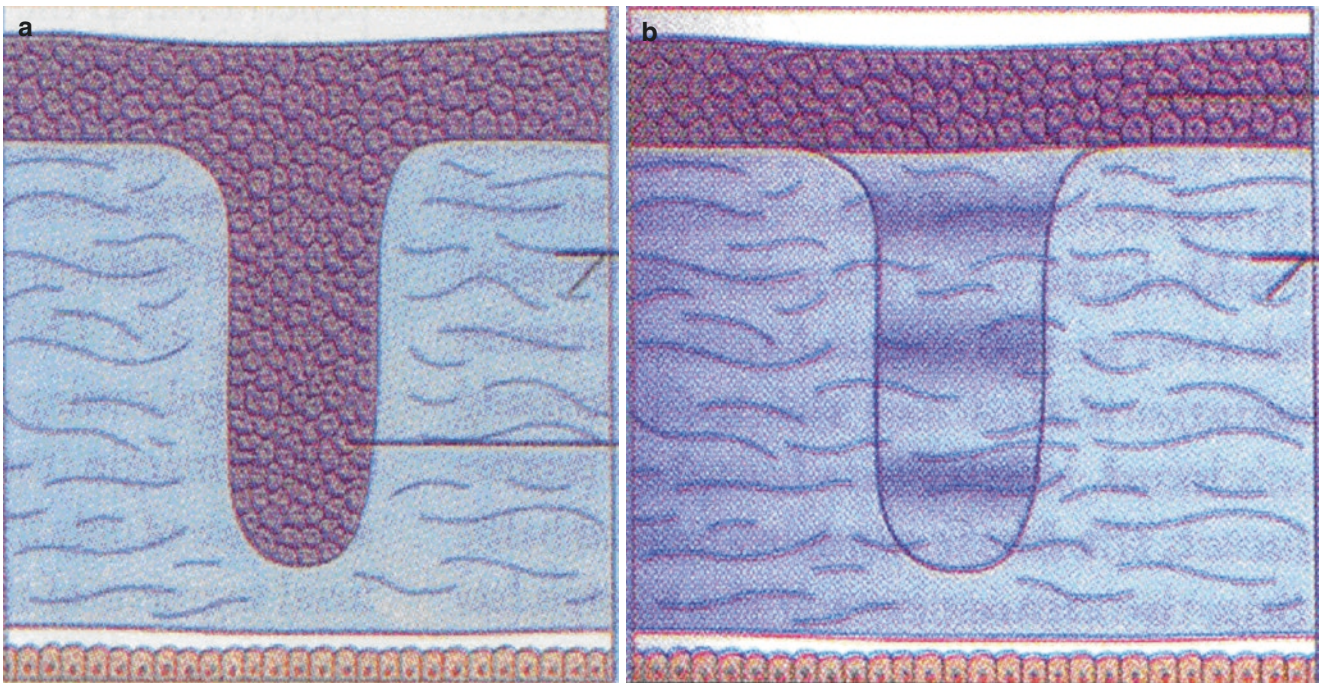

Fig. 37.20 The drawings illustrate the early replication and migration of epithelium into the wound, followed by the formation of a plug (day 1–2 postoperatively) (**a**); the successive stromal phase of wound healing (month 1–2 postoperatively) activates keratocytes into myofibroblasts with collagen deposition and plug displacement; late phase or stromal healing (month 3–12 postoperatively) includes collagen formation and cross-linking (**b**) (Modified from Probst LE. Complex cases with LASIK, Slack 2000)

not ablate at the same rate as adjacent stroma and thusly causing irregular postoperative surfaces when treated with surface ablation procedures if not dealt with (i.e., they should be removed, wounds sutured, then remove sutures waiting 1 year for improved healing, followed by topo or wavefront link).

37.3 Progressive Post-RK Hyperopization: Suturing and Cross-Linking the Cornea

Twenty to thirty percent of the total eyes previously operated with RK are now overly hyperopic with a strong

probability that this percentage will grow with time [1]. The pace of the hyperopic shift can be roughly estimated to be 1 diopter every 6–8 years. The blurring of vision at both distance and near is referred to as being "relentless progressive." Early techniques focused on steepening the central cornea by compressing the mid-periphery with placement of a variety of circumferential and interrupted intrastromal purse-string sutures. Our limited experience (three cases) with the "lasso" 10/0 nylon compression suture (Fig. 37.21) did not confirm the good outcomes reported in the literature [53–55]. We found all the approaches of intrastromal suturing for overcorrected RK (purse-string, interrupted radial, or combined stitches) to be unacceptable in predictability, complicated by a significant regression of the effect during the early postoperative period, and a challenging technique even for the meticulous, expert corneal surgeon. A stable result was not expected to be achieved for at least 6–12 months postoperatively. The depth of suturing must be at least 50% of the stromal thickness; otherwise the unpleasant "gift" of irregular astigmatism, recurrent corneal erosions, and extrusion through a melted superficial stroma may be experienced. As progressive hyperopization with corneal instability may be interpreted as an ongoing peripheral keratoectatic process, a riboflavin-mediated stromal collagen cross-link procedure (i.e., a 30-min application of UVA light—5.4 J/cm^2 at 370 nm of wavelength—after topical application on the debrided corneal surface of a solution of 0.1% riboflavin-5-phosphate and dextran, every 3–5 min) could have a treating rationale. Preliminary, although anecdotal, results suggesting stabilization have been already reported, but longer follow-up data is obviously needed.

37.4 The Intrastromal Corneal Ring Segment Option

The same concepts of corneal bioptics validated for excimer laser surgery [56, 57] are applicable to undercorrected or complicated sequelae of radial and astigmatic keratotomy. Intrastromal corneal ring segment implantation finely tunes the refractive outcome, enlarges the functional optical zone, reduces higher-order aberrations (irregular astigmatism), and improves the physiological corneal shape toward being more prolate (Fig. 37.22). This sometimes translates into a gain of four or five lines of uncorrected and best-corrected visual acuity and always in a significant improvement of contrast sensitivity and quality of vision in general.

When a post-RK true iatrogenic keratectasia shows progression, photoablative surgery is forbidden, and lamellar or penetrating keratoplasty becomes an option. However, before proceeding with a transplant surgery, we believe it is worth treating these cases with a couple of symmetrical (same thickness), asymmetrical (different thickness) (Fig. 37.23), or one single INTACS or Ferrara ring segment. The rationale of segment's choice is still controversial and mainly left to the surgeon's experience.

Despite these apparently ideal features, we must remain aware of the following safety issues:

- The risk of incision dehiscence during channel dissections or segment positioning. Similar to what has been described during penetrating keratoplasty [58], when the dissector passes through the cuts, even though no particular resistance is encountered, it always creates torque that separates and potentially opens the old wounds. This

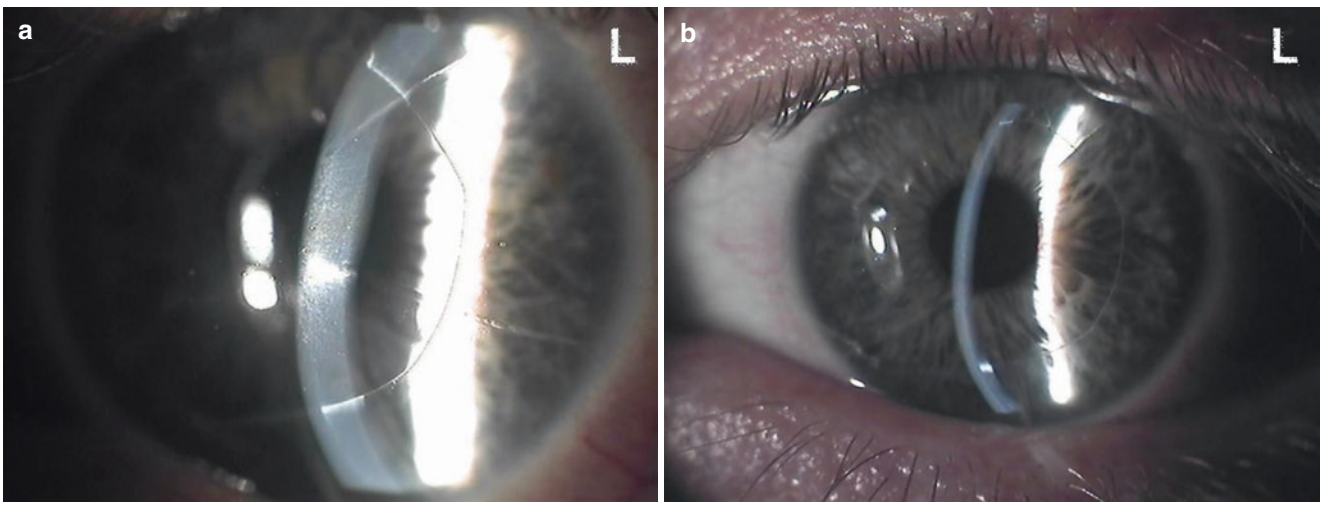

Fig. 37.21 "Lasso" circumferential 10/0 nylon compression suture after overcorrected RK. Magnification x16 (**a**) and x10 (**b**) (Courtesy of Gianni Alessio, MD)

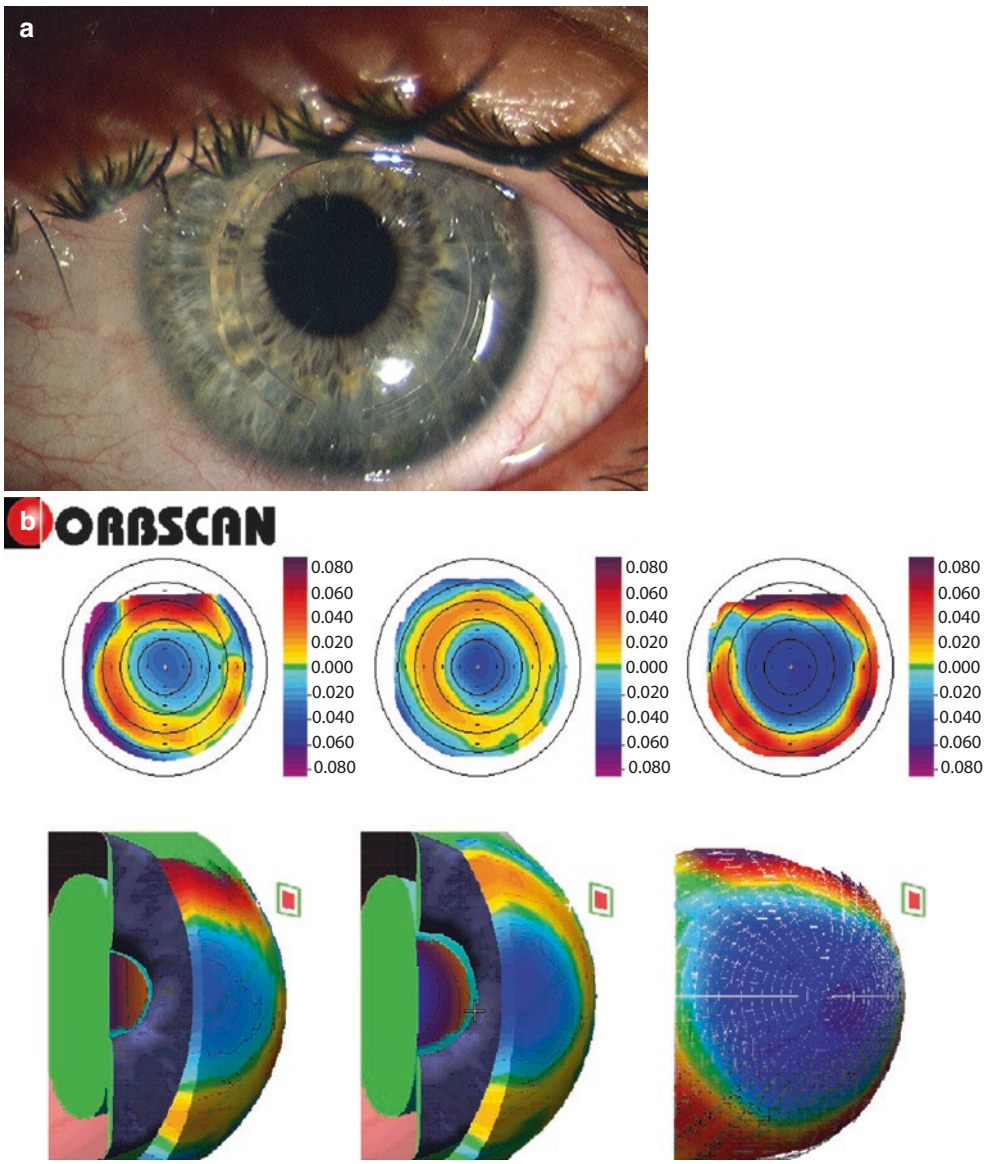

Fig. 37.22 Slit lamp image (**a**) and postoperative versus preoperative Orbscan anterior elevation difference maps (**b**) of an undercorrected RK treated with INTACS insertion

separation would require watertight closure with placement of extra sutures in the keratotomies and discouraging any placement of the implants.

- Considering these elements are space occupying and strain enhancing and place the wound under constant tension over time, another potential risk is the delayed postoperative opening and wound melt (Fig. 37.24).
- Neovascularization (Fig. 37.25).

37.5 The Phakic IOL Option

37.5.1 Case #10

A 25-year-old lady submitted to 16-cut RK for high myopia (−8.00) and one unsuccessful circumferential intrastromal suturing for extreme overcorrection (2 years after surgery, CDVA was 20/25 with +8.00 + 2.50 × 0°). Significant (minimum K-reading was 28.76 D) but regular, symmetrical flattening of the central cornea was observed on examination (Fig. 37.26a). A custom-made hyperopic toric phakic IOL (Visian ICL, Staar) was implanted horizontally through a temporal incision in the posterior chamber. Since a wide anterior segment was available for the implant, despite the very flat cornea, the white-to-white "rule of thumb" was considered unreliable for this case, and the choice of the overall length of the implant was made on the basis of the horizontal sulcus diameter, as measured with VHF echography (Artemis 2, Ultralink) and by using the Lovisolo phakic IOL sizer software [59] (Fig. 37.26b). A slight overcorrection was planned, taking into account the age of the patient and the relentless progression of the hyperopic shift. In day 1 after surgery, UDVA was 20/25. Three years after implantation, CDVA is 20/20 with sph −0.50, UDVA is 20/30^{+}.

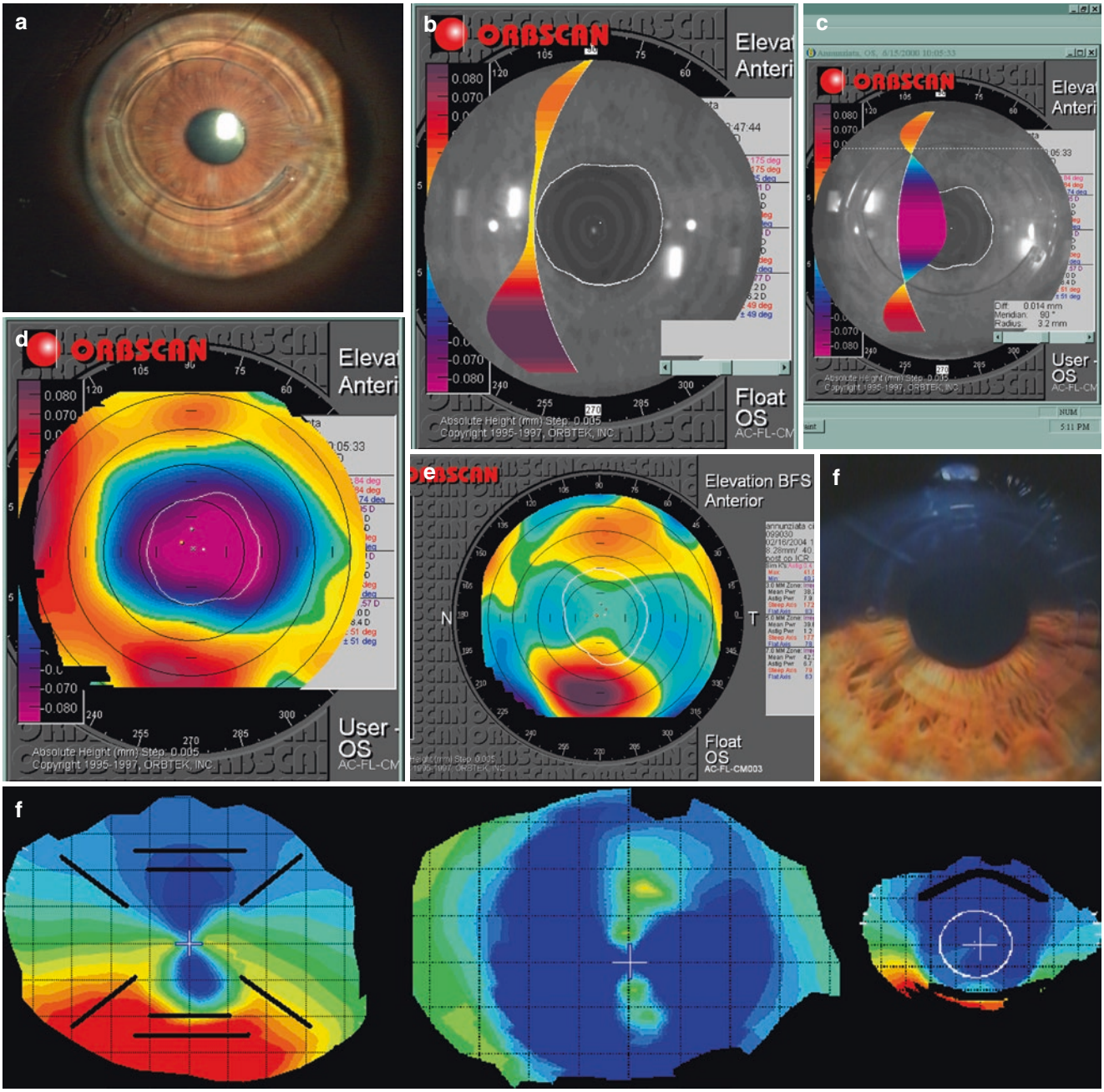

Fig. 37.23 Case report #5. A superior 0.25 mm and an inferior 0.45 mm INTACS (**a**) were implanted at 70% of stromal depth, with incision site positioned temporally, to treat the high ATR astigmatism (CDVA: 20/100 with +2.75 −6.00 × 85°) caused by the inferior ectasia (preoperative elevation map is shown in Fig. 37.4a, the anterior corneal surface profile in Fig. 37.23**b**). Early postoperative outcome was improved (CDVA = 20/25 with +1.25); Orbscan profile (**c**) and topography (**d**) show the central flattening and wide optical zone created by the rings. At the 6-year postoperative follow-up exam, a moderate instability can be observed (**e**); CDVA is still acceptable (20/30 with +0.75 + 1.50 × 20°). Case #6 was managed similarly, with insertion of a pair of symmetrical Ferrara ring segments (**f**), and gave an even better outcome (postoperative UDVA = 20/25). Orbscan anterior elevation map difference (**g**, *middle*) shows the coupling effect (steepening of the flattest meridian and flattening of the steepest one) induced by the segments

37.6 The Wavefront-Based Glasses Option

Beyond the crystal clear transparency and the uneven, smooth regularity of its surface, the ideal optical qualities of the cornea, from a purely theoretical standpoint, should have an ellipsoidal geometry with an adequate shape factor (asphericity) and with its apex perfectly centered on the visual axis. Inadequate shape factor (as in oblate geometries) results in spherical aberration, while a decentered apex generates coma and oblique incidence astigmatism. Higher-order

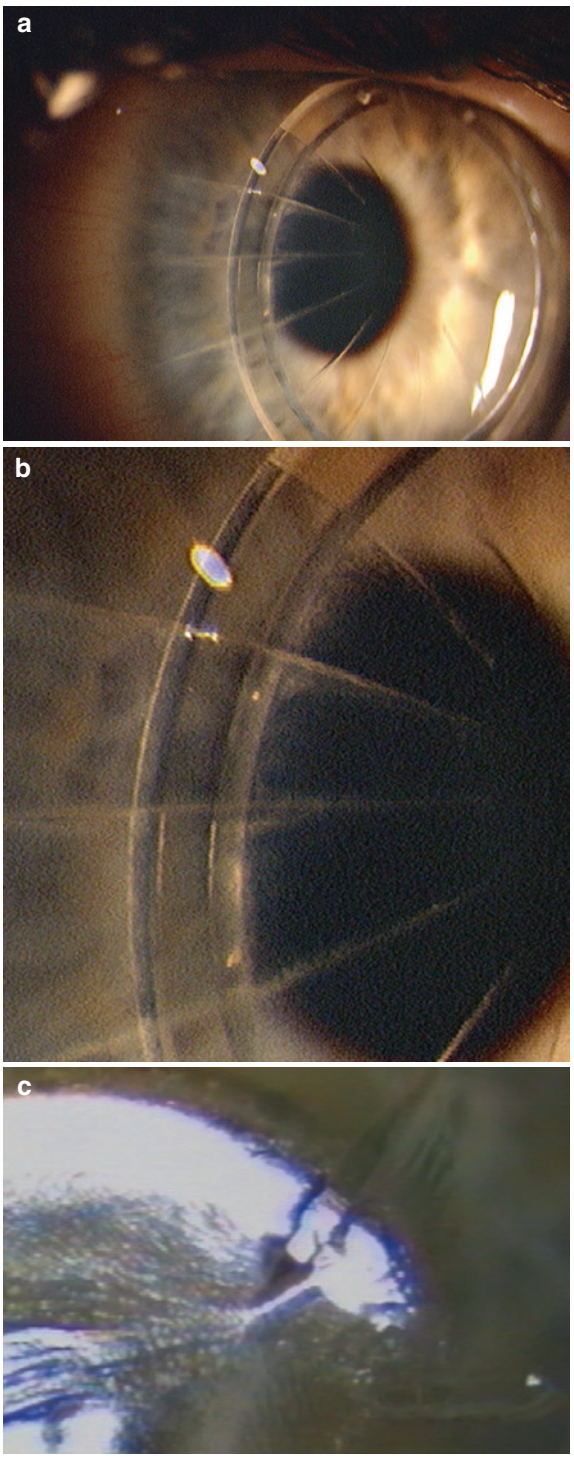

Fig. 37.24 During the dissection pass of case #7—undercorrected, decentered RK—we experienced the external dehiscence of the cuts at 8.30 and 10 o'clock. We decide to position two symmetrical INTACS implants and not to place sutures. Three days post-op, the eye was unremarkably tranquil, vision was 20/20 uncorrected (!), the oblate shape of the cornea partially restored, and the depth of implantation was 70% of the corneal thickness. After 3 months, we noticed a slightly grayish opacity of epithelium and superficial stroma above the segments in the two opened wound (**a**, **b**). After 6 months at those sites, significant epithelial erosions and stromal melt occurred, and we were compelled to remove the segments. A similar case (#8) happened 3 months after insertion of one single Ferrara ring in a post-RK severe iatrogenic corneal ectasia, probably an unrecognized forme fruste keratoconus (**c**)

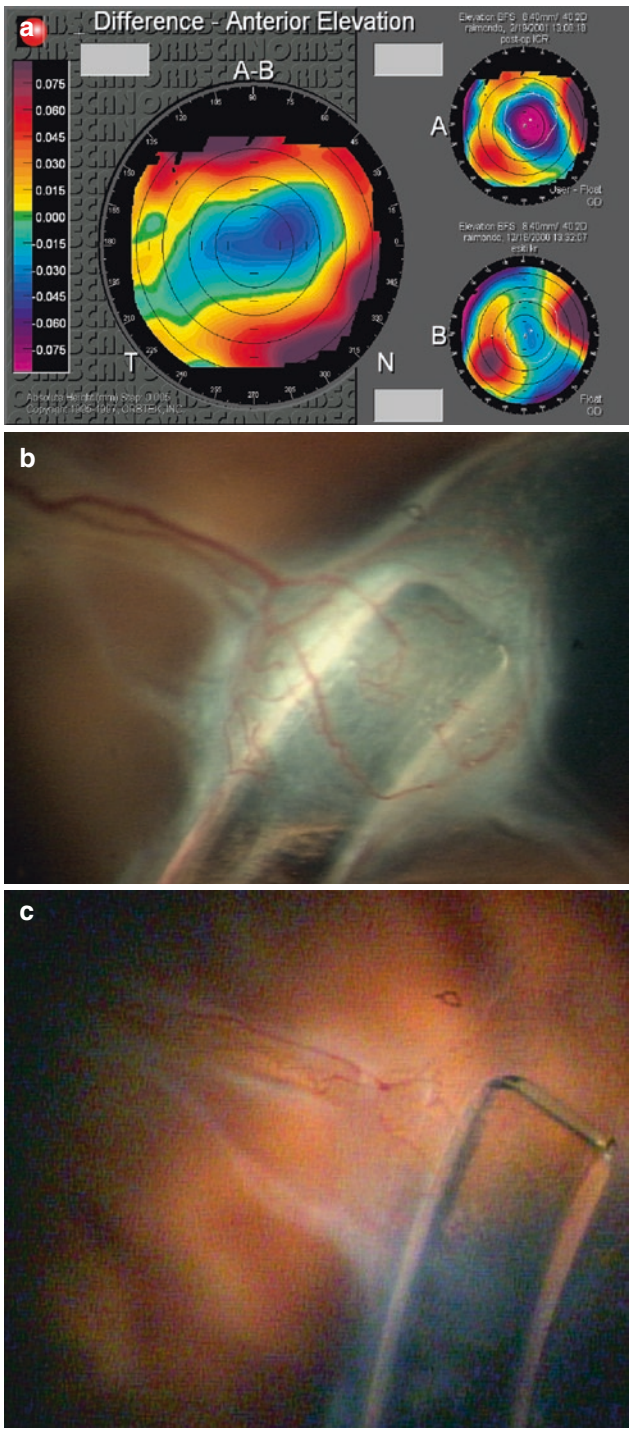

Fig. 37.25 In case #9, a combination of radial and curvilinear cuts caused an irregular corneal shape with high asymmetric astigmatism (CDVA = 20/90 with −6.00 cyl × 40°). Intraoperatively, immediately after activating the suction, the old radial wound adjacent to the new incision site (positioned at 105°) opened. Surgery was completed with insertion of two 0.45 mm INTACS segments, and the opened cut was sutured with one 10/0 nylon stitch. Suture was removed after 3 months. The outcome can be observed in the Orbscan anterior elevation difference map (**a**). Five months after surgery, a new vessel developed from the limbus, in correspondence of the opened wound and invaded the superficial corneal around the edge of the ring (**b**). Steroid topical therapy plus argon laser applications induced a significant regression. Four years postoperatively, the ring segments are still in situ and the cornea looks clinically quiet (**c**). CDVA is 20/50 with +1.25 + 1.75 × 125°

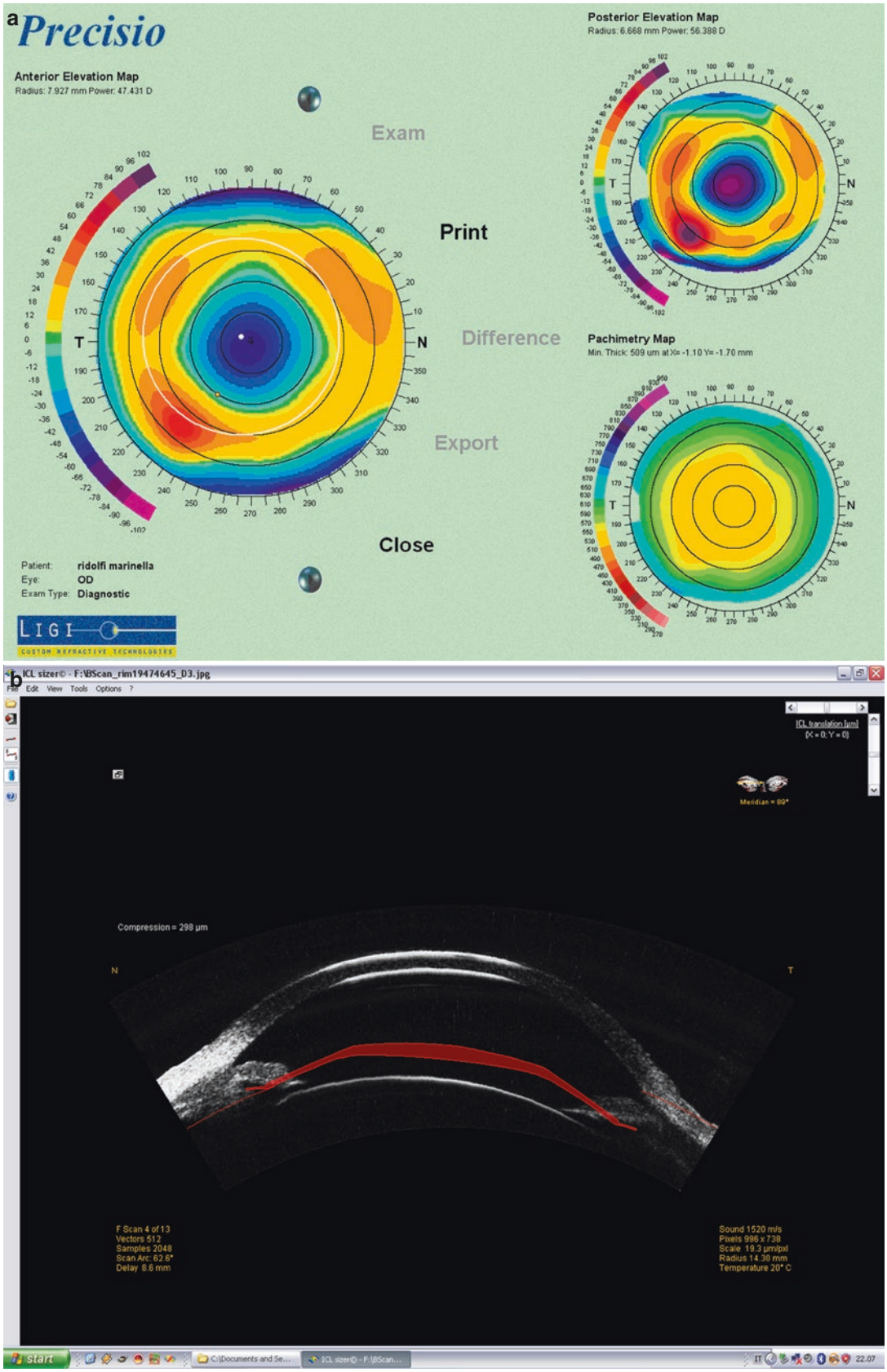

Fig. 37.26 *Precisio* corneal maps (**a**) and VHF echography image with hyperopic ICL simulation (**b**) obtained with the Lovisolo ICL sizer software [16] of case #10

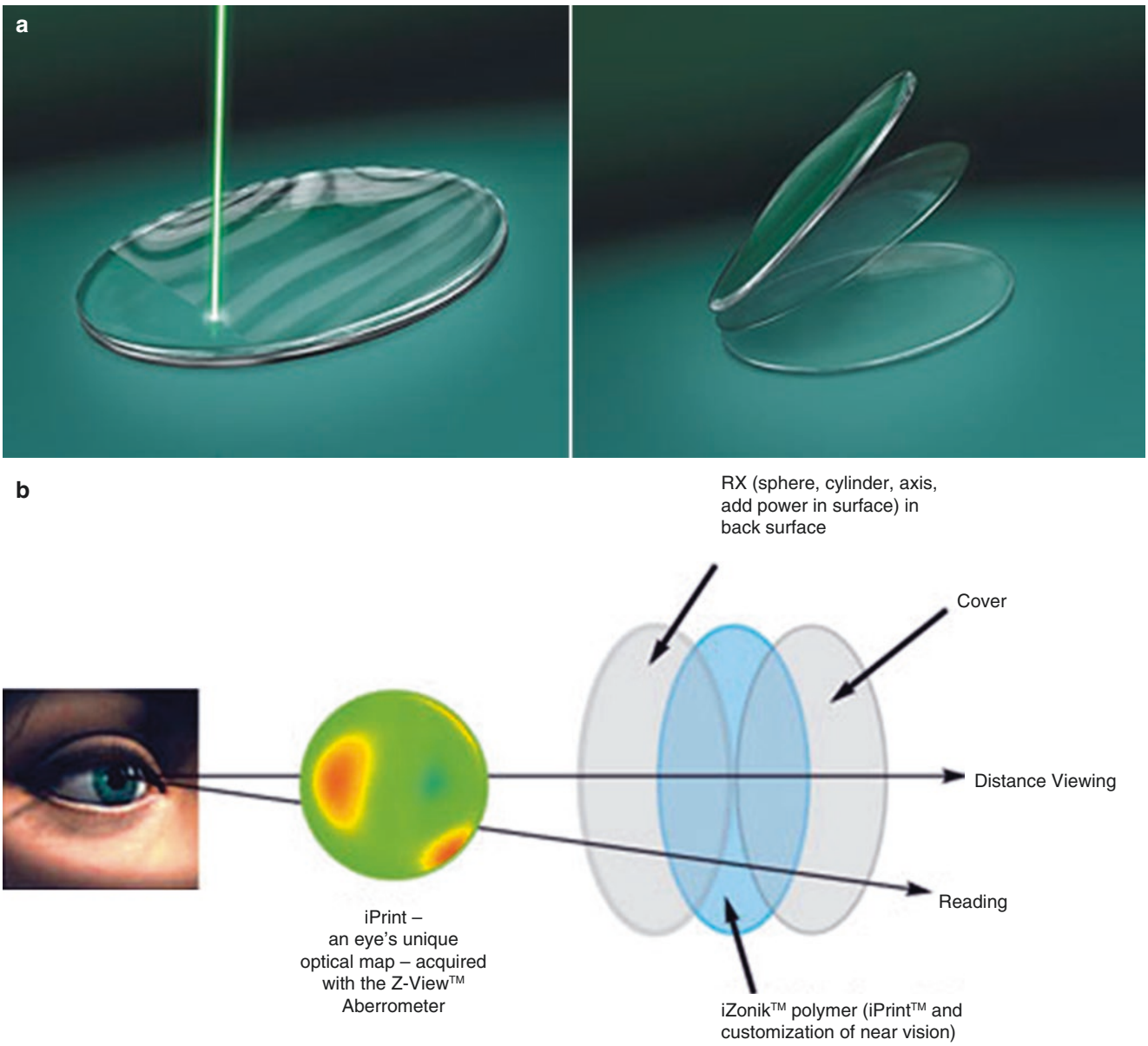

Fig. 37.27 In the *iZon*™ (Ophthonix) wavefront glasses, a programmable polymer undergoes a point-by-point process (**a**) on the basis of the digital aberrometry data; then it is sandwiched between front and back surface blanks to create a multiple composition layer of the lens (**b**) a 1.6 index with antireflective, UV-blocking, scratch-resistant, and hydrophobic coat

aberrations (HOA) are mainly caused by surface irregularities. After a successful RK procedure, the lower-order aberrations (spherical defocus and cylinder, regular astigmatism) generally find a significant improvement. However, the most frequent visual complaints reported by RK patients are loss of best-corrected vision or loss of quality of vision such as with ghost images, double vision, glare, halos, comets, starburst radiating lines, or other light distortions, essentially at night. These disturbances are essentially due to iatrogenically induced higher-order aberrations (HOA) that are not correctable by conventional means like standard glasses and soft contact lenses that are designed to correct only the lower orders (sphero-cylinder). Wavefront-guided spectacle lenses have become available on the market (Fig. 37.27). Such spectacle lenses are programmed on a point-for-point basis, to address beyond the lower orders, up to the sixth order of Zernike polynomials; they have the potential to reduce the unique aberrations of the keratotomized eye, thus improving symptoms, and may correct the lack of crispness and clarity of vision (visual acuity, low contrast visual acuity, and contrast sensitivity). Requisite for any aspheric lens introduced in the eye's optical system, is meticulous mounting and

alignment with the visual axis to be optimally efficient. The distance between lens and ocular surface should be minimized, as well as the eye movements, in favor of the movements of the head. Since they are expensive, the real utility of these glasses is still debatable. Wavefront-guided contact lenses follow the same principles mentioned above and would be beneficial in post-RK patients.

37.7 The Contact Lenses Option

37.7.1 Case #11

Five years after a 16-cut RK procedure, the right eye of a 29-year-old lady showed a CDVA of 20/20 with sph +1.25 cyl +5.00 × 5° (Fig. 37.28). Disabling visual symptoms, mainly glare, were described under mesopic light conditions which did not improve with glasses. Videokeratoscopy (Fig. 37.28c) and corneal topographies (Fig. 37.28e) showed the ectatic changes of the inferior incisions, which were responsible for the nighttime complaints of the patient. While with a photopic pupil size of 3 mm the optical quality of the central corneal zone remained good, as soon as the pupil dilated, the patient suffered increasing amounts of coma (due to the vertical asymmetry), spherical aberration (due to the hyper-oblate profile), and higher-order aberrations (due to surface irregularities) (Fig. 37.28d). Given its lack of flexibility, a rigid gas-permeable (RGP) contact lens may perfectly compensate for the aberrations caused by the altered shape and profile of the anterior corneal surface. The tear meniscus that centrally fills the space behind the posterior surface of the contact lens compensates for more than 90% of the anterior corneal surface aberrations reducing the aberrations to less than 10% of their manifest values. Therefore, when the front surface is designed with the optimized curvature, the RGP lens compensates for both lower and higher orders of aberration, providing the best visual performance achievable with any means. The rigid, inflexible nature of the lens collaterally creates positioning and stability problems especially when conventional RGP geometries are used. Standard RGP contact lenses have been designed for physiologically prolate corneas and are too

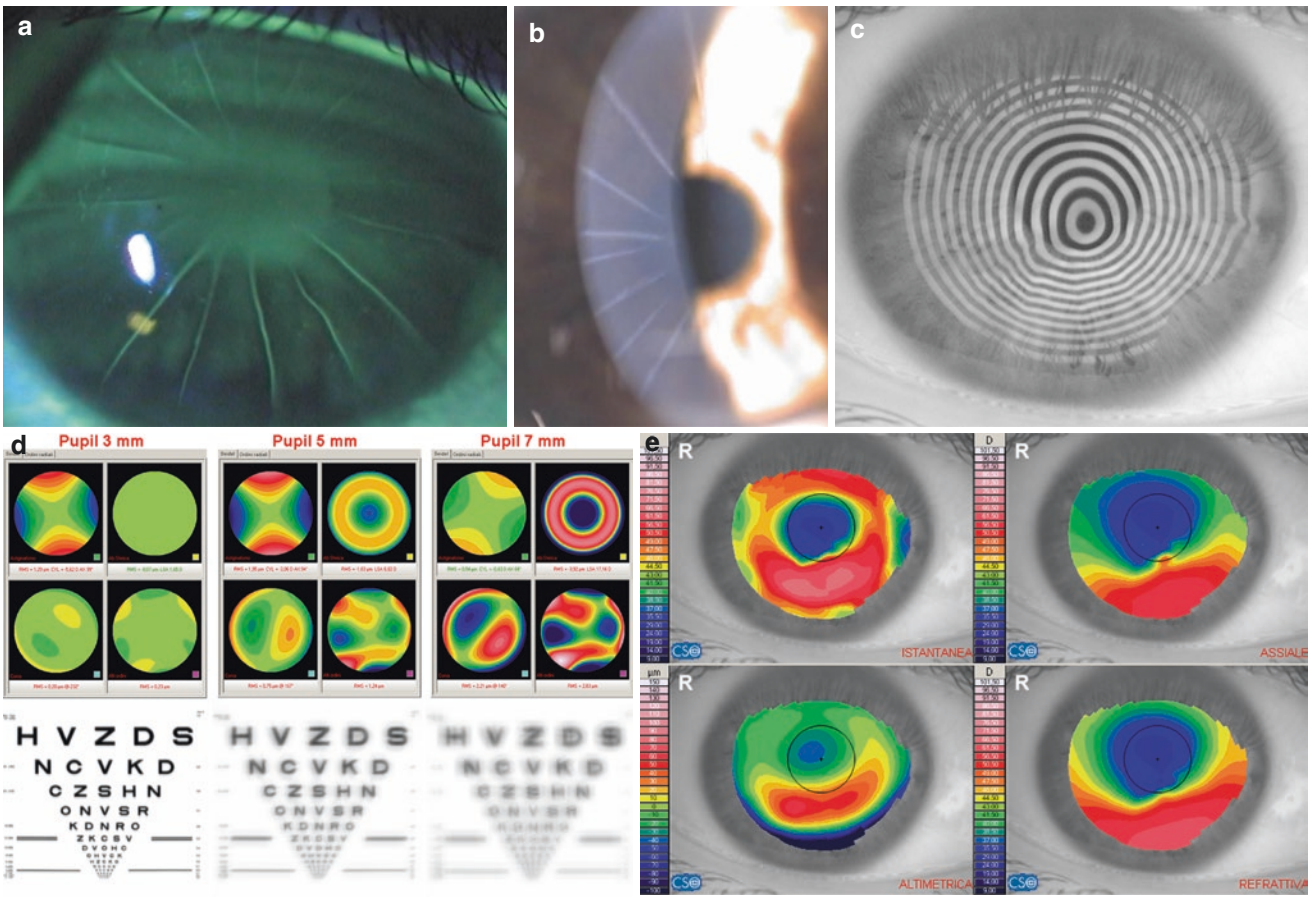

Fig. 37.28 Slit lamp images with and without fluorescein staining (**a**, **b**), keratoscopy (**c**), corneal aberrometry (**d**), and tangential, axial, altitudinal, and refractive corneal maps, where the circles represent the photopic pupil diameter (**e**) of the case report #11 (see text for description)

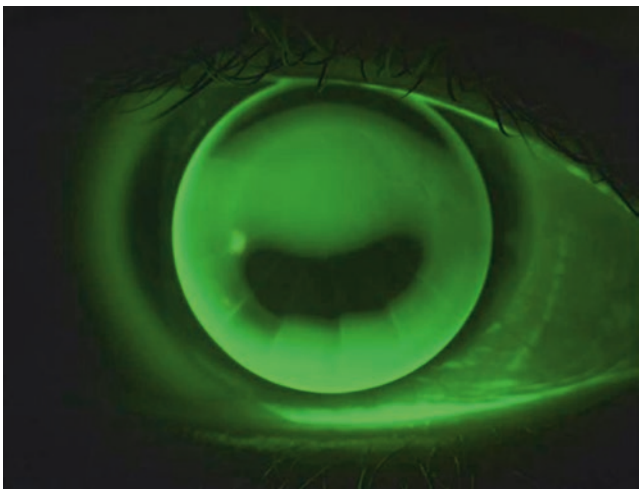

Fig. 37.29 Reverse geometry RGP contact lens fit in the case report #11 (see text for description). Fluorescein staining under *blue cobalt filter* illustrates the significant vertical asymmetry. The steeper peripheral zone allows the lens to stay stable and centered

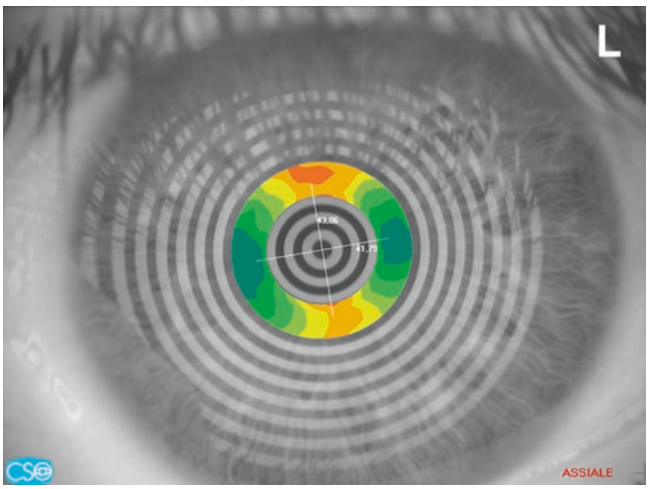

Fig. 37.30 The circular crown colored area represents the zone of the cornea utilized for keratometry measurements and for computerized videokeratography Sim-K index. The central pupillary area is not measured

mobile and, in general, poorly tolerated: the solution to this problem is the piggy back with a soft contact lens under the RGP one. When the RGP optical zone is optimally aligned to the center of the cornea, the lens will have excessive edge lift. Conversely, if the back optic zone radius (BOZR) is reduced to minimize the peripheral edge lift, the optical zone excessively vaults at the center of the cornea. Instead, the oblate elliptical shape of post-RK corneas requires a reverse geometry RGP contact lens [60–63]. This nonstandard design utilizes a peripheral zone curve that is steeper than the optical zone, allowing a proper alignment of both critical areas. Figure 37.29 shows the reverse geometry RGP CL used in case #10.

37.8 IOL Power Calculation After RK

When keratotomized eyes undergo cataract surgery, overestimation of the corneal power made by conventional keratometers is the main factor responsible for the choice of an IOL power that is too low with an undesired hyperopic refractive surprise using conventional calculation formulas [64–66]. The origin of the error lies in the inaccuracy of the approximations made in the measurement of corneal power. Conventional keratometers measure the sagittal curvature of the anterior surface in a small paracentral area [24]. Keratometers use a fictitious refractive index (variable from 1.3315 to 1.3375, dependent on the manufacturer [67]) that considers the refractive effect of the corneal posterior surface of an average eye to provide the corneal dioptric power. After RK, the reversed asphericity is the reason why the central part of the cornea is flatter than the one measured by the keratometer. Inside the pupillary area, the central cornea becomes flatter than the portion of cornea that lies over the marginal zone of the pupil, so its prolate shape becomes oblate (with reverse asphericity) leading to the so-called radius error. This phenomenon increases with the amount of surgical correction [68, 69]. Moreover, the mean corneal flattening is more evident in the posterior than in the anterior corneal curvature, with a decreased anterior-to-posterior corneal curvature ratio.

Keratometers measure a portion of cornea that does not include the central pupillary area. The measured area is limited to the portion of cornea that reflects the keratometric targets (Fig. 37.30) that is constituted by a circular crown with a diameter that varies between approximately 2 and 4 mm and a width that varies between 0.1 and 0.4 mm, based upon the characteristics of the keratometer and the measured surface curvature [70, 71].

With the same keratometer on a steeper cornea, a portion of cornea closer to the center is measured, whereas on a flatter cornea, a more peripheral zone is measured. Due to the Stiles-Crawford effect (SCE) of the first type [72, 73], the area of the cornea that covers the central pupillary zone provides a brighter image than the one formed by the portion of the cornea that covers the marginal zone of the entrance pupil. It follows that the central cornea, which is not measured, has a more dominant role in the formation of the foveal image than the portion of cornea that is usually measured by keratometers. In a normal cornea with an average asphericity, this phenomenon is of little impact because the sagittal curvature varies slightly from the center to the keratometer measuring area, but when asphericity has high absolute values, differences between central and paracentral

curvature cannot be neglected (Fig. 37.31). Moreover, the anterior-to-posterior corneal curvature ratio, which is assumed to be constant when the keratometric index is used to convert measured radii into diopters, is changed by surgery producing the so-called keratometric index error or index of refraction error. The number of incisions is directly proportional to both posterior and corneal flattening and inversely proportional to the anterior/posterior curvature ratio, while the fictitious keratometric index tends to significantly increase in eyes with higher numbers of radial incisions.

It is for these reasons that the measurement of the corneal curvature for optical purposes should provide the average value, weighted by the SCE (i.e., a Gaussian weighing) of the whole corneal area covering the entrance pupil (mean pupil power) and considering both anterior

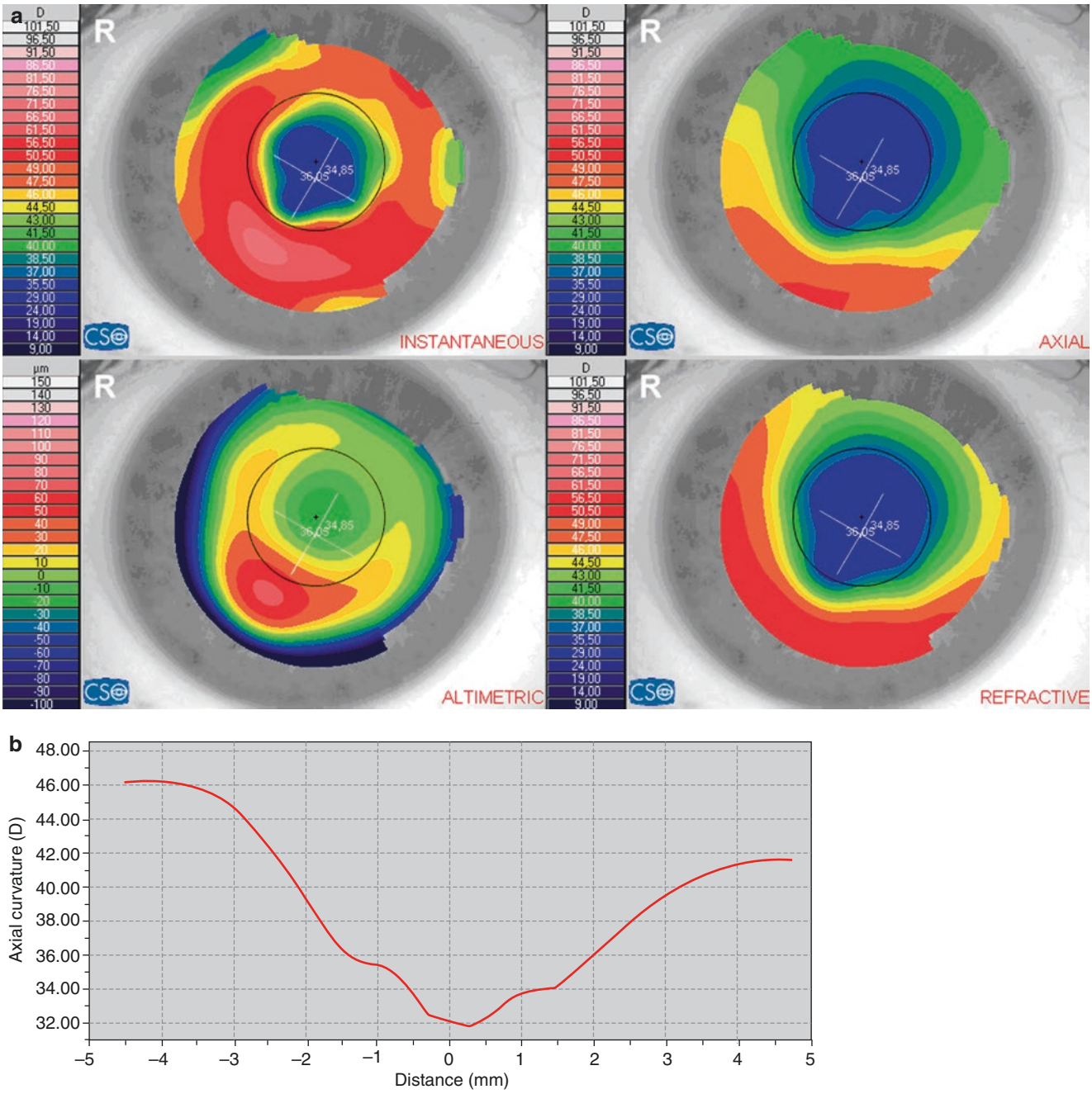

Fig. 37.31 Instantaneous (**a**, *upper left*), axial (**a**, *upper right*), elevation (**a**, *lower left*), and refractive (**a**, *lower right*) corneal maps and the corresponding sagittal curvature profile (**b**) of a typical post-RK cornea. The average simulated keratometry (sim-K) is 35.74 D, while the mean pupil power is 32.75 D

and posterior corneal surfaces. For the reasons we have described, this measurement cannot be performed by conventional keratometers but can be obtained by computerized videokeratographers.

In a conventional IOL power formula, K-readings are also used to calculate the effective lens position (ELP), that is, the estimated postoperative distance between the anterior corneal surface and the principal optical plane of the IOL. The assumption is that flat cornea curvatures generally mean shallow anterior chamber depths and more anterior positioning of the IOL. This principle is obviously not applicable to post-RK eyes, whose anterior corneal surface has been flattened, but the unaltered anterior chamber is usually deep and wide leading to the so-called IOL formula error [74, 75]. To correct this artifact, which is subject to the error produced by the corneal power overestimation, Aramberri proposed a modification to the SRK/T formula, by using the presurgical K-value, obtained by preoperative keratometry or topography for the ELP calculation and the postsurgical K-value by the clinical history method for IOL power calculation by the vergence formula [74]. Double-K modification of the SRK/T formula greatly improves the accuracy of IOL power calculation after RK, but it is sometimes impossible to adopt because the preoperative corneal curvatures are not always available.

Several methods have been proposed for optimizing the calculation of IOL power in RK patients. An oversimplified, empirical method proposed by Lyle and Jin [76] proposed a fixed subtraction of 1.00 diopter from the average K-reading (adjusted *K*) which is inserted in a formula that averaged the result between the Binkhorst and the Holladay formulas but unfortunately showed no significant accuracy [77].

The *clinical history* method [78, 79] and its variants [80–82] substantially considered the changes in refraction induced by the procedure from the preoperative keratometric readings. The *contact lens* method [78, 79, 83] subtracts the difference between the manifest refraction with and without a hard contact lens of known base curve from that base curve plus the power of the lens. The drawbacks of this method lie in the high variability of refractive measurements with and without contact lenses. Accuracy varies on the basis of the rigid contact lens fit and significantly decreases with decreasing visual acuity and with increasing media opacity [84]. The intraoperative *aphakic refraction technique* has many variants proposed by different authors. Mackool et al. [85, 86] first described a technique in which the cataract is removed, the aphakic eye is refracted 30 min later, the IOL power is calculated by using a nomogram developed by the same authors, and the IOL is eventually implanted. Ianchulev et al. [87] used intraoperative automated refraction, while Ahmed and Toufeeq [88] performed intraoperative retinoscopy after the fit of +10.0 D disposable soft contact lens to minimize retinoscopic error. The latter authors concluded that intraoperative retinoscopy after phacoemulsification is useful but not accurate in estimating corneal power or axial length of the eye. The obvious disadvantage of this approach is the need to return to the operating room for IOL implantation. It also uses oversimplified formulas (Mackool and Ianchulev multiplied the measured refractive error by a fixed, albeit different, value: 1.75 and 2.01, respectively) and is prone to the errors secondary to the vertex distance dependence of the aphakic refraction and the biomechanical instability of the keratotomized cornea immediately after cataract surgery [89], which commonly show variable amounts of transient hyperopia in the early postoperative period which should gradually resolve after 8–12 weeks. This is felt to be due to the stromal edema around the radial incisions, producing a temporary enhancement of central corneal flattening. Sometimes, due to a lack of corneal stability, the postoperative refraction can continue to slowly shift myopic over several months. The decision to plan for an IOL exchange or a piggyback IOL, because of unsatisfactory final postoperative refraction, should not be made until at least 2 months have passed and two consecutive refractions, 2 weeks apart (at the same time of the day), are stable.

The use of *topographic data* has been advocated by several authors and is actually considered the more precise alternative to standard keratometry [90–95]. Modern computerized videokeratographers allow us to measure thousands of points in a wide area of the anterior corneal surface and provide us plenty of keratometric indices: simulated keratometry (sim-K); minimum K-reading (min-K); curvatures at 3, 5, and 7 mm; central keratometry (Kc); ACP (average corneal power); etc. However, the crucial question remains: which one is the most adequate for calculating IOL power? Han and Lee [91] reported that in highly myopic eyes with previous RK, the flatter keratometric value between sim-K and the 3-mm zone mean keratometric value from Orbscan II was the closest to the true postoperative RK keratometric value of the central cornea. Several authors reported a large variability of results depending on different parameters and topographers considered, with the less predictable outcomes occurring in corneas with eight or more RK incisions and in which ones with abnormal topographical equivalent refraction values distribution profile.

Awwad et al. back calculate retrospectively IOL power in patients already implanted using the Aramberri double-K adjusted Holladay 1 formula assuming pre-RK keratometric values to be 43.86 (thus without needing such data) and looking for the best way to estimate post-RK ACP: they found better IOL estimation using the average of all the topographic data central to the 3 mm area of the cornea. Similarly, the Zeiss Atlas method, used on the ASCRS web site for post-RK IOL calculations, estimates the central corneal power taking average of the 1 mm, 2 mm, 3 mm, and 4 mm

ring. Comparable results were obtained with only rotating Scheimpflug camera-based post-RK IOL power calculation: Potvin et al. described an algorithm taking into account Holladay 1 double-K formula using a preoperative K of 43.86 D and a postoperative K of the mean sagittal front keratometry at the 4 mm zone centered over the pupil and the thinnest local pachymetry measurement.

In our opinion, the use of topographic data (we strongly suggest the use of the average curvature of the corneal areas that cover the entrance pupil weighted on the Style-Crawford effect [96]) offers the greatest precision of IOL power calculation as compared with keratometric data. Importantly, however, clinical experience teaches us that repeatability of measurements is lower with computerized videokeratographs than with keratometers and that the possibilities of error increase in short distance videokeratographer [97]. For this reason, we suggest an accurate verification of the instrument calibration and taking more measurements of the same eye with elimination of the extremes and calculating the average of the central values. If the conventional keratometric targets have a regular appearance, it is useful to compare keratometric readings with sim-K, and if these values greatly differ, new measurements should be obtained.

In post-RK eyes, we have been using the *Camellin-Calossi formula* [96] for more than 6 years, 100% of our postoperative refractions lie in the ±1.00 D range (predicted versus achieved refraction), and 95% are in the ±0.75 D range. The formula originates from a theoretical one that was empirically adjusted in two parameters: (1) the corneal power (D_c) and (2) and the prediction of effective lens position (*ELP*).

Differently from other third-generation formulas that often use keratometry as the main predictor, and similar to Haigis [89], Camellin and Calossi have chosen a K-independent method to estimate ELP. The variable ACD_{post} is a function of the anterior chamber depth previous to cataract surgery (ACD_{pre}), of the lens thickness (*CT*), of the axial length (*L*), and of the ACD constant (ACD_{const}). To estimate the real corneal power, they use the average curvature, weighted according to the SCE, of the corneal area that covers the entrance pupil. The real corneal power is calculated considering a relative keratometric refractive index that is a function of the actual corneal curvature (*r*), the type of keratorefractive surgery performed, and the surgically induced refractive change (*SIRC*). In case of laser ablative surgery, the prime cause of error is the conversion from curvature radius to dioptric power of the cornea [98] since photokeratectomy modifies the ratio between anterior and posterior corneal surfaces. The real corneal power is calculated using a relative keratometric refractive index that is a function of the SIRC. At this time, it was assumed erroneously that when incisional surgery has been performed, the ratio between anterior and posterior corneal surfaces has not been modified and the average central curvature was considered as the radius (*r*), weighted according to SCE, of the corneal area that covers the entrance pupil. Then, the real corneal power is calculated using Gaussian optics equation adopting a keratometric refractive index (*n*) of 1.332. After RK, conventional K-readings should only be used when reliable topographic measurements are not available (for instance, when huge variations of corneal asphericity or reflections of the Placido disk mires out of the optical zone are found).

After the recent discovery that RK induces changes of the anterior-to-posterior corneal curvature ratio, "keratometric index error" should also be considered before converting the curvature of the anterior corneal surface into the dioptric power of the whole cornea. This error can be avoided with methods independent from any keratometric index, such as ray tracing based on Snell law or the Gaussian optics formula. Promising results have been showed by Waisbren et al. that developed an AS-OCT-based formula for calculating IOL power using anterior, posterior, and net corneal power and pachymetry measured by OCT, axial length, and anterior chamber depth measured by partial coherence interferometry and postoperative refractive error.

Another way to calculate the IOL power addressing the errors related to RK could be using the internal software of a Scheimpflug camera combined with a Placido disk corneal topographer, but no studies have been published about this topic.

37.8.1 Case #12

A 58-year-old man was referred for IOL power calculation, as a cortico-nuclear cataract had developed in his left eye, 16 years after bilateral RK for compound myopic astigmatism (pre-RK refraction was OD: sph −4.00 cyl −1.50 × 20°, OS sph −4.75 cyl −2.00 × 150°). As shown by corneal topographies (Fig. 37.32), the excessive flattening of central cornea led to a significant overcorrection (CDVA was OD = 20/20 with sph +5.00, OS = 20/200 with sph +3.00 cyl +0.50 × 180°). A-scan ultrasound biometry data of the left eye was axial length, 25.9 mm; lens thickness, 4.45 mm; and anterior chamber depth, 3.87 mm. Mean keratometry was 37.50 D. Asphericity of the optical zone was strongly oblate (*Q* = 2.14). To calculate the actual corneal power, we utilized the averaged power in the pupillary area, as obtained from the CSO topographer, that with the Camellin-Calossi formula gave us a power of 35.86 D (very close to the corrected keratometric value given by the same formula for an achieved correction of −8.00 D, 36.02 D). For an A-constant equal to 118.5, the Camellin-Calossi formula calculated a power of +23.66 D for emmetropia. Figure 37.33 summarizes the IOL powers obtained with different formulae with standard keratometry values. An IOL of +24.00 D was

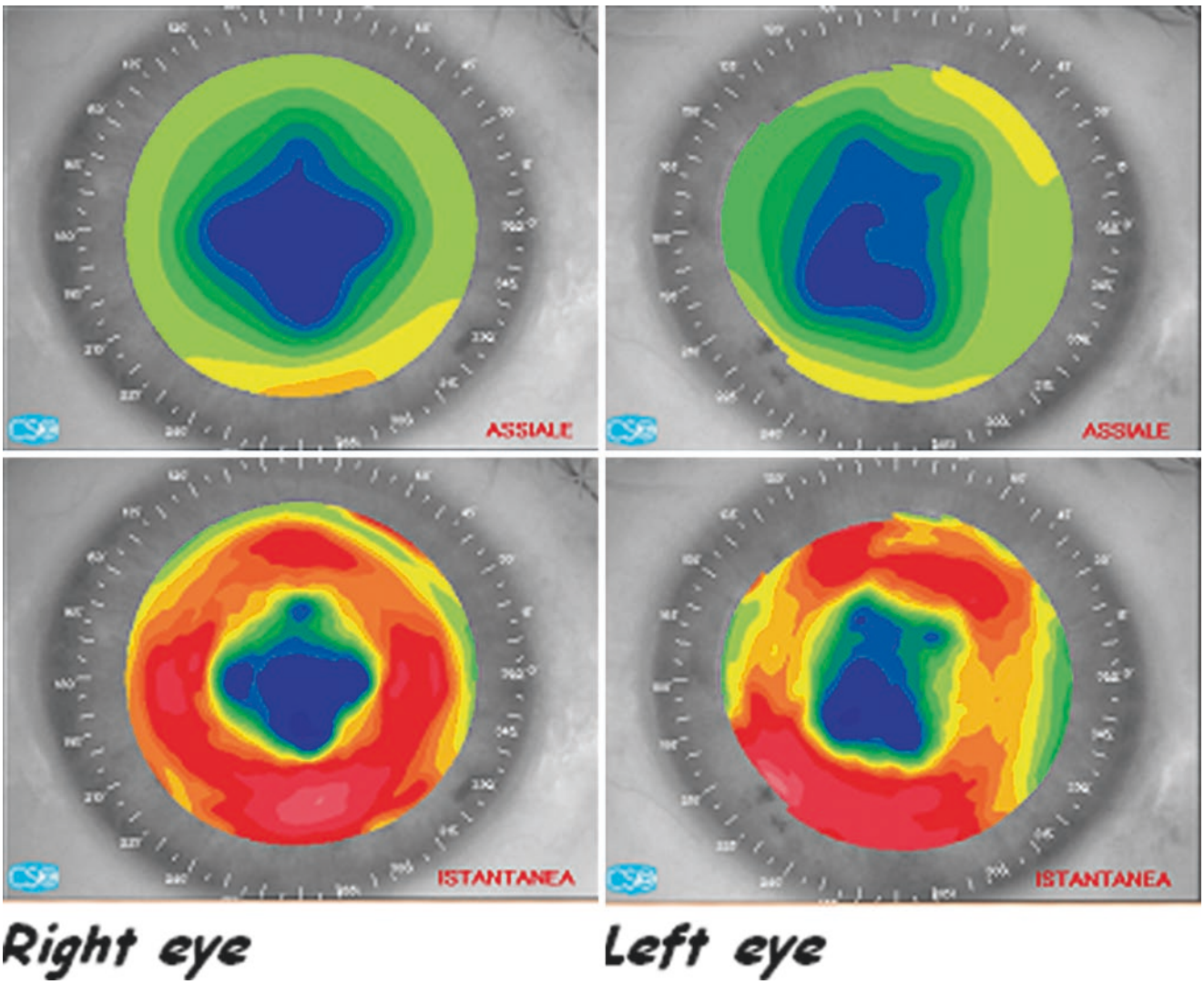

Fig. 37.32 Corneal topographies of the case report #12 (see description in text)

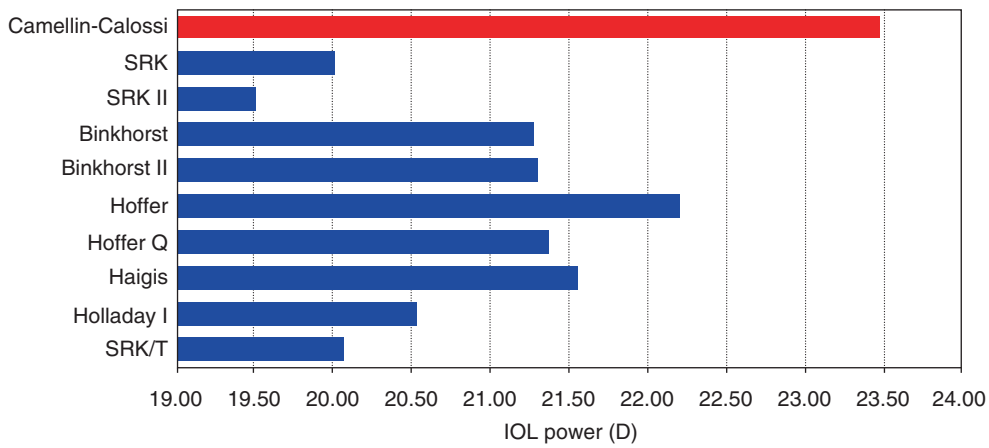

Fig. 37.33 Comparison of IOL power obtained in the case report #12, left eye, with different formulae

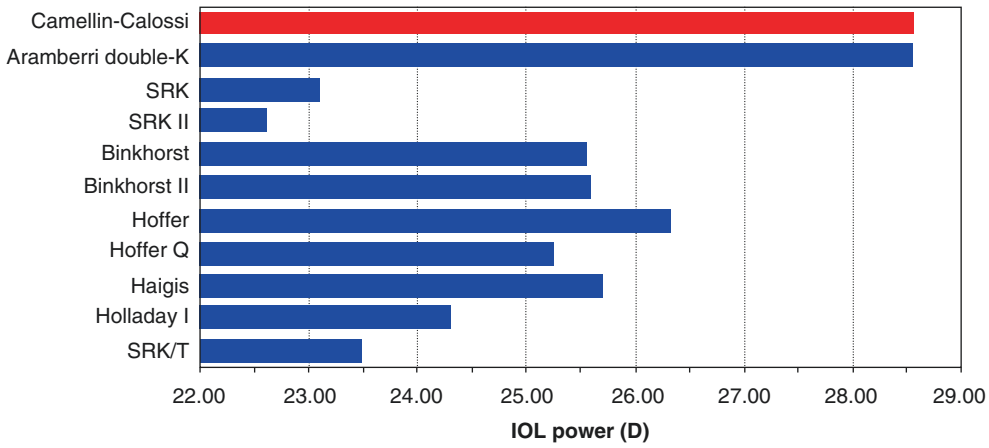

Fig. 37.34 Comparison of IOL power calculated for the right eye of the case report #12, with different formulae and methods

implanted; 1 month after surgery, uncorrected visual acuity was 20/20, improving to 20/20+ with cyl −0.50 × 90°. The great outcome and the anisometropic difficulties in binocular vision (the right eye was the dominant one) motivated to consider the option of a clear lens extraction surgery in the right eye.

Considering the good visual acuity of the right eye, we have tried to compare the data obtained from different methods to get the effective corneal power. OD mean K-reading was 36.00 D, the contact lens method gave us a value of 33.75 D, while the mean pupillary power obtained from videokeratography (CSO) was 34.5 D. By using the Camellin-Calossi formula, the corrected keratometric value for a myopic corneal correction of −9.00 D was 34.49. The Q-value of the optical zone was 4.5. A-scan US axial length was 25.2 mm, lens thickness 4.45 mm, and ACD 3.64 mm. For an A-constant of 118.5, the Camellin-Calossi gave us a power of +28.56 D for emmetropia. A similar value (+28.54 D) was obtained by using the double-K Aramberri formula as combined with the value of effective corneal power obtained with the contact lens method. Figure 37.34 makes the comparison of IOL power obtained with different formulae with standard keratometry values.

Take-Home Pearls

- Following the marketing hype of radial keratotomy in the 1980s and 1990s, refractive surgeons will be faced with several decades of iatrogenic challenges.
- RK patients are likely to progressively increase toward hyperopia at a mean rate of 1D per 6–8 years.
- RK patients may have multiple contributory factors to visual disturbances such as too small optical zones, prolate asphericity, irregular astigmatism, and decentrations beyond the lower-order progressive aberrations.
- LASIK for correction of stable RK refractive errors should be considered in patients with eights or less incisions, with a thicker than normal flap to minimize possibility of flap fragmentation.
- Whole eye wavefront may not be accurate for complex RK corneas, whereas repeatable corneal elevation-based custom refractive surgery may be more accurate.
- Restoring physiologically normal asphericity is an important aspect of decreasing visual disturbances.
- Intrastromal rings may improve asphericity. However, as space occupying elements, they may contribute to wound strain and delayed wound opening sequelae.
- Relentless progressive hyperopia is difficult to manage even with suturing techniques.
- Keratometer readings on RK eyes are unreliable for use with IOL calculations.
- The Camellin-Calossi formula currently produces the highest IOL predictability for post-RK eyes.

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Management Complications of Intracorneal Ring Segment Implantation

38

Alfredo Vega-Estrada and Jorge L. Alio

Core Messages

- Intracorneal ring segment (ICRS) implantation is a safe and effective surgical technique with low rates of complications.
- The use of femtosecond laser for the creation of the stromal tunnel increases the safety of ICRS implantation.
- A high risk of losing lines of vision after ICRS implantation is observed in patients with good visual function prior to the procedure.
- It is advisable to demonstrate the stability of keratoconus prior to ICRS implantation, as halting progression of the disease has not been demonstrated with this surgical technique.

38.1 Introduction

Intracorneal ring segments (ICRSs) are small devices made of synthetic materials that are designed to be implanted within the stroma aiming to change the geometry and the refractive power of the corneal tissue. The idea of implanting a corneal ring into the cornea was first proposed by Blevatskaya in 1966 [1]. The shape of the initial design was a completed 360° full ring that leads to several complications and in consequence was rapidly abandoned. In the coming years, the ring segment design was extensively investigated and changed for the current C-shaped segments that we know today. It was demonstrated that ICRS could act as spacer elements between the collagen fibers of the corneal tissue, thus inducing an arc-shortening effect that in consequence flattens the central area of the cornea [2]. Some investigators found that the flattening effect could induce a refractive change in the cornea depending on the thickness and the diameter of the segment [3]. In 1999 Intacs Technology received the FDA approval for the correction of low to moderate myopia using ICRS. Nevertheless because of the good results obtained with excimer laser when correcting refractive errors, ICRS was relegated and not often used as a refractive surgery technique.

Due to the capability that ICRSs have in modeling the geometry of the cornea, in the year 2000, Prof. Joseph Colin proposed the use of these devices for the treatment of keratoconus for the first time [4]. Since then, several authors have reported the benefit of using ICRS in keratoconic eyes with the added value of delaying or avoiding more complex interventions like keratoplasty procedures [5–8].

Nowadays ICRS implantation represents one of the main therapeutic approaches for the treatment of keratoconus. Even when they are not frequent, the purpose of the present chapter is to describe the complications related to ICRS implantation in patients with corneal ectatic diseases.

38.2 Surgical Procedure-Related Complications

In order to implant the ICRS in the corneal stroma, it is necessary to create tunnels or channels deep in the cornea where the segments will be inserted. These channels can be performed using a manual or mechanical technique or with the femtosecond laser-assisted technique.

For the mechanical technique, we must mark the center of the pupil in order to guide the treatment. Then with a calibrated knife set at 70% of the corneal depth, a corneal incision is performed. Afterward, two circular dissectors are

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inserted in the incision in a clock- and anticlockwise movement in order to perform the stromal channels.

In the femtosecond laser-assisted technique, a coupling interface is placed over the cornea with a disposable device that allows a precise focus of the laser beam, thus creating a dissection at the desired depth. The tunnel is then created at approximately 80% of the corneal pachymetry without directly manipulating the eye. Finally, the ICRSs are inserted in the created tunnels.

Complications related to the surgical technique are more often observed when using the mechanical approach in comparison with the femtosecond laser. This is basically due to the fact that in the femtosecond laser-assisted technique, a more precise depth into the corneal stroma can be achieved in comparison with the one using the mechanical dissection. The intraoperative complications that are more often observed are segment decentration, inadequate depth of the tunnels, and asymmetry of the segments [6].

Anterior or posterior perforation or superficial and too deep stromal channels may occur during the dissection maneuver with the circular dissectors. Figures 38.1 and 38.2 show an anterior optical coherence tomography image of the cornea of a patient in which superficial and very deep ICRSs were implanted, respectively.

In order to avoid such complications, it is recommended to perform a proper thickness measurement specifically at the incision site. Nowadays there are several instruments that can provide a pachymetry map with a high accurate measurement of the corneal thickness in different areas of the cornea. These devices can provide a corneal pachymetry of the specific area between 5 and 7 mm where most of the different ICRS designs are implanted. Figure 38.3 shows a pachymetry map generated with anterior optical coherence tomography.

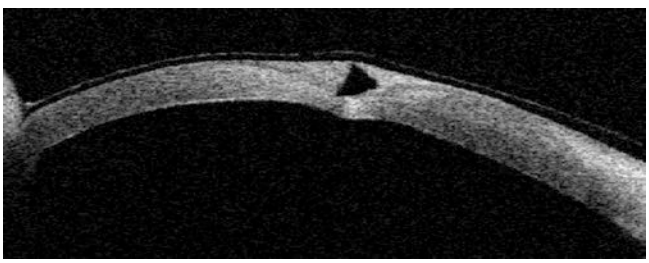

Fig. 38.1 Anterior optical coherence tomography image of the cornea showing an ICRS implanted too superficially

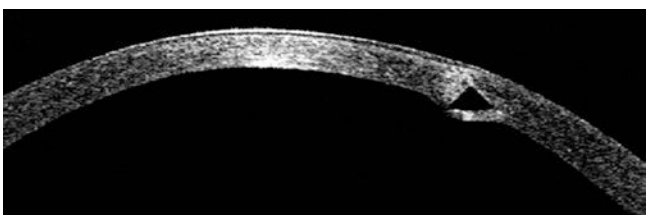

Fig. 38.2 Anterior optical coherence tomography image of the cornea showing an ICRS implanted too deep

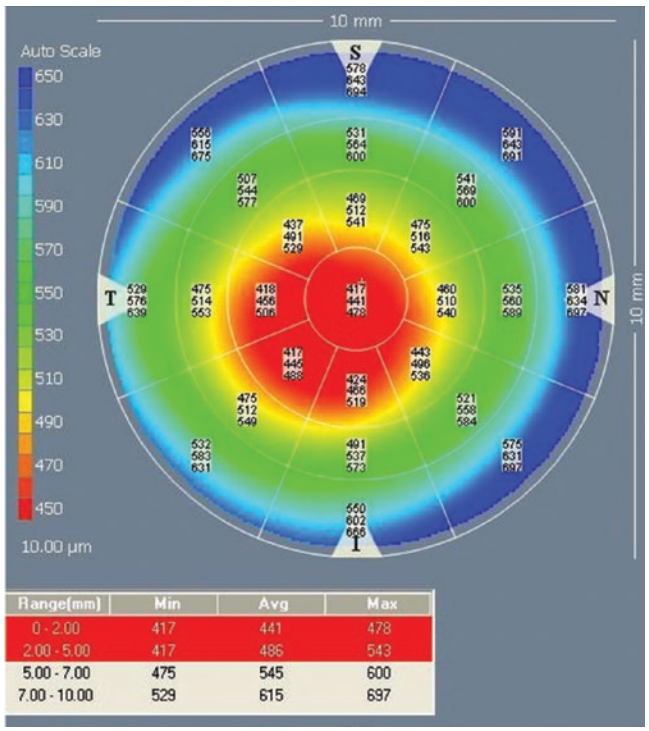

Fig. 38.3 Pachymetry map performed by anterior optical coherence tomography

Additionally, checking the intraocular pressure during mechanical dissection and performing a uniform rotational movement with a dissecting spatula are mandatory not only to avoid anterior or posterior perforation but to achieve a uniform tunnel depth. Usually, when implanting the segments, just a minimal resistance can be found. Thus, in those cases when a major resistance is observed when inserting the ICRS, it may be due to the fact that we are entering in a different plane than the one created with the dissector. In the case one of the aforementioned complications occur during the surgical procedure, surgery must be canceled and postponed to be completed 3 months after the first complication event.

As previously mentioned, surgical complications with the femtosecond laser-assisted technique are not common. Nevertheless, in some cases the dissection depth may be set too deep; thus dissection bubbles may be seen in the anterior chamber. This may lead to an endothelial perforation and is reported to happen in 0.6% of the procedures [9]. In this case, and if we haven't dissected the complete channel yet, it is not necessary to postpone the procedure. A new dissection depth may be placed more superficially in the device and continued with the surgical procedure can be continued. Other complications that are specifically related to the femtosecond laser-assisted technique are incomplete channel

formation with an incidence of 2.6% of cases [9], vacuum loss which occurs in around 0.1% of cases where just in a few cases it is necessary to use a new suction ring for a proper vacuum, and subconjunctival hemorrhage that is related to the suction ring and usually resolves spontaneously after 2 or 3 weeks.

38.3 Postoperative Complications

After implanting ICRS, is there are several complications that may occur. Nevertheless, these complications are not frequent, and most of them are not clinically relevant.

One of the most serious complications that may appear after ICRS implantation is *infectious keratitis*. This complication can be present one day postoperatively or even weeks or months after the procedure. The literature reports an incidence of 1.9% of patients having infectious keratitis after ICRS implantation when using the manual technique and 0.1% when using the femtosecond-assisted technique [6, 10]. Management of this complication should be performed in the same way that is done when treating a standard infectious keratitis. We must identify the microorganism that is present by performing a corneal culture or polymerase chain reaction (PCR) [11]. Empirical treatment using fortified topical antibiotics against both aerobic and anaerobic organisms should be instituted after performing the culture. Once we have the results of the antibiogram, specific treatment should be started. In those cases when the infection is located in a small area and there is no significant melting of the cornea, the segment can be kept within the channel. Nevertheless, in those cases when a severe infection is present, the ICRS channel is compromised, or if there is not a proper evolution of the case, the ICRS should be explanted. In the latest, copious irrigation of the tunnel with balance saline solution (BSS) and antibiotics should be performed [12]. Segment explantation should not be the first choice and must only be considered the last option when medical treatment fails.

Segment *extrusion* or *migration* is one of the complications that may be seen relatively frequent after surgery. According to the literature, this complication is more frequent when dissecting the stromal channel with the manual technique than with the femtosecond laser [6, 10]. Kwitko and coworkers found an incidence of extrusion and migration as high as 19.6% of the cases when using the mechanical surgical procedure for stromal tunnel creation [10]. On the other hand, Coskunseven et al. reported segment displacement in just 0.8% of patients when using femtosecond laser-assisted technique [6]. Segment extrusion or migration can occur at any time after the procedure but is usually more often observed as a late complication mainly in those atopic patients with an eye-rubbing habit. Depending on the severity of the segment displacement and mainly when the migration induces epithelial defect and stromal inflammation, this event may lead to more severe complications like infectious keratitis and corneal melting. To perform a rapid and adequate diagnosis in order to institute the proper treatment with topical steroid, antibiotic drops and also a contact lens placed when needed may avoid a procedure for segment explantation. Another approach that may reduce the incidence of segment extrusion is to place a 10-0 nylon suture in the incision site [6]. In those cases when all the aforementioned recommendations fail and there is a severe inflammation or infection of the cornea, segment explantation should be indicated. Finally, it is highly recommended in keratoconic patients and most of all in those with an eye-rubbing habit to prescribe topical antihistaminic treatment in order to reduce the rubbing frequency, thus decreasing the risk of segment extrusion.

Other postoperative complications that may be seen after ICRS implantation are *corneal neovascularization* and *channel deposits* (Figs. 38.4 and 38.5, respectively). Corneal neovascularization usually occurs as a late complication and mainly in those patients who wear contact lenses or when the stromal channel is dissected too close to the limbus. Channel deposits around the segment is the most frequent complication observed after ICRS implantation, and its incidence has been reported to be as high as 60% [13]. According to Ruckhofer et al., these deposits are composed of intracellular lipids, and their density increases in relation to the segment thickness and time within the stromal channel [14]. These deposits may not induce any optical or anatomical alteration in the cornea. As we can see, channel deposits are a very

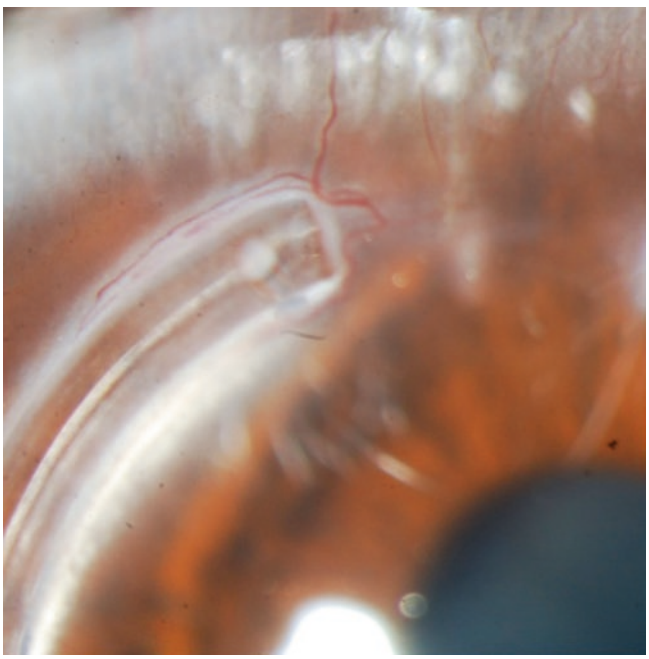

Fig. 38.4 Corneal neovascularization after ICRS implantation

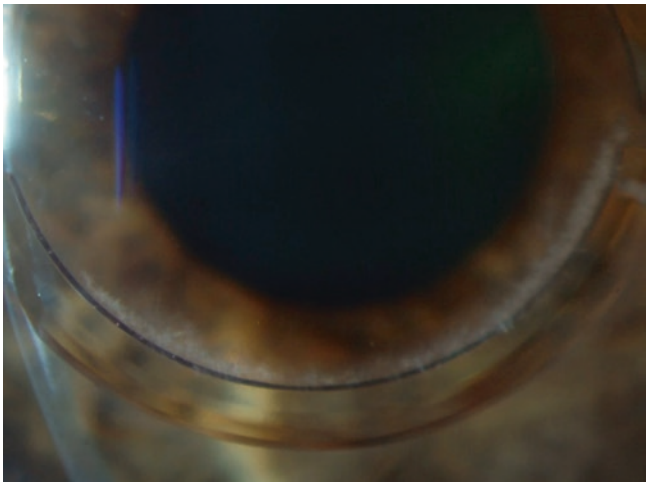

Fig. 38.5 Deposits within the channel after ICRS implantation

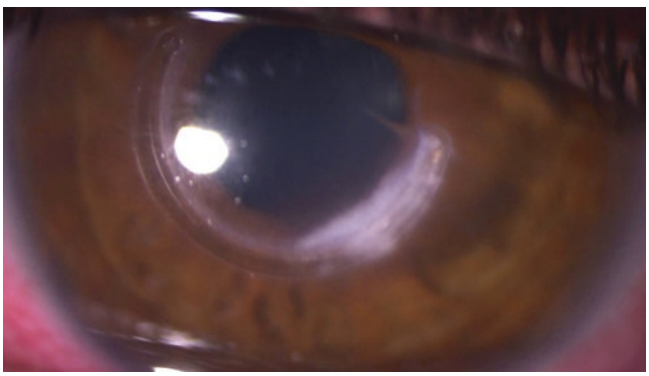

Fig. 38.6 Infectious keratitis after ICRS implantation

common finding after ICRS implantation, but they are completely benign, and no treatment is required when they are observed. At this point, it is important to mention that channel deposits are asymptomatic and do not induce any inflammatory reaction within the corneal stroma. Figure 38.6 shows an image of localized corneal infiltrate around the ICRS of a patient with fungal keratitis. At this case we can clearly see the difference with channel deposits as the clinical appearance in fungal keratitis is with an asymmetric infiltrate, inducing an inflammatory reaction within the corneal stroma, and potentially leading to corneal melting if not properly treated.

Another severe complication that can be observed after ICRS implantation is *corneal melting*. Its incidence is very low, less than 0.2% according to the investigation carried out by Coskunseven et al. [6]. When it is present, usually there is a significant corneal thinning in the tissue surrounding the segment, or it is related to a severe infection which leads in most of the cases to segment explantation. A recent study analyzing the new design of ICRS with more than 340° of arc length has reported complications, such as corneal melting, which suggest that a close follow-up of patients implanted with this ICRS design should be performed [15].

38.4 Optical-Related Complications

Regarding the complications that are related to the visual function and optical quality of the patients, we can find reduction of the visual acuity and an increase in the corneal higher-order aberrations after ICRS implantation.

In terms of visual acuity, the authors of the present chapter carried out an investigation in which it was observed that those patients with visual acuity better than 0.9 in the decimal scale had a high risk of *losing corrected visual acuity* after ICRS implantation [8]. Nowadays, a general evaluation of surgical safety should consider that the percentage of loss of two or more lines of corrected vision after a surgical intervention at 6 months of follow-up must be between 1 and 5% [16]. A study by Vega-Estrada et al., analyzing the outcomes of ICRS according to the vision of the patients, showed that this condition happens in more than 35% of the patients with visual acuity better than 0.9 [8] (Table 38.1). Thus, ICRS implantation in patients with good visual function should not be considered as a safe technique to avoid the risk of losing visual acuity lines that may happen in these patients. Other causes that may lead to vision loss after ICRS implantation that have been proposed by other authors are the severity of the disease [17] or inadequate selection regarding symmetrical or asymmetrical segment implantation [5].

In relation to corneal higher-order aberrations, most of the studies have shown that ICRSs have the capability of modeling the corneal tissue, thus leading to a reduction of the corneal aberrations [8, 18]. Nevertheless, there are some studies published in the scientific literature that report that *corneal aberrometric coefficient may increase* after ICRS implantation in patients with grade I keratoconus and those in which the corneal aberrations were less than 3 microns before surgery [12]. This way, it is highly recommended to bear in mind these findings when selecting the patients in order to avoid increasing high-order aberrations after ICRS implantation.

Regarding the stability of the procedure, most of the studies that have analyzed the long-term results of ICRS implan-

Table 38.1 Percent loss of ≥ 2 lines of usual acuity following ICRS implantation

Keratoconus	Lost ≥ 2-line CDVA
Visual acuity > 0.9	37.8%
Visual acuity > 0.6 <0.9	20.6%
Visual acuity > 0.4 <0.6	9.4%
Visual acuity > 0.2 <0.4	4.6%
Visual acuity < 0.2	3.7%

CDVA corrected distance visual acuity

tation report stability of the visual and refractive variables. Nevertheless in these studies, just cases with stable form of the disease were evaluated, or there was no distinction between stable and progressive cases [18–20]. As a matter of fact, we performed a study analyzing just progressive cases of keratoconus implanted with ICRS, and observed that a *major regression* of visual and refractive outcomes occur after a long period of time [21]. Thus, in order to provide long-term stable outcomes to our patients, ICRS implantation should be recommended after confirming stability of keratoconus, in order to avoid a regression of the benefit achieved after surgery.

38.5 ICRS Explantation

ICRS explantation due to complications varies significantly from 0.98% to 30% [22]. In the study conducted by Pokroy and Levinger [23], the authors found that at least 10% of the patients implanted with ICRS will need an "adjustment" of the procedure usually consisting in rotating or explanting the segments in order to treat or avoid a significant complication. A study by Alió et al., demonstrated that ICRS can be safely and easily explanted with most of the visual and refractive variables coming to values close to the ones found preoperatively [24].

Conclusions

In conclusion, ICRS implantation is a safe procedure for the treatment of corneal ectatic disorder with low rates of complications. Due to advances in technology, the femtosecond laser-assisted technique is clearly more safe with significantly less complications than the manual technique. Patients with good visual function and those with unstable keratoconus are poor candidates for ICRS implantation. Further studies with large samples of patients, long-term follow-up, and new segment designs are needed in order to provide more scientific information and understand one of the few therapeutic alternatives for corneal ectatic disorders.

Take-Home Pearls

- Intracorneal ring segment (ICRS) implantation is a safe and effective procedure for the treatment of keratoconus patients.
- ICRSs are able to regularize the surface of the cornea and reduce corneal higher-order aberrations in patients with keratoconus.
- Complications after ICRS implantation are rare when using the femtosecond technology for stromal dissection.
- Patients with good visual function and those in which stability of keratoconus has not been demonstrated are poor candidates for ICRS implantation.
- ICRS implantation is a reversible procedure in which visual and refractive variables are expected to come to preoperative levels after ICRS explantation.

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Corneal Inlays: Complications

39

M. Emilia Mulet and Jorge L. Alio

Core Messages

- There are different types of corneal inlays that can correct refractive error or presbyopia.
- Complications can be due to misplacement of the intracorneal inlay. However, the majority of visual problems are produced by lack of adaptation or patient neuroprocessing difficulties.

39.1 Introduction

Presbyopia treatments include corneal refractive procedures with monovision or multifocal ablations with certain disadvantages such as poor predictability, regression, limited effectiveness, and irreversibility [1–4]. Clear lens surgery, with multifocal and accommodating intraocular lenses (IOLs), reduces contrast sensitivity and can cause optical phenomena and have a moderate predictability of their accommodative effect [5–8]. In the early stages of presbyopia, clear lens surgery can be too invasive.

Corneal inlay implantation is an alternative approach to correct presbyopia, but it is not a definitive procedure. The advantages of corneal inlays are that they are additive and do not remove tissue, preserve future options for presbyopia, and are removable [9–11]. This advantage is also the cause of an increase in the rate of inlay explants and dissatisfaction. This is because it is less invasive to inlay explants than repositioning or removing and exchanging an IOL, which involve intraocular surgery with serious potential retina complications [12], with the same or worse ocular symptoms.

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Older inlay model designs were thicker and less biocompatible and had low water content. Anterior placement or nonporous inlays affected the movement and diffusion of the aqueous, oxygen, glucose, and other nutrients to the anterior portion of the cornea, resulting in necrosis and tissue breakdown [13–15]. These complications are rare with a thinner profile, small diameter, higher permeability, and better biocompatibility in recent models of inlays.

39.2 Inlay Types

There are currently three types of models of inlays existing in the market: inlays that rely on the principle of pinhole optics, refractive inlays that alter the index of refraction with a bifocal optic, and inlays that change the corneal curvature. There are differences between these designs:

39.2.1 The Kamra™ Corneal Inlay

The Kamra™ corneal inlay (ACI7000 PDT AcuFocus, Irvine, California, USA) is opaque and ring shaped and has a central aperture. It is made of polyvinylidene fluoride and it is pigmented with carbon nanoparticles for opacity. It has a 5-μm-thick artificial aperture with an outer diameter of 3.8 mm and a central aperture (inner diameter) of 1.6 mm. Its 8400 pseudorandomly arranged microperforations (5–11 μm) allow nutritional flow of aqueous, oxygen, and nutrients and waste transport through to the stromal tissue. The ring blocks the peripheral light rays and allows only the central rays to pass unhindered. Therefore these microperforations also allow approximately 7.5% light transmission through the annulus of the inlay. The outer and inner edges are free of these porosity holes in order to reduce potential light diffraction points and to increase the structural robustness of the design. The small aperture optic to increase the eyes' depth of focus improves near and intermediate visual

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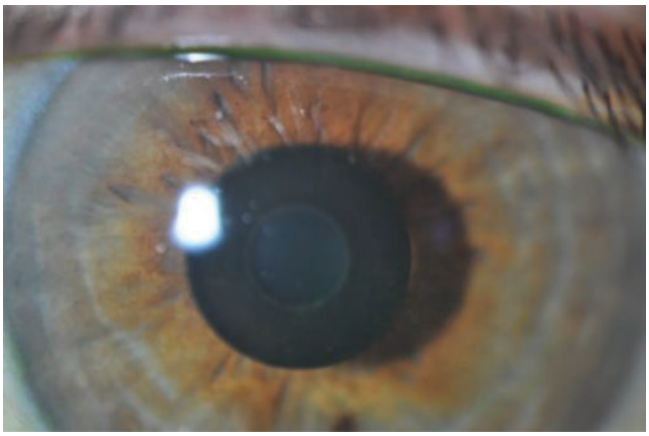

Fig. 39.1 Kamra

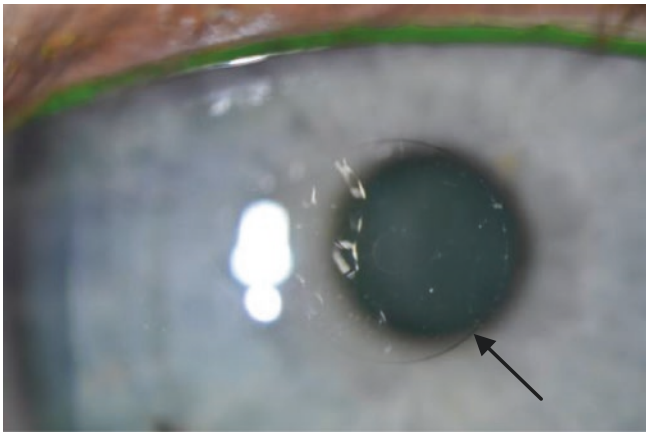

Fig. 39.3 Flexivue inlay hole

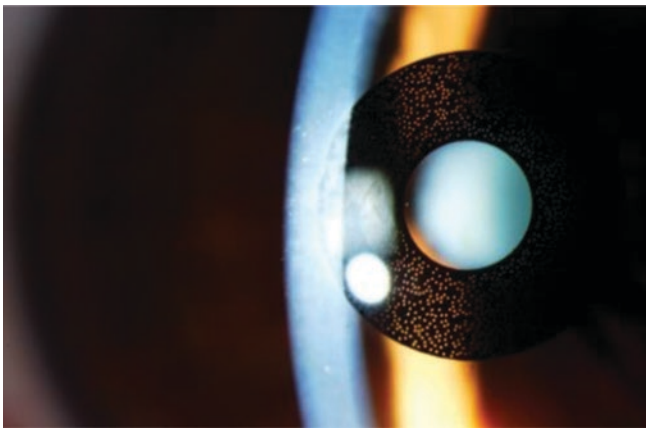

Fig. 39.2 Holes of the Kamra™ inlay

acuity in presbyopic eyes without affecting binocular distance vision or a minimally affecting it (Figs. 39.1 and 39.2).

39.2.2 Raindrop™ Near Vision Inlay

Raindrop™ Near Vision Inlay was formerly known as Presbylens in the United States and Vue + Lens in Europe (Revision Optics, Lake Forest, California, USA). This inlay reshapes the anterior curvature of the cornea to enhance near and intermediate vision. The tiny (2.0 mm diameter) inlay is a thin transparent permeable hydrogel inlay with a hyperprolate shape. It is 1.5–2 mm in diameter and varies in thickness from 10 microns in the periphery to 32 microns in the center. Its refractive index (1.376) and water content are similar to those of the cornea. It has no additional refractive power. Being permeable, it allows transmission of nutrients through it.

Also, the Raindrop Near Vision Inlay typically is placed within the cornea of the nondominant eye under a Lasik-style flap created with the femtosecond laser. When in position, the inlay changes the curvature of the cornea so the front of the eye acts much like a multifocal contact lens. It alters the eye's refractive power by increasing the central radius of curvature of the cornea overlying the implant, because the inlay is thinner at the edge than in the center (Fig. 39.3).

39.2.3 Presbia Flexivue Microlens™ (Presbia PLC, UA)

Another corneal inlay designed for the correction of presbyopia is the Presbia Flexivue Microlens, developed by Ireland-based Presbia PLC.

This inlay provides a bifocal effect and adds refractive power to the central cornea by implanting a refractive addition of +1.5 to +3.5 diopters in 0.25 D increments. The Flexivue inlay is of biocompatible hydrophilic acrylic material (Contaflex CI26, a copolymer of hydroxyethyl methacrylate and methyl methacrylate) that includes an ultraviolet filter. A 0.51 mm diameter hole in the center of the inlay facilitates the transfer of oxygen, water, and nutrients to the cornea.

It measures just 3.2 mm in diameter and is available in a range of powers, depending on the patient's near vision needs. The inlay provides power through a donut-shaped, high-refractive index lens that provides distance vision through its central zone (1.6 mm diameter), that is, plano. Also throw the pupillary periphery outside the inlay, and near vision through the curved portion of the 3–2 mm diameter inlay. The corneal inlay can be removed and replaced with a higher or lower power lens if needed.

This inlay is not yet FDA-approved for use in the United States, but it has received a CE mark in the European Union (Figs. 39.4 and 39.5).

Corneal inlays are implanted in the nondominant eye of emmetropic eyes within a corneal flap or pocket after the Intralase femtosecond laser (Abbott Medical Optics, Inc.). The aim is to center the inlay on the presurgical position of the first Purkinje reflex.

Intracorneal inlays are intended to be placed intrastromally. Placement of the ACI on the stromal bed centered over the pupil in the eye is expected to increase the depth of focus of the eye by reducing the circle of blur. Based on theoretical calculations of small aperture optics, the ACI is expected to provide presbyopic subjects with improvement of near vision [16, 17].

Under binocular conditions, the effect of having an inlay eye with a range of vision from distance to near combined with the uncorrected vision in the fellow presbyopic eye, (which will essentially have good distance acuity with reduced near acuity) is similar to the contact lens modality known as "modified monovision." In one form of modified monovision for emmetropic presbyopes, one eye is fitted with a multifocal contact lens (distance and near zones), while the other eye receives no correction. Both eyes work together to provide binocular distance vision, while the corrected eye is the primary near vision eye (monovision at near) [17].

Tolerance to monovision for most subjects is limited to a refractive disparity of approximately 1.5 D less than the range needed for the best functions [18, 19].

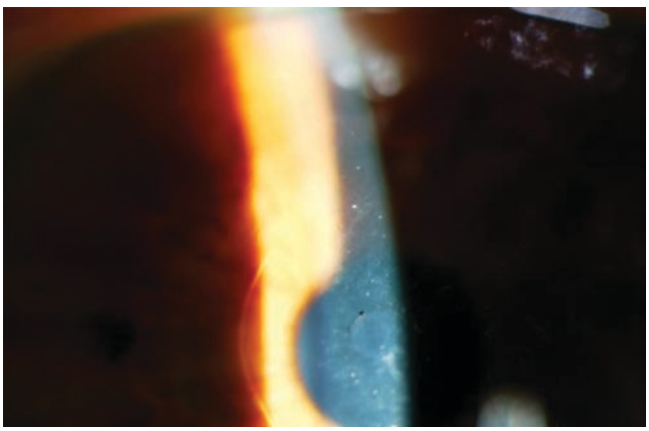

Fig. 39.4 Flexivue inlay implanted

39.3 Complications

39.3.1 Visual Acuity

39.3.1.1 Decrease of Distance Visual Acuity

Recent inlays have resolved complications of the anterior models and materials such as hydrogel corneal inlays. There include melting, migrations, inflammatory membrane, and others [13–15].

Inlay implantation is a procedure that provides stable vision and improves the binocular uncorrected near visual acuity to J2 or better [20–25]. It also improves the uncorrected intermediate visual acuity and slightly reduces the uncorrected distance visual acuity (UDVA), but this seems to recover for a period of time postoperatively [21]. Some authors have reported UDVA loss between 13% and 37% [11, 24–26] after a 3-year follow-up. The changes in best corrected distance acuity are transient, and no permanent reduction in visual acuity has been found [11].

39.3.1.2 Difficulty in Reading

Difficulty in reading in dim light. The aperture design inlays reduce the amount of light entering the eye making reading difficult. The percentage of patients who needed glasses for near vision decreased significantly after inlay implantation. Patients needed near vision glasses after surgery ranging between 9% and 13.6% [11, 21, 25] for all near vision day activities. Dependency on classes increases for night activities such as driving or reading in dim light, to 40% [21, 27].

39.3.1.3 Contrast Sensitivity (CS)

Contrast sensitivity (CS) loss is minimal at the highest spatial frequencies with photopic light in the eye with the inlay treatment, but when measured binocularly, there is no contrast sensitivity loss at any spatial frequency. In mesopic light the CS loss in the inlay eye is similarly less than the

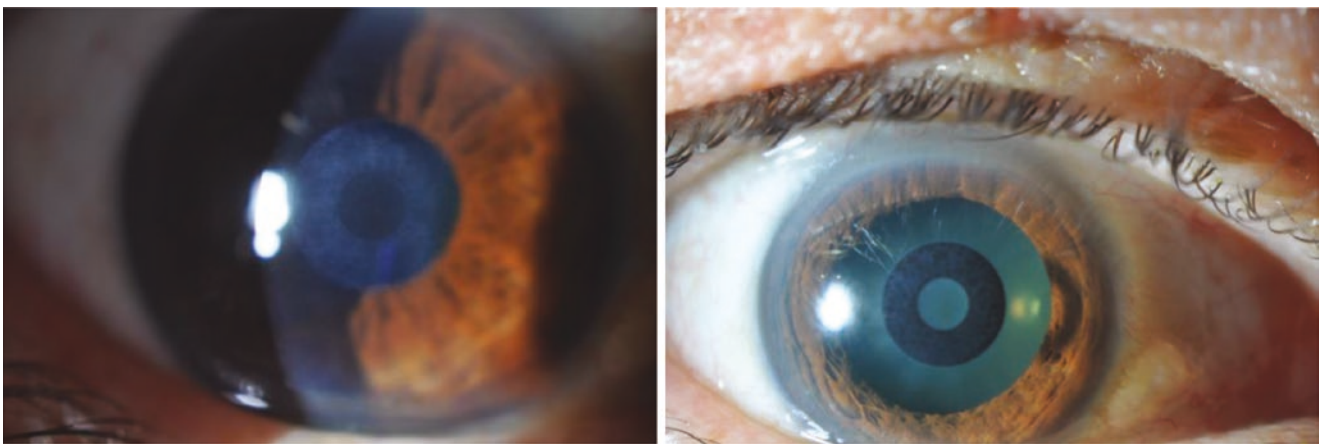

Fig. 39.5 Corneal opacity

standard deviation of the measurements [22, 23]. Contrast sensitivity, when tested in addition to glare as a pupil-dependent function and under mesopic conditions, shows a more pronounced loss with Kamra™ inlay [24].

However eyes with inlay treatment have a better contrast sensitivity when it is compared with accommodating intraocular lenses or multifocal intraocular lenses [28].

39.3.1.4 Induction of Optical Aberrations

One of the most important advantages of inlays is that their procedure is additive and does not require tissue to be removed. This is in contrast to laser refractive correction or pseudophakia, preserving future options for presbyopic correction or cataract surgery. Also, it is possible to combine other procedures as cataract surgery or Lasik [2, 29]. Another advantage is its reversibility if removed [10, 11]. However some results differ and the change in corneal curvature has been reported to induce corneal aberrations [2, 21]. A statistically significant increase in total higher-order aberrations as well as mean spherical aberrations at 3 and 4 mm pupil diameter was reported [26, 30, 31]. The increase in total aberrations and spherical aberrations might be related to decentration in combination with the refractive periphery in the Flexivue™ inlay model [25].

39.3.1.5 Pupil Size

Pupil size may affect vision in cases of refractive inlays. In small pupils, most of the pupillary area is occupied by the inlay, making distance vision difficult. In larger pupils, only a small part of the pupillary area is covered by the inlay making near vision blurry [21].

39.4 Diagnosis Restrictions

Diagnosis restrictions are possible with the Kamra inlay due to the small diameter aperture. Annular shadows are visible on all scans that darken the optic disk. Forty-five percent of the scans were suitable with restrictions to glaucoma diagnosis [24] and fundus evaluation. The transparent inlays Flexivue™ and Raindrop™ do not interfere with preoperative evaluation of the anterior and posterior segments, and they do not have to be removed for cataract surgery [25].

39.5 Inlay Descentration

This can occur in the early postoperative period due to inadequate flap adhesion. The complication of slight decentration of the inlay produces dissatisfaction due to the result of late neural adaptation. The inlay is recentered (from 3 months to 1 year) in the postoperative period because misplacement caused an insufficient increase in UNVA and UIVA and a decrease in UDVA (0.3–61.2%). After the replacement of the slightly decentered inlay, the visual acuity improved significantly [20, 22, 26].

39.6 Flap Related

Flap-related events observed during the first 3 months after surgery were epithelial defects, misaligned flap, and mild diffuse keratitis (DLK) (1.6%) [22, 32, 33]. Interface epithelial ingrowth was observed requiring lifting and smoothing of the flap [24].

39.7 Epithelial Ingrowth

Epithelial cells may accidently get implanted in the interface and grow around the corneal implant. The ingrowth opacifies the interface and may cause blurry vision, photophobia, and starburst [34]. Inlays that were recentered developed flap striae requiring lifting and smoothing of the flap, after 3 months. Interface epithelial ingrowth was observed requiring a repeat flap lift and debridement of the epithelial cells on the interface [20, 24, 35].

Extracellular matrix and cellular debris that result from the degeneration of keratocytes are also evident around the inlay, but this activity decreases over time. No inflammatory cells or neovascularization is observed around the inlays [35].

39.8 Central Corneal Haze

Central corneal haze was observed in 9% to 14% of patients, and it was resolved with steroid treatment. A strong correlation between the haze rate and implantation depth in the cornea has been found [11, 22]. The placement depth of each inlay design varies and depends on the mechanical properties and different mechanisms of action. Inlays that are designed to alter surface curvature tend to be implanted more superficially [36], but the models that use a different index or small aperture are implanted deeper, 3/5–3/4 depth with less impact on oxygen and nutrient diffusion in the corneal stroma [37–40] (Fig. 39.5).

39.9 Epithelial Iron Deposits

Epithelial iron deposits appear as central, spotlike deposits similar to those of other corneal techniques like epikeratophakia, in a half-moon shape in the inferior cornea, parallel to the outer margin of Kamra™ inlay, or in a ring formation [24, 41]. Corneal topography showed central corneal flattening in eyes with a central iron dot. The location of the iron ring was also

associated to a corresponding area of corneal flattening [41]. The hole in the center of the Flexivue Microlens™ corneal inlay provides a path for nutrients and hydrostatic flow to corneal structures [35, 38], and cases of corneal thinning or deposits on the interface have not been seen.

39.10 Endothelial Cell Loss

The endothelial cell count and endothelial morphology in the operated eyes were not significantly changed in most of the studies [26, 35]. Only one study showed a moderate decrease (5.7%) in the endothelial cell count 6 months after surgery, and the endothelial cell appearance in the surgical eyes was normal [41].

39.11 The Explantation of the Inlay

The explantation of the inlay was necessary between 0.3% and 37% of patients [20, 22, 41]. Inlay removal was due to dissatisfaction with their vision, misalignment associated to epithelial ingrowth or associated decreased visual acuity, and problems with night vision. None of the explants were related to the biocompatibility of the corneal inlay material or caused by metabolic compromise of anterior corneal tissue [35, 42].

39.12 Symptoms

39.12.1 Halos, Glare, Doble Vision, Fluctuation in Vision, or Blurred Vision at Night

The most frequently reported symptoms are night vision problems and halos after 1 year of the implant occurring in between 0.3% and 62.5% of patents [21–27], and in 3.8% the symptoms were reported as severe, and marked in 0.3% [22]. Pain, light sensitivity, and discomfort symptoms were rated as absent or mild in 53–99.1% of the cases [22, 23]. A reduction in illumination in proportion to the ratio of the obscuration (design of Kamra inlay) is sensitive to diffuse changes but relatively insensitive to focal changes. Levels of glare and halos are comparable to those observed with different designs of multifocal IOLs [5–8].

39.12.2 Dry Eye

Subjects report dryness as mild or absent in 95.3% and severe between 0.2% and 4.1% [22, 23]. This is a common side effect of Lasik, and it can be severe because the corneal nerves are cut during the flap creation, and this adverse effect cannot be attributable to the inlay implant [39, 43]. Creation of a corneal pocket instead of a corneal flap for inlay might decrease the incidence of dry eye, because most peripheral corneal nerves are preserved [26, 35].

39.13 Satisfaction

Patient satisfaction with the three types of inlay ranged between 75% and 95% [20, 21, 25, 26, 44, 45].

Younger patients showed a lower subjective satisfaction score, although they reported a greater reduction in their dependency on reading glasses. The younger patients are able to accommodate to some degree and have lesser difficulties seeing near objects. Also lower satisfaction depends on cultural and racial requirements [21].

Conclusion

In conclusion, corneal inlay complications have been reduced significantly with the new models, materials, and designs, with increases in their biocompatibility and porosity and a reduction in their thickness. There were no cases of necrosis or neovascularization, but the complications and symptoms that can occur can be possibly reduced with a well-centered implant, placed deeper in the stromal pocket instead of a corneal flap. Strict patient selection is required for tolerance to monovision. Corneal inlays are a safe and effective alternative for presbyopia treatment.

Take-Home Pearls

- Inlay implant is a safe and reversible procedure for presbyopia or refractive treatment.
- Proper patient selection is required.
- We can reduce the complications if the inlay is implanted in a corneal pocket or if it is implanted deeper in the cornea.

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Complications of Corneal Collagen Cross-Linking

40

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Core Messages

- Corneal CXL procedures allow the treatment of corneal ectasias but are responsible for some side effects.
- Early and late postoperative assessment of the cross-linked patient is important to detect postoperative complications and to manage them properly.
- Corneal CXL has been proposed for different corneal pathologies other than ectasias, such as some infections, and edema due to pseudophakic bullous keratopathy, corneal transplant rejection, and Fuchs' endothelial dystrophy.
- All the modifications to the CXL standard protocol aim to minimize side effects, maintaining an adequate therapeutic effect and extending the indication of the treatment.

40.1 Introduction

Corneal cross-linking (CXL) represents a fundamental evolution in the treatment of corneal ectasia pathologies improving corneal biomechanical properties [1]. Although it is a relatively safe procedure, some side effects and complications can occur; thus, it is very important to diagnose them early. CXL effect involves the interaction of ultraviolet rays with riboflavin producing free radicals and photo-oxidation that photopolymerize the corneal stroma, increasing collagen fibril interconnections [2]. For its mechanism of action, CXL can be useful in the treatment of many infective keratitis, in stabilizing corneal procedures, and as a therapeutic option for conditions involving corneal edema [3]. The first and most validated technique, proposed in 1996 by a research group at the Dresden Technical University, is "epi-off" CXL which removes the corneal epithelium before starting UVA irradiation [4]. Although this procedure allows the best penetration of riboflavin inside the corneal stroma, epithelium removal is linked to most of CXL complications. Other CXL strategies have been proposed to reduce the duration of the treatment and its complications [5]. The aim of recent researches is thus, to find the best irradiation technique combined the best imbibition strategy improving CXL efficacy and safety.

40.2 Effect of CXL on Cornea

From a biomechanical point of view, it has been widely demonstrated that human corneal rigidity increases immediately after CXL with a 328.9% increase of Young's modulus [6]. A study using rabbit eye proved that the effect of stiffness persisted 8 months posttreatment [7].

From a histological point of view, the whole corneal cell population has been largely studied [44–47].

The epithelium is fully regenerated by peripheral epithelial cells within 3–4 days after the "epi-off" procedure but remains very thin in the apex of the keratoconus (10–20 μm) 1 month after CXL, resembling to preoperative data between 3 and 6 months after the treatment. Limbal stem cell damage is avoided, thanks to the protective effect of the overlying epithelial cells [8].

Keratocyte loss is observed immediately after CXL. In spaces left by keratocytes, apoptosis leads to lacunar edema that persists for 4–6 weeks and then resolves with keratocyte repopulation. Nuclear keratocyte activation leads to an increase in the density of the extracellular matrix with more new collagen fibers 3–6 months after the treatment [9]. After

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CXL, keratocyte have been observed as a stromal demarcation line that could represent the transition zone between corneal cross-linked tissue and corneal non-cross-linked tissue. Refractive surgeons observed that a deeper demarcation line was associated with a larger decrease in central corneal thickness (CCT). They hypothesized that this line represents the activation of keratocytes, which is followed by the repopulation of keratocytes and new collagen synthesis [10].

Nerve fibers disappear after the procedure. In the first month, the subepithelial plexus regenerates, and during second and third postoperative months, there is a restoration of anterior-midstromal fibers with a normal corneal sensitivity in the sixth month after the CXL [11].

Endothelial damage threshold was determined by animal experimental studies that showed significant necrosis for high energy dose (4 mW/cm^2 radiation on epithelium and 0.5 mW/cm^2 on endothelium) [6]. However, few cases of endothelial damage post-CXL have been reported [12]. In corneas with a thickness of 400 μm, the radiation to avoid cytotoxicity of this layer should be 0.18 mW/cm^2 [13].

40.3 Early Postoperative Assessment of the Cross-Linked Patient

All patients should be instructed on how to follow postoperative regimen. It is important to inform them that they will experience some pain, photophobia, tearing, and red eye after the procedure. To prevent discomfort during the procedure and pain straight after the surgery, it is recommended to perform local anesthesia. Early assessment starts at the surgery room and should be performed during the healing process, to reduce pain and avoid infections. All patients after CXL are applied with a therapeutic contact lens that supports reepithelialization and reduces pain. After this procedure, patients should instill antibiotic, cycloplegic, and steroid drops. The most commonly used topical antibiotics are the broad-spectrum ones. Cycloplegic paralyzes the ciliary muscle relieving pain due to ciliary spasm secondary to ocular inflammation. The Contact lens is removed after full epithelialization. Some surgeons give steroid after removing the contact lens and others straight after the procedure, continuing the instillation for up to 10–20 days [14, 15]. Steroids act as an anti-inflammatory agent that prevents the development of corneal scars. Antibiotic and cycloplegic drops are administered usually for 7 days after the treatment until the achievement of full reepithelialization and improvement of acute inflammation. All surgeons give hyaluronate sodium drops six times daily, for approximately 5 weeks postoperatively. It is important to use preservative-free eye drops as preservatives can interfere with reepithelialization. Some doctors give oral amino acid supplements for 7 days [15].

Postoperative pain could be intense. It is associated with epithelium debridement. It may need oral analgesics [3]. Some authors give oral ibuprofen 400 mg (three times a day) and codeine phosphate 30–60 mg (four times a day) [7]. Some surgeons give three vials of benoxinate 0.4% with instructions to be administered if the postoperative pain is severe and with maximum dosage of one drop every 2 h for a maximum of 48 h. Treatment of postoperative pain should be individualized due to the different pain thresholds among patients [7].

As mentioned, another issue of early postoperative assessment is controlling the healing process up to full epithelialization. It is important to restore the epithelium as quickly as possible. It helps to improve patient's comfort and visual acuity and also reduces the risk of infection acting as a protective barrier. To prevent haze, some surgeons recommend vitamin C. It is based on researches made on PRK patients. But some surgeons found no additional effect on prevention of haze after refractive surgeries compared to the effect of topical mitomycin-C alone [16]. Control visits are set up 1–2 days after the procedure, 5–7 days, 2 weeks, 4 weeks, 3 months, 6 months, 1 year, and then every year. Authors of different publications about CXL, perform different examinations on control visits. But everyone should check visual acuity, intraocular pressure (IOP), refraction, keratometry, full slit-lamp examination, pachymetry, and topography. Additionally, some authors compare endothelial cell count and biomechanical properties of the cornea before and after CXL [2].

40.4 Early Postoperative Complications and Their Management

Several case reports describe the *melting process* after collagen CXL for keratoconus [17]. One case presented severe corneal haze, endothelial precipitates, and inflammatory cells in the anterior chamber the first postoperative day. This evolves with very slow reepithelialization and progressive thinning resulting in a descemetocele, with perforation in the second postoperative month [18]. This case suggests paying particular attention to patients with delayed epithelialization conducting very close follow-up, promoting epithelialization and preventing corneal perforation using, e.g., PRP, topical application of matrix regeneration therapy, or amniotic membrane transplant. Another case of acute corneal melt with perforation was reported 1 week after CXL associated with uncontrolled use of topical diclofenac and proparacaine eyedrops [18]. Bilateral corneal melt with *perforation* was observed in a patient with Down syndrome and stable keratoconus with thin corneas who underwent simultaneous bilateral CXL. The described complication occurred in one eye 1 week postoperatively and in the second eye 4 weeks

postoperatively and required emergency corneal grafts [18]. This case highlights how important is the right preoperative selection of patient: corneas were very thin and with a lack of evidence of disease progression. Another example of Par patient selection is a 45-year-old patient with severe atopic disease and keratoconus who developed corneal melting after CXL and deep anterior lamellar keratoplasty due to subclinical infection with herpes simplex virus. He required penetrating keratoplasty and intensive antiviral and immunosuppressive systemic treatment [18]. Patients with atopic disease have high risk of postoperative healing delay and prolonged epithelialization, being more susceptible to infection and at a higher risk of procedure failure (Fig. 40.1).

Another group of early postoperative complications includes *infective keratitis* (Fig. 40.2). Several causal agents have been reported. Acanthamoeba has been related to eye washing under the tap water [19]. A patient who underwent CXL for keratoconus presented 1 day postoperatively with a painful red eye due to polymicrobial keratitis caused by *Streptococcus salivarius*, *Streptococcus oralis*, and coagulase-negative *Staphylococcus* sp. This patient removed and "cleaned" his therapeutic contact lens in his mouth before reapplying it in his eye [18]. Thus it is very important to instruct patients before surgery about the postoperative treatment regimen and behavior necessary to minimize postoperative complications. Other cases of bacterial keratitis were caused by *E. coli*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* [20–22]. It is crucial to prevent contamination of the surgical field during removal of the epithelium as well as to avoid contamination of riboflavin drops. Excimer laser corneal episcrape no-touch technique could be a useful tool to reduce the possibility of transferring pathogens, and single-use packaging for the riboflavin solution is essential in order to avoid contamination.

One patient with no previous history of herpetic keratitis developed geographical ulcer related to herpes simplex virus [23]. *Reactivated herpetic keratitis* and neurodermitis have also been reported after CXL. It seems that UVA light can be a potent trigger of reactivation of latent HSV infection [18]. Potential risk factors for that are topical corticosteroids instillation and mechanical trauma caused by epithelial debridement, which can lead to actual damage of the corneal nerves. Surgeons should treat patients with a medical history of corneal herpetic disease only in selected cases providing a systemic and topical antiviral treatment. Patients should be informed about the possible complications. Diffuse lamellar keratitis (DLK, stage III) during the first posttreatment days after CXL for iatrogenic keratectasia was reported. The microbiology culture was negative, and the DLK resolved in 2 weeks after intensive treatment with topical steroids [18].

Surgeons should be aware of these complications and be able to discover them quickly and treat them properly. In such cases, it is very important to closely monitor the patients until complete reepithelialization.

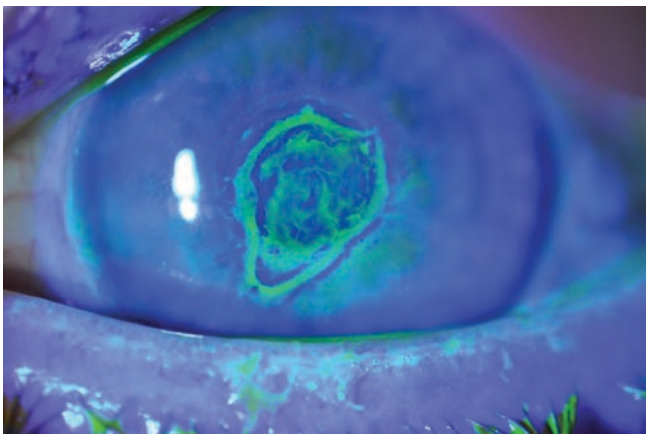


Fig. 40.1 Delayed epithelialization after CXL

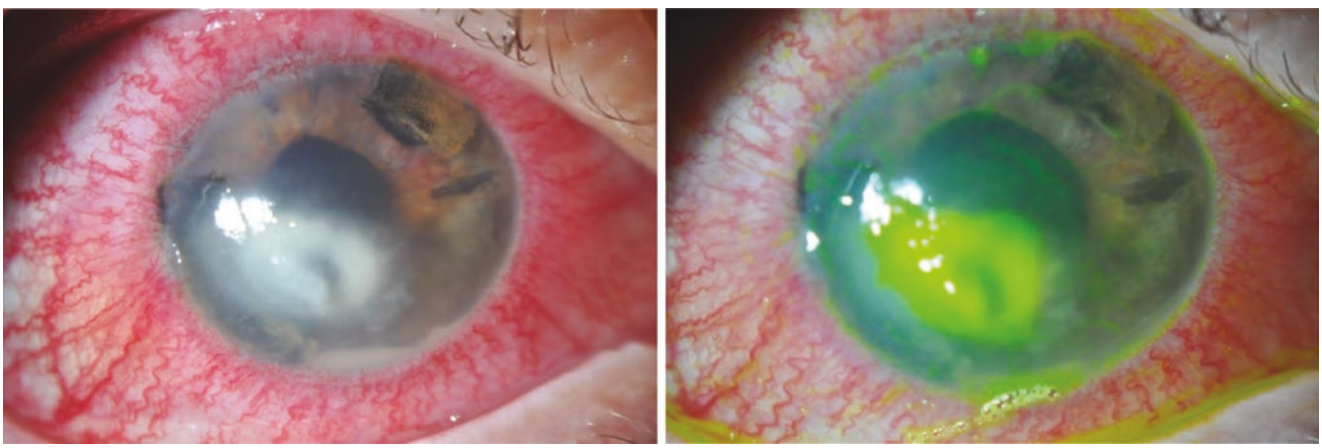


Fig. 40.2 Bacterial keratitis with corneal ulcer and stromal melting after CXL

40.5 Late Postoperative Assessment of the Cross-Linked Patient

At the first month visit, the most important factors that should be checked are visual acuity, full slit-lamp examination, monitoring healing process, and IOP. In the late postoperative, penon, doctors should focus on examinations that will assess the effect of CXL in stopping the progression of keratoconus. IOP measurements following CXL show overestimation caused by change in corneal biomechanics, leading to increased corneal rigidity. The difference in IOP measures following CXL ranged from 1.2 to 3.1 mmHg depending on the tonometer used [24, 25].

Reliable topography and refraction could be obtained minimum after 1 month postoperatively. Remodeling of the stroma and epithelium affects refraction and topographical readings during at least the first month after the procedure. According to Kanellopoulos, it takes even 1 year before the thickness maps are reliable [8]. Topography obtained 1 month after CXL paradoxically shows an increase in the steepness of the cone. Those findings are visible until the epithelium is fully restored. The effect of flattening of the cornea is evident after 6 months from the procedure [14]. Optical coherence tomography and very high frequency digital ultrasound arc-scanning technology show that the epithelium acts as a smoothing agent that reduces corneal power, astigmatism, and irregularity of keratoconic corneas [26]. Elevated cornea readings in the short time after the procedure are due to epithelium debridement.

Corneal thickness reduces shortly after CXL. It usually improves after the first 6 months and at 1 year returns to baseline values [27].

In the late postoperative period after CXL, we can investigate histological and biomechanical corneal changes. As previously mentioned, there is a significant decrease in the mean anterior keratocyte density at 1, 3, and 6 months postoperatively, while the posterior keratocyte density doesn't change after CXL [10]. Late changes in corneal stroma after CXL include collagen fiber diameter increases and reorganization of collagen fibrils in a parallel, lamellar structure similar to a non-keratoconic cornea [3]. Macroscopically the cornea shows significant flattening with reduction of *K* values [28].

Greenstein et al. measured biomechanical changes after corneal collagen cross-linking with the Ocular Response Analyzer (ORA). To describe the biomechanical properties of the cornea, two core metrics are used: corneal hysteresis (CH) and corneal resistance factor (CRF). Initially there was a significant increase in CRF between baseline and 1 month. This is concomitant with the corneal thinning that is seen 1 month after CXL [27, 29]. Thinner corneas seem to be correlated with lower CRF values. This suggests that the increase in CRF is an indication of corneal strengthening at 1 month. In this study, the ORA metrics of CH and CRF did not significantly change over time or 1 year after CXL [29]. Further clinical studies are needed to elucidate the in vivo biomechanical changes consequent to the CXL procedure.

40.6 Late Postoperative Complications and Their Management

A common complication of CXL is *corneal haze* (Fig. 40.3). Studies show that the depth of the CXL can be observed by following the demarcation line seen in the corneal stroma or by grading the corneal haze with the slit lamp. Several authors reported transient stromal haze resistant to topical steroids appearing 2–3 months after CXL and associated with an increased extracellular fibrillar matrix density, which was greater in patients with more advanced keratoconus [30–32, 40–43]. In these patients, dark Vogt microstriae are also present, a non-detectable finding in patients with early-stage disease. Management with topical preservative-free steroids promotes the resolution of the opacities in 30–40 days. Preoperative confocal analysis in those patients older than 20 years showed strong Vogt striae and dark, reticular-patterned microstriae in the anterior stroma to a depth of 80 μm, while preoperative confocal analysis in patients

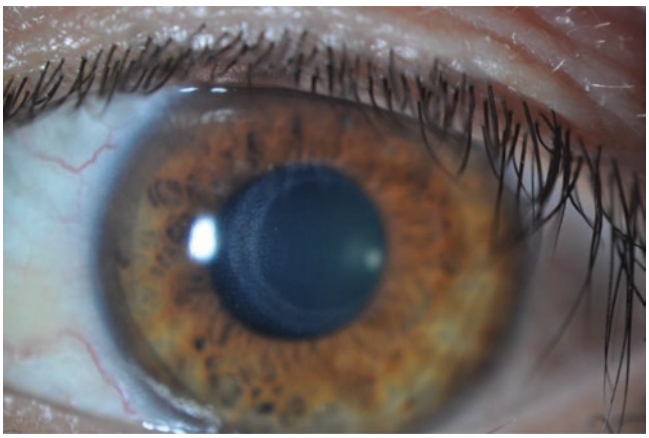


Fig. 40.3 Corneal haze after CXL

younger than 20 years old revealed hyperactivated keratocyte nuclei [31]. These could be risk factors for corneal opacity after CXL. The natural history of corneal haze after CXL was objectively quantified: it was greatest at 1 month, plateaued at 3 months, and significantly decreased between 3 and 12 months [39]. Changes in haze did not influence postoperative clinical outcomes [30]. Other factors connected with post-CXL corneal haze are stromal swelling, pressure changes, proteoglycan-collagen interactions, and glycosaminoglycan hydration. Those patients developing significant corneal haze after CXL had lower preoperative corneal thickness, and mean keratometry significantly increased. Using Scheimpflug image densitometry, some authors found corneal haze in 90% of cross-linked patients. Greenstein et al. compared two groups after CXL: at 1 year, haze remained significantly elevated compared with baseline values in keratoconus, unlike the ectasia group where the slit-lamp haze returned to baseline levels. From 3 to 6 months, the mean CXL-associated corneal haze measured by densitometry decreased more in the ectasia subgroup than in the keratoconus subgroup. Authors of the research observed that CXL-associated haze measured by densitometry was significantly correlated with several clinical parameters like corrected distance visual acuity, maximum *K* value, mean *K* value, and thinnest pachymetry.

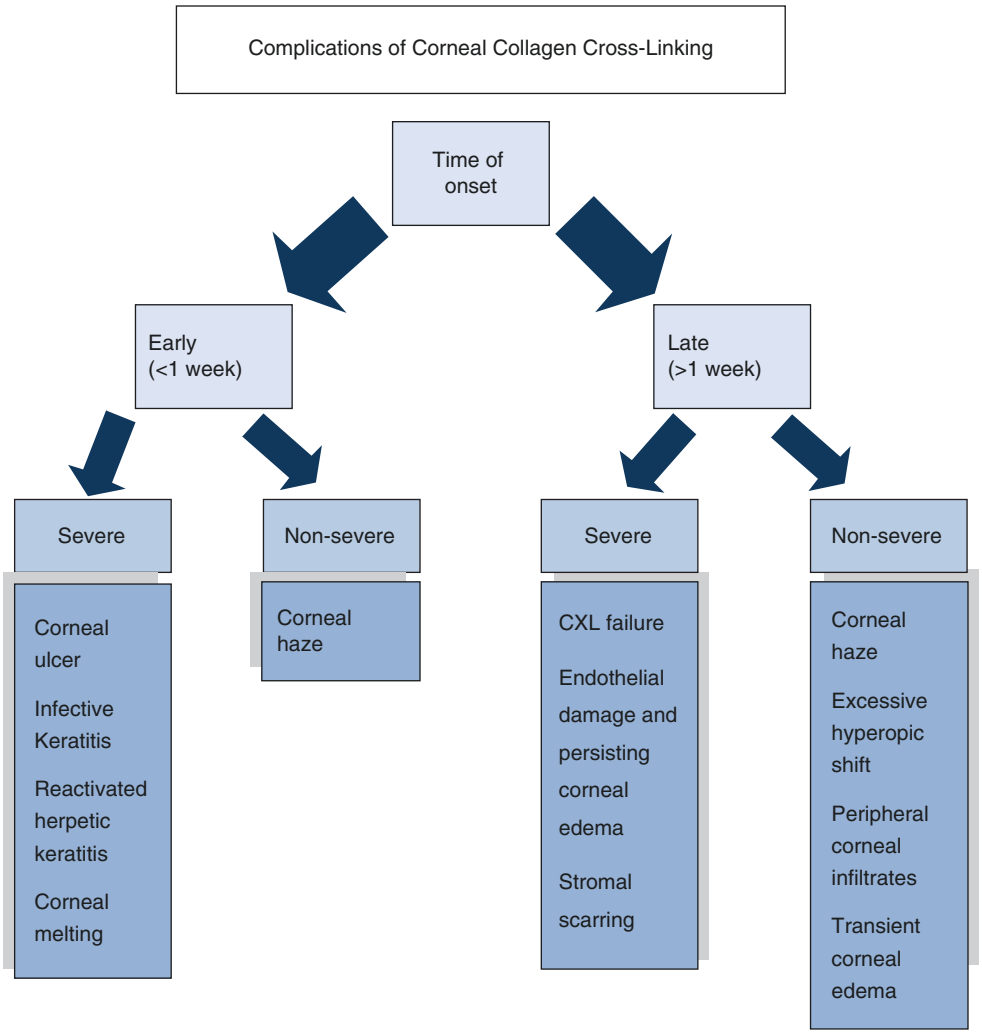
Another complication to take into account is *stromal scarring*. It has been associated with high K_{max} values (mean 71.1 D) at the apices and thin corneas (mean 420 μm) [32].

Endothelial cell loss should also be considered as a possible complication. It is very important for appropriate selection of patients. The main risk factor for endothelium damage is thin cornea, less than 400 μm [13]. Endothelial cells are safe in eyes with sufficient corneal thickness. However, we should take into account that after riboflavin and dextran solution imbibitions, corneal thickness decreases. This can be related either to evaporation through the denuded corneal surface or to the oncotic effect of 20% dextran used to form iso-osmolar riboflavin solution. This effect can increase the risk of endothelial damage leading to persisting corneal edema requiring corneal transplant. In other cases, transient anterior stromal edema could be related to lacunar spaces secondary to keratocyte loss assuming spongy or honeycomb aspect [9]. A miscalibration of the fluence or of the distance of UV light sources could expose patients to potential toxic levels of UV light that could create significant corneal opacities and severe damage of the anterior segment. These changes include corneal neovascularization, pigment clumps on the back of the cornea, and iris atrophy with intraoperative floppy iris syndrome or persistent epithelial defect extended beyond the limbus, suggesting limbal stem cell damage. Endothelial damage after CXL is a very rare complication, but it may happen. To prevent this complication, the surgeon should be sure that the corneal thickness is more than 400 μm, and should remove the lid speculum during the instillation of riboflavin drops to prevent excessive thinning secondary to evaporation. The equipment should be calibrated often.

In some cases after cross-linking, peripheral *sterile infiltrates* are observed. They occur as a result of enhanced cell-mediated immunity to staphyloccocal antigens deposited at high concentrations in areas of static tear pooling beneath the contact lens. In observations of Koller et al., sterile infiltrates occurred in 7.6% of the eyes (out of 105 in total). They resolved within 4 weeks with treatment of dexamethasone four times a day [33].

Another late complication of CXL is an atypical *big hyperopic refractive shift* that has to be taken into account in hyperopic patients. O'Brart demonstrated continued statistically significant flattening of corneal topographic parameters with a mean hyperopic shift of almost 0.8 D 7 years after CXL in 36 eyes, hyperopic shift over +2 D in 8 eyes (22%), and over +3 D in 4 eyes (11%) [34]. Very excessive hyperopic shift has been described in a 28-year-old woman with flattening greater than 14 D and in a 14-year-old boy with flattening of 7 D after 12 months. Another report of 11 D corneal flattening associated with over 220 μm corneal thinning has been described in a 23-year-old woman at 5-year follow-up [28]. The pathophysiology of excessive hyperopic shift is yet unclear. It may be due to a central cone location and a more advanced disease resulting in a greater CXL and wound healing effect.

Failure of CXL is defined as keratoconic progression after treatment. In one study of 117 eyes from 99 patients who underwent CXL, the failure rate was 7.6% [33]. Preoperative risk factors for worsening after CXL are age older than 35 years, cornea thickness less than 400 μm, maximum *K* reading greater than 58 D, female sex, and VA better than 20/25. To avoid keratoconus progression, appropriate qualification of patients is necessary. Surgery of the second eye should be performed straight after healing of the first eye. Due to relevant safety of the procedure, it could be even performed bilaterally on the same day.



40.7 Extending Indication of CXL

As discussed, the most common use of CXL is to manage ectatic corneal disorders. The top indication is keratoconus, where CXL halts the progression. The best candidates to CXL are patients with progressive keratoconus who still have good corrected visual acuity (RETICS classification grades II and III) [35]. Nevertheless, recent investigations propose new applications of CXL with promising results.

Among ectatic disorders other than keratoconus, CXL showed encouraging results in pellucid marginal degeneration with a safe profile despite the decentered treatment toward the limbus [18].

In post-LASIK ectasia patients treated with the CXL procedure, *K*-values progression was documented in patients with additional risk factors for ectasia progression, such as neurodermitis, allergy treated with systemic steroids, preexisting keratoconus or subsequent pregnancy [18]. In this group of patients, frequent follow-up is important, and eventual retreatment may be necessary. Most controversial is the use of CXL at the same time of LASIK, as a prophylaxis against myopic or hyperopic regression or to reduce the incidence of postoperative ectasia. Although intriguing, there is limited evidence that prophylactic CXL will be efficacious.

Few data are available about CXL in post-RK ectasia: A case report showed no significant improvement after the treatment; thus, a large cohort with long follow-up time is necessary to determine the real potential efficacy in this case. However, it has been suggested that patients with prior incisional refractive surgery should not be considered for CXL because the contraction of the collagen lamellae can cause the rupture of keratotomy incisions [18].

Therapy-resistant infectious keratitis associated with corneal melting presented positive outcomes after CXL. The progression of the melting process was halted avoiding emergency keratoplasty in several cases. Bacterial cases show a better time to reepithelialization compared to fungal, *Acanthamoeba*, and culture-negative cases, with a higher risk of requiring corneal transplantation in fungal and *Acanthamoeba* cases [36]. When using CXL for this indication, it would be advisable to discontinue all topical

antibiotics and avoid fluorescein instillation for at least 24 h prior to the treatment, because these substances are stronger absorbers of UVA irradiation at the 365 nm wavelength than riboflavin.

Some case series suggest an anti-edematous effect of CXL when used in pseudophakic bullous keratopathy, corneal transplant rejection, and Fuchs' endothelial dystrophy with improvement in corneal transparency, corneal thickness, and ocular pain 1 month postoperatively [18]. However, a regression to preoperative values is observed 6 months after the procedure.

Appropriate patient selection for standard CXL	
Indications	Contraindications
• Clinical evidence of progressive keratectasia • Age < 35 years • Visual acuity <20/25 • Pachymetry >400 μm • Keratometry readings <58 D	• Pregnancy and breastfeeding • Patients with prior incisional refractive surgery • Age can be a risk factor associated to visual loss, but no limit has been established • Best corrected visual acuity ≥20/25 • Pachymetry <400 μm • Keratometry readings >58 D • Cornea with central opacity • Serious dry eye syndrome

40.8 Standard Technique and Other CXL Protocols

A critical issue in order to obtain an effective CXL is stromal riboflavin concentration. Tight junctions between epithelial cells constitute a major barrier to the penetration of riboflavin. Because of this, the epithelium is removed to maintain an adequate stromal riboflavin concentration, in the standard technique, but this removal causes most of the CXL complications. All the modifications to the standard protocol listed in this paragraph are currently under investigation and aim to minimize its side effects maintaining an adequate stromal riboflavin concentration and extending the indication of the treatment.

40.8.1 Standard Protocol

Standard "epithelium-off" protocol, also known as Dresden protocol, is used in a standardized way from 2007, 11 years after its description. It is the most studied among CXL procedures and has to date the best demonstrated efficacy in halting corneal ectatic disorder progression. It consists of corneal de-epithelialization of 8–9 mm diameter after the application of topical anesthetic. Then the instillation of one drop of an isotonic 0.1% riboflavin and 20% dextran solution every 2 min for 30 min saturating the corneal stroma. After checking complete stromal saturation using the slit-lamp, UVA radiation at 5.4 J/cm^2 (3 mW/cm^2) is applied for 30 min. Finally, after this treatment, a therapeutic contact lens with topical corticosteroids, antibiotics, and nonsteroidal anti-inflammatory agents is fitted until regeneration of the epithelium [37].

40.8.2 Epi-On CXL

The efficacy of epithelium-on (transepithelial) techniques is controversial. Several methods have been studied to increase epithelium permeability to riboflavin including the use of tetracaine, superficial epithelial scraping, benzalkonium chloride, ethylenediaminetetraacetic acid, mechanical epithelial disrupters, incomplete debridement in a crosshatch pattern, stromal channels, and corneal pocket and flap [36]. Iontophoresis is the application of a low electric gradient to enhance molecular transport. Although it allows improved penetration of riboflavin through an intact epithelium over other transepithelial techniques, iontophoresis still does not achieve riboflavin concentrations comparable to the standard cross-linking protocol [10]. Recent studies in rabbits suggest some potential advantages for novel transepithelial approaches, like riboflavin nanoemulsions that could penetrate the corneal epithelium presenting greater stromal concentration compared to standard techniques. Such results need to be proven in human eyes.

40.8.3 Short Time CXL

Another line of investigation studies the reduction of treatment time optimizing CXL parameters, for example, using higher radiation intensities for shorter times to achieve the same level of radiation exposure according to the Bunsen and Roscoe law. Accelerated treatment could have more rapid overall corneal recovery after CXL, which could improve the patient comfort and safety profile. However, the effectiveness is controversial, and only few studies provided encouraging results: using 30 mW/cm^2 for 3 min, 10 mW/cm^2 for 9 min, and 9 mW/cm^2 for 14 min [5].

40.8.4 Thin Corneas CXL

Because standard treatment is contraindicated in corneas with a stromal thickness of less than 400 μm to avoid damaging the endothelial cells with the UV radiation, various methods of CXL have been developed to treat this patient population with varying degrees of success [37]. Corneal thickness can be increased to 400 μm instilling a hypo-osmolar riboflavin solution. The CXL effect is comparable to that in a 400-μm-thick cornea due to a great swell of the posterior stroma [38]. Using this technique, it is possible to treat corneas with a minimum stromal thickness of 320 μm.

Another factor that can be modified is total irradiation dose that can be decreased in accordance with the thickness of the stroma. A shorter irradiation time at 3 mW/cm^2 irradiation intensity avoids reaching endothelium toxicity threshold of 0.63 J/cm^2 in thin corneas when no hypo-osmolar riboflavin solution is available for topical application. Some surgeons suggested the application of UV radiation through contact lens.

Because the toxicity threshold of endothelial cells is much higher without riboflavin, endothelial cells would be protected, even in thin corneas (KXLTM technique), with a brief application of riboflavin to the surface allowing a sufficient concentration in the anterior stroma without riboflavin reaching the endothelium. However, a prerequisite for this procedure is a short irradiation time with a high irradiation intensity (equal dose) to keep the diffusion time short. Unfortunately, no clinical experiences with this technique can currently be cited.

An increase in the concentration of riboflavin to 0.2% leads to a greater absorption of UV light in the anterior stroma and a decrease in UV exposure of the endothelium.

Combinations of various techniques described above may increase safety during the CXL of thin corneas.

40.8.5 The Athens Protocol

The Athens protocol aims to improve the stability and refraction keratoconus patients, minimizing complications by combining CXL with topography-guided trans-PRK. This simultaneous procedure appeared to be superior to sequential treatments in the rehabilitation of keratoconus with minimal haze formation and a reduction in the patient's time away from work [37].

Take-Home Pearls

- Corneal cross-linking (CXL) represents a fundamental evolution in the treatment of corneal ectasia pathologies.
- Epi-off CXL has to date the best demonstrated efficacy in halting the progression of corneal ectatic disorders.
- Epithelium removal is linked to most of CXL complications.
- Proper patient selection allows the reduction of CXL complications.
- Patients' instruction about the postoperative treatment regimen and behavior allows us to minimize postoperative complications.
- In the early postoperative period, it is crucial to closely follow-up patients until complete reepithelialization.

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CXL for Post-LASIK Ectasia

41

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Core Message

- Cross-linking, as a treatment for post-LASIK ectasia, is a safe and effective procedure.

41.1 Introduction

Ectasia following LASIK is a rare complication but also one of the most feared situations that can occur after uneventful corneal laser surgery. The actual incidence is undetermined, but it has been estimated to be 0.04–0.66% after LASIK surgery [1–5]. It may be apparent immediately following LASIK surgery or years after, generally occurring within 2 years of surgery [6, 7]. Post-LASIK ectasia represents about 96% of all secondary ectasias after refractive surgery, while 4% are related to photorefractive keratectomy (PRK) surgery [8, 9].

Clinically, it is manifested as two distinct entities: The first is a central forward bowing that presents minimal irregular astigmatism, and the second is a keratoconus-like ectasia with paracentral thinning and resultant significant irregular astigmatism [10]. Histopathologic analysis of eyes with post-LASIK ectasia has shown features similar to keratoconus [11]. On morphological examination of two cases with corneal ectasia, Kim et al. reported a forward protrusion of both the anterior and posterior corneal surfaces, epithelial detachment, Bowman's membrane breakage and folding, and irregular lamellae [12]. Forward movement of the posterior corneal lamella appears to occur routinely following LASIK in a nonprogressive manner [13, 14]. Guirao [15] described a model used to examine the influence of myopic LASIK on corneal elastic properties. Based on this model, it was proposed that corneal thinning caused by ablation produces an elastic deformation of the posterior corneal surface that depends on intrinsic corneal parameters (curvature, Young's modulus, Poisson ratio, and thickness) and extrinsic parameters such as IOP and the ablation profile [10, 15].

The primary aim of corneal cross-linking is to halt the progression of corneal ectasia. To obtain a strengthening of corneal tissue, the use of riboflavin is combined with ultraviolet A (UVA) irradiation. Riboflavin plays the role of a photosensitizer in the photopolymerization process and, when combined with UVA irradiation, increases the formation of intrafibrillar and interfibrillar carbonyl-based collagen covalent bonds through a molecular process that has still not been completely elucidated [10, 16].

It was shown that during the early aerobic phase of the process of cross-linking, riboflavin molecules are excited to a single or triplet state, and stromal proteins undergo a photosensitized oxidation via interaction with reactive oxygen species [17, 18]. During the second anaerobic phase, when oxygen is depleted, corneal stroma interacts with reactive species of radical ions. This photochemical reaction results in an increase of corneal rigidity, collagen fiber thickness, and resistance to enzymatic degradation, with consequent decrease of stromal swelling and permeability maximally, above all in the anterior stroma [10, 17, 19].

41.2 Role of CXL in Post-LASIK Ectasia Management

Since progressive keratoconus and post-LASIK ectasia share a number of characteristics, it was assumed that cross-linking could be used to stop progression in post-LASIK ectasia. In a prospective comparative case series, Kymionis et al. attempted to investigate the corneal tissue alterations after collagen cross-linking in five eyes with progressive keratoconus and five eyes with iatrogenic keratectasia after LASIK,

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using corneal in vivo confocal microscopy. Both keratoconic and post-LASIK corneal ectasia eyes revealed similar morphological alterations [20].

Cross-linking experiments on bovine corneas, where laser in situ keratomileusis-like flaps were created, showed an immediate increase of the flap adherence force, while the cornea remained clear. The effect gradually decreased during organ culture, although it remained twice the level of control corneas after 3 weeks in culture [21].

Kohlhaas et al. [22] first described the successful use of cross-linking to treat post-refractive keratectasia in 2005. Several studies have since demonstrated the stabilization of corneal ectasia after cross-linking treatment, although the effect seems to be less robust than in keratoconus, presumably because of the lack of biomechanical corneal contribution of the flap [23–29].

41.2.1 Procedure

The standard treatment protocol is also known as the "Dresden protocol."

After topical anesthesia, the speculum is inserted and the epithelium is debrided with a Kuhnt-type corneal scarifier (Fig. 41.1). Meticulous manipulations should be performed in order to prevent dislocation or amputation of the existing flap. Alternatively 20% alcohol in a corneal well for 60 s can be applied to remove the epithelium. Isotonic riboflavin 0.1% is instilled every 2 min for 30 min. The corneal penetration of riboflavin is checked with a slit-lamp using a blue light. Instillation should be continued until riboflavin is observed in the anterior chamber. Corneal thickness measurement is then performed to ensure corneal thickness more than 400 μm; otherwise, hypotonic riboflavin is instilled. UVA radiation is started at a distance of 5 cm from the apex of the cornea.

By adjusting the aperture, only the unepithelialized cornea is radiated and the limbus is avoided. During the application of UVA radiation, riboflavin is instilled every 2 min. After 30 min of radiation treatment, the cornea is thoroughly washed with BSS. A drop of antibiotic is instilled and a bandage contact lens is applied.

41.2.2 Combined Cross-Linking Procedures (CXL Plus)

Intrastromal corneal ring segment implantation combined with ultraviolet-A/riboflavin corneal collagen cross-linking has been reported to be a safe and effective solution in treating corneal ectasia [30]. According to one case report, the initial improvement of SE and *K* values in a patient with post-LASIK keratectasia treated with Intacs SK was followed by a slight regression 1 month later, which was subsequently successfully reversed using cross-linking [31]. The optimal method for combined CXL and ICRS placement has not yet been determined. Further well-designed randomized controlled studies with long-term follow-up are needed for clarification.

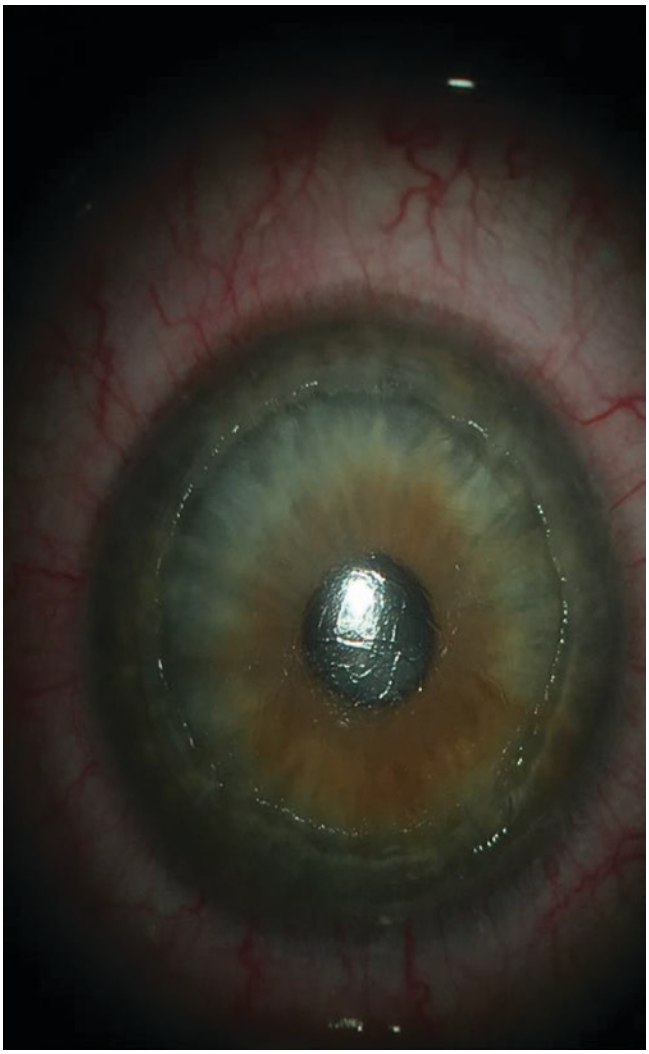

Fig. 41.1 Corneal epithelium has been debrided with the use of a kuhnt type corneal scarifier revealing microstriae developed during past flap creation

In 2011, Kanellopoulos and Binder [32] introduced the "Athens protocol" a combination treatment using simultaneous CXL and PRK in patients with post-LASIK ectasia. The goal was to use PRK to improve visual outcomes by normalizing the corneal surface, reducing irregular astigmatism, and potentially reducing the refractive error, in addition to the corneal stabilization effect of corneal CXL. Twenty-seven of 32 eyes had an improvement in uncorrected distance visual acuity and CDVA to 20/45 or better at the end of follow-up, 4 eyes showed some topographic improvement but no improvement in CDVA, 2 of the 32 eyes had corneal ectasia progression after the intervention, and 1 of the treated eyes subsequently required a penetrating keratoplasty [32].

41.3 Complications

There is an increased risk of cornea infections due to epithelial scraping performed during cross-linking. Factors such as the use of bandage soft lens and postoperative use of topical corticosteroids increase the risk of corneal infection. There are no large-scale studies evaluating the rates of infection following CXL. There are, however, case reports in the literature of bacterial, polymicrobial, acanthamoebic, and even herpetic keratitis following CXL procedures [33–38]. Kymionis et al. presented a case of herpetic keratitis with iritis after corneal cross-linking with riboflavin and ultraviolet A for keratoconus with no prior herpetic infection [37]. The patient was treated with oral steroids and acyclovir, with significant improvement. Few small patient series described the formation of sterile stromal infiltrates following CXL [39, 40].

A transient decrease in corneal innervation and corneal sensitivity can be observed up to 6 months after CXL [41]. No significant effect of CXL can be detected on basic tear secretion and tear film stability [42].

In vitro exposure of limbal epithelial cells to UVA dosages similar to those used during CXL promoted expression of genes involved with apoptosis. The addition of riboflavin reduced the damage caused but did not prevent it completely [43]. Several studies on cadaveric eyeballs have shown the toxic effects of the combination of riboflavin and UVA on limbus epithelial cells [44–46]. Authors suggest the use of metal shields or polymethylmethacrylate rings to protect limbus epithelial cells during a cross-linking procedure. There are no in vivo studies evaluating the effect of CXL on limbus epithelial cells.

Transient corneal haze is a common complication of corneal cross-linking. In a prospective clinical trial, corneal haze after cross-linking either for keratoconus or for post-LASIK keratectasia was objectively quantified. It peaked at the first postoperative month, plateaued at 3 months, and was significantly decreased between 3 and 12 months. Interestingly by 12 months, corneal haze had not completely returned to baseline in the entire cohort and the keratoconus subgroup; however, it returned to baseline in the ectasia group [47].

The cytotoxic risk to endothelial cells is related with the preoperative corneal thickness. The standard irradiance of 3 mW/cm^2 combined with the application of riboflavin 0.1% results in a significant and relatively sharp drop in UVA light of up to 95% and a resultant irradiance of the corneal endothelium (in a 500 μm thick cornea) of only 0.15 mW/cm^2 (=0.27 J/cm^2) [48, 49].

Corneas with less than 400 μm are at increased risk and should only be cross-linked after appropriate preoperative and intraoperative stromal swelling induced by the application of hypo-osmolar riboflavin drops [50, 51]. However, transient intraoperative thinning can take place during the cross-linking procedure, increasing the risk of endothelial damage even in corneas with apparently sufficient preoperative thickness [52, 53].

In 2007, Kymionis et al. reported a case of diffuse lamellar keratitis during the first postoperative days after corneal cross-linking in a patient with post-laser in situ keratomileusis corneal ectasia. After intensive treatment with topical corticosteroids, the DLK resolved during the following 2 weeks [54].

Contraindications to undergoing standard CXL treatment are the presence of corneal thickness of less than 400 μm, severe cornea scarring or opacification, history of herpetic infection, history of poor epithelial wound healing, severe ocular surface disease, history of immune disorders, pregnancy, and breastfeeding [55, 56].

41.4 Refractive Outcome

A number of studies have presented the outcomes of cross-linking for post-LASIK ectasia (Table 41.1) [17].

Poli et al. reported the 6-year results of standardized epithelium-off corneal collagen cross-linking (CXL) for treatment of progressive corneal ectasia. At 6 years, CXL stabilized primary and iatrogenic corneal ectasia in 89% of the patients with significant improvement in corrected distance visual acuity [57]. Similar results were reported by Yildirim et al. In this retrospective study, 20 eyes were enrolled with a mean follow-up of 42 months. Both UDVA and CDVA were significantly improved and the maximum *K* value decreased during the follow-up period [29].

Richoz et al. reported that ectasia after LASIK and PRK was arrested by CXL with stabilization or improvement of CDVA and K(max) after a mean follow-up of 25 months [27].

Vinciguerra et al. studied 13 eyes treated with cross-linking for post-LASIK ectasia with a 1 year follow-up. After 1 year post-LASIK surgery, ectasia was stabilized, while best spectacle-corrected visual acuity improved [24].

Accelerated CXL was introduced in clinical practice in order to shorten the time required for a CXL procedure. This technique is based on the Bunsen-Roscoe law of photochemical reciprocity. That is, the same photochemical effect can be achieved with reducing the irradiation interval provided that the total energy level is kept constant by a corresponding increase in irradiation intensity. The only study to date which evaluated the efficacy of accelerated cross-linking on patients exclusively with post-LASIK ectasia was conducted by Marino et al. [58]. The study enrolled 40 eyes of 24 patients that attained at least 2 years of follow-up. All eyes stabilized after treatment without any further signs of progression and no statistically significant changes in the mean UCVA, BCVA, and keratometry. In addition, 72.5% of the patients presented stable or gains of Snellen lines over time [58].

Table 41.1 Studies presenting the outcomes of CXL in post-LASIK ectasia

Study	Type	Number of eyes	Follow-up	Results
Poli et al. (2015) [55]	Prospective case series	36	6 years	CXL stabilized primary and iatrogenic corneal ectasia in 89% of the patients
Marino et al. (2015) [50] Accelerated Corneal cross-linking	Prospective case series	40	2 years	All eyes stabilized after treatment without any further signs of progression and no statistically significant changes in the mean uncorrected distance visual acuity, corrected distance visual acuity, mean keratometry, and steep keratometry
Yildirim et al. (2014) [25]	Retrospective case series	20	42 months	Corneal collagen cross-linking yielded long-term stability in cases with post-LASIK corneal ectasia without significant side effects. Improvements in visual acuity, cylindrical refraction, and maximum *K* values occurred
Richoz et al. (2013) [23]	Retrospective case series	26	25 months	Ectasia after LASIK and PRK was arrested by CXL with stabilization or improvement of CDVA and Kmax after a mean follow-up of 25 months
El Wahab et al. (2012) [54]	Prospective nonrandomized	20	2 years	BCVA improvement, Kmax decrease
Salgado et al. (2011) [21]	Prospective case series	22	12 months	Cross-linking in patients with iatrogenic keratectasia stabilized the UCVA and BCVA as well as the maximum *K*-readings
Hersh et al. (2011) [24]	Randomized control trials	49 keratoconus 22 post-LASIK ectasia	1 year	Keratoconus patients had more improvement in topographic measurements than patients with ectasia. Improvement of UDVA, CDVA, maximum *K* value, and the average *K* value
Vinciguerra et al. (2010) [20]	Prospective case series	10 post-LASIK 3 post-PRK	1 year	One year after surgery, CXL appears to stabilize eyes with ectasia consequent to excimer laser refractive surgery and improve BSCVA
Kymionis et al. (2009) [16]	Prospective comparative case series	5 post-LASIK 5 keratoconus	1 year	Corneal alterations after corneal cross-linking were similar in both keratoconic and post-LASIK corneal ectasia eyes
Hafezi et al. (2007) [19]	Case series	10	Up to 25 months	Increase in BCVA, decrease of Kmax

As Table 41.1 depicts, the number of studies which evaluated the effects of cross-linking on patients exclusively with post-LASIK ectasia is small, and follow-up time was usually brief [57].

However results from these studies clearly highlight that cross-linking as a treatment for post-LASIK ectasia is a safe and effective procedure.

Take-Home Pearls

- The primary aim of corneal cross-linking is to halt the progression of corneal ectasia.
- The effect of corneal CXL for post-LASIK ectasia seems to be less robust than in keratoconus, presumably because of the lack of biomechanical corneal contribution of the flap.
- Standard CXL treatment should not be used in corneas with less than 400 μm thickness.

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Part X

The Patient

Predicting the Unhappy Patient and Patient Expectations

42

Soraya M.R. Jonker, Nayyirih G. Tahzib, and Rudy M.M.A. Nuijts

Core Messages

- The relationship between patient expectations, the medical outcome, and patient satisfaction is complex.
- It is important to determine patients' motivations and expectations before surgery.
- Patients should be educated on the potential side effects of refractive surgery.
- In case of complications, patients should be informed as soon as possible, whereby the doctor should try and maintain their trust.

42.1 Introduction

With the increasing amounts of new and improved keratorefractive surgery treatments for the correction of the refractive error, the importance of systematic evaluation of the treatment outcome has grown. Until about 10 years ago, the evaluation and comparison of refractive surgery techniques were mainly focused on the objective, clinical outcome such as the residual refraction, the visual acuity, and the number of Snellen acuity lines lost or gained after the procedure.

Patient satisfaction after cataract and refractive surgery, however, entails the greater area of quality of life and functional status as self-perceived by the patient. The area of measuring patient satisfaction is complex and multidimensional, since it is influenced by the combination of subjective quality of vision, personal expectations, and personality type [1–3]. It is important that refractive surgeons understand patient motivations for seeking surgery, since this can influence their postoperative satisfaction. In order to predict the unhappy patient, it is important to:

1. Identify what are the expectations and motivations of patients before undergoing refractive surgery.
2. Describe the population of satisfied and dissatisfied patients.
3. Identify parameters responsible for patient dissatisfaction.

Patient satisfaction can be defined by the difference between the patient's expectation before surgery and the outcome after surgery. An example is the "disconfirmation-of-expectations" model, which explains that if perceived performance is evaluated as worse than the expectation, negative disconfirmation results in dissatisfaction (Fig. 42.1). This model closely adheres to the current theory of "undersell and overdeliver" to achieve satisfied patients in corneal and lenticular refractive surgery.

Fig. 42.1 The "disconfirmation-of-expectations" model, explaining that when perceived performance is evaluated as worse than the expectation, negative disconfirmation results in dissatisfaction

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42.2 Patient Questionnaires

One of the most effective and efficient ways to study patient expectations and motivations is by using validated questionnaires, which systematically ask patients about their experiences [3–7]. Self-administered questionnaires, rather than physician-administered questionnaires, enable a more objective view of patient satisfaction and quality of vision. When a test is administered by a physician, results may be biased, and patients might feel compelled to always answer in the affirmative.

Several studies have used questionnaires for the assessment of patient expectations and satisfaction. Realistic preoperative patient expectations seem to correlate well with postoperative patient satisfaction, meaning that a good understanding of patient motivation for seeking refractive surgery is important [8]. Primary reasons for seeking refractive surgery such as laser in situ keratomileusis (LASIK) are a desire for freedom from spectacles or contact lenses (32.1%) and spectacle or contact lens intolerance (30.4%) [9–11].

Many studies in the literature show that the level of patient satisfaction after refractive surgery was generally higher than 90%. However, these studies also show that there are night-vision complaints (NVC) which range from about 5 to 30%, depending on the time these complaints were measured [5, 7, 8, 12]. Ten years ago, we described patient satisfaction and self-perceived quality of vision after myopic LASIK and Artisan lens implantation and tried to define clinical parameters of patient satisfaction after these procedures. We used a validated questionnaire which covered seven quality of vision scales, including global satisfaction, quality of uncorrected and corrected vision, quality of night vision, glare, daytime driving, and night driving [4, 5]. In terms of overall satisfaction, we found that more than 90% of patients in both groups were satisfied with their visual outcome and would be willing to have the surgery done again if they could do it over. For uncorrected vision, about 65% of patients in both groups said that their uncorrected vision after surgery was better than their best-corrected vision before surgery. About 65% of patients reported that their night vision was the same or better after surgery; however, a group of about 35% reported that their night vision was worse. It is important to add, however, that about 35% of patients with NVC reported having them before surgery. Glare complaints increased in about 50% of patients in both groups after surgery.

Similar but slightly less positive results were reported by two more recent studies: one looking at patient satisfaction in a small group of patients implanted with an Implantable Collamer Lens (ICL) [13] and a comparative study looking at patient satisfaction 5 years post-LASIK or ICL implantation [14].

42.3 Clinical Parameters as Predictors of Patient Satisfaction: Two Examples of Refractive Surgery Techniques

42.3.1 Artisan Phakic Intraocular Lens Implantation Patients

Clinical parameters that can predict patient satisfaction after Artisan lens implantation are the refractive outcome (uncorrected and corrected visual acuity, sphere, cylinder and spherical equivalent), pupil size, lens centration, the pupil-optical zone disparity (meaning, the disparity between the pupil size and the optical zone of the lens), and higher-order aberrations (HOA). Our results showed higher levels of global satisfaction and subjective uncorrected vision when the residual error was small. Glare complaints did not depend on lens decentration, which was probably related to the fact that about 90% of these cases had lens decentrations lower than 0.5 mm. Pupil sizes were measured with a digital infrared pupillometer (P2000 SA pupillometer, Procyon Instruments Ltd., London, UK). We found that glare complaints increased with higher amounts of pupil-optical zone disparity in scotopic light conditions (Fig. 42.2), but not in mesopic-low conditions. Study of optical aberrations (Zywave aberrometer, software version 3.21, Bausch & Lomb Technolas, Munich, Germany) showed higher levels of glare and night-driving complaints with increasing amounts of HOA after surgery [11].

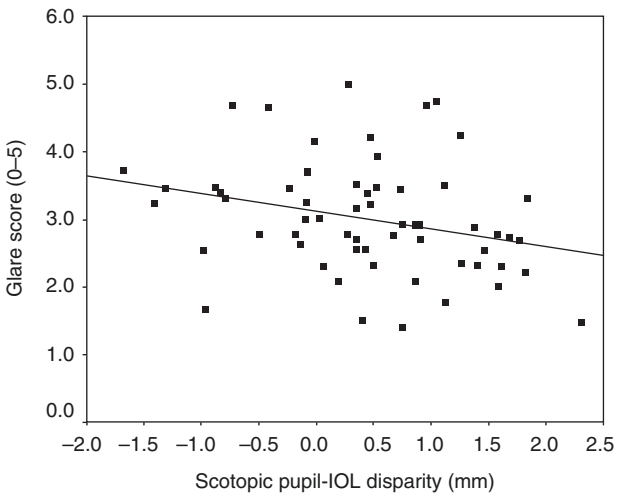

Fig. 42.2 Glare score versus the scotopic pupil-optical zone disparity after Artisan phakic intraocular lens implantation for the correction of myopia ($r = -0.28$, $P = 0.03$)

42.3.2 LASIK Patients

Clinical parameters that can predict patient satisfaction after LASIK are also the refractive outcome, the ablation depth, and the pupil-optical zone disparity. Our results showed higher levels of subjective uncorrected vision when the residual error was small. There was no correlation between night vision and the ablation depth or between glare and the scotopic pupil-optical zone disparity (Figs. 42.3 and 42.4) [10].

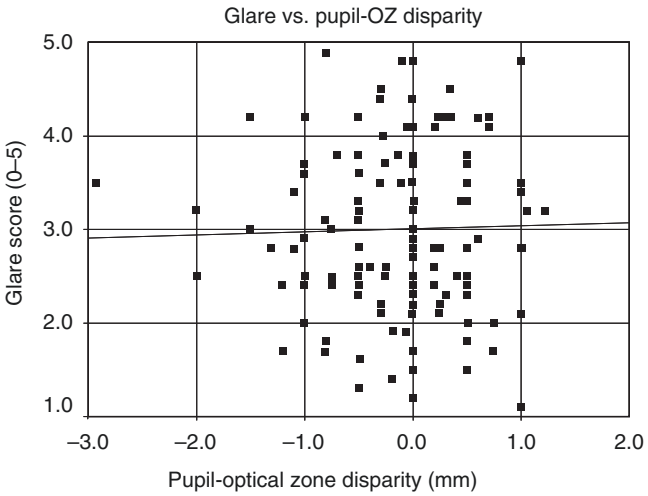

Fig. 42.3 Glare score versus the scotopic pupil-optical zone disparity after myopic laser in situ keratomileusis ($r = 0.03$, $P = 0.75$)

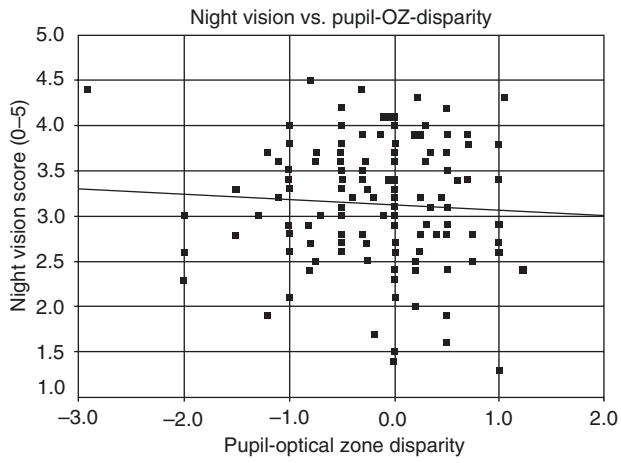

Fig. 42.4 Night-vision score versus the scotopic pupil-optical zone disparity after myopic laser in situ keratomileusis ($r = -0.06$, $P = 0.50$)

42.4 Discrepancy Patient Satisfaction and Night-Vision Complaints

NVC are the main downsides after refractive surgery and have been reported in the literature, ranging from 12 to 57% in patients; they appear to diminish after the first 6 postoperative months [5, 7, 12, 15–19]. It seems that there is a discrepancy between patient satisfaction and NVC. Despite the relatively high occurrence rate of NVC, patients are generally very satisfied after surgery. One possible explanation for this discrepancy may be that patients simply adapt to their new condition [5, 12]. Also, the benefits of surgery such as the reduction in contact lens and spectacle dependence might be greater than the disadvantages of NVC. Also, patients who wore rigid gas-permeable contact lenses and spectacles before surgery might show an easier acceptance and an increased level of tolerance to glare and halos.

42.5 Risk Factors for Night-Vision Complaints

Three reports on patient satisfaction after LASIK treatment [7, 12, 18] showed that predictors for NVC were:

1. Preoperative level of myopia (more than 5 diopters)
2. Preoperative uncorrected visual acuity
3. Preoperative contrast sensitivity levels
4. Increasing age
5. A flatter preoperative corneal curvature
6. Surgical enhancements
7. Optical zones smaller than 6 mm
8. Postoperative residual error higher than 0.5 diopters from emmetropia
9. The postoperative residual cylinder

The pupil size was not shown to be a significant predictor of NVC in any of these studies.

42.6 Other Postoperative Reasons for Dissatisfaction

Common subjective complaints after refractive surgery in dissatisfied patients are blurred distance vision (59%) and glare and night-vision disturbances (44%) [7, 12, 16, 20, 21]. Common complications are under- and overcorrection (30%), irregular astigmatism (30%), dry eyes (4–30%), glare (up to 48%), and difficulty with night driving (17%) [20–25]. Common recommendations for management are nonsurgical treatments (68%) consisting primarily of medication and contact lenses [20, 24].

42.7 Managing the Unhappy Patient

Clinical diagnoses that may lead to a suboptimal outcome after laser surgery are:

1. Myopia higher than 12.0 diopters and/or high astigmatism (20.7%)
2. Patients with thin corneas or insufficient corneal thickness (8.2%)
3. Keratoconus (6.4%)
4. Cataract (5.7%)
5. Hyperopia and/or hyperopic astigmatism (4.1%) [26]

There are some ways to try to prevent dissatisfying postoperative outcomes and resulting unhappy patients.

1. Carefully consider the pupil size and the choice of optical zone size.

   There is variable evidence in the literature on excluding patients with large pupils [7, 12, 16, 27]. Higher myopic corrections generally require smaller optical zones, which in turn increased ablation depth and risk of NVC [12]. Our earlier mentioned study showed increased glare with higher amounts of pupil-optical zone disparity in scotopic light conditions, but not with the "real life" mesopic-low pupil size [11]. A recently published review found no significant correlation between preoperative pupil size and the occurrence of NVC's after LASIK with a 6.0 mm ablation zone but suspects that a correlation might be present in case of ablation zones smaller than 6.0 mm [28].

   The quality of manual pupil measurements is highly related to the experience of the examiner and thus can be subject to bias [29, 30]. Multiple automated infrared pupillometers are commercially available and can provide good repeatability [31–34].
2. Apply wavefront-guided treatments.

   Wavefront technology was developed to categorize and treat HOA induced by refractive surgery. HOA can cause glare and halos and lead to decreased quality of vision. A few studies have shown increased satisfaction, a reduction in HOA, and night-vision complaints after wavefront-guided treatments [17, 35, 36]. Several studies have indicated the advantages of wavefront-guided over conventional ablations in terms of decreased HOA and subjective complaints [37–39], but a 2011 meta-analysis of eight randomized controlled trials (RCTs) reporting on a total of 995 patients showed no clear evidence of superiority of the wavefront-guided versus the traditional LASIK. However in case of high preoperative HOA, wavefront-guided treatment should be preferred over traditional LASIK [40].
3. Topography-guided ablation for irregular corneas.

   HOA in symptomatic post-LASIK corneas have been shown to be an average of 2.3 times greater in comparison to normal post-LASIK corneas [41]. Recent studies indicate that customized ablation based on corneal topography is safe and effective and can lead to fewer NVC and less increase of HOA compared to conventional ablation [42–44].
4. Patients with visual symptoms should be advised to be patient and wait for healing or "adaptation."
5. Try and treat the residual cylinder if there is a low uncorrected visual acuity with glasses or additional procedures.
6. Use pharmacological pupillary constriction methods to reduce NVC and HOA.

Take-Home Pearls

- Uneventful refractive surgery with a good clinical outcome would be expected to lead to a high level of patient satisfaction, unless the patient's preoperative expectations were unrealistic.
- It is important to determine patient's motivations and expectations before surgery, since the relationship between patient expectations, the medical outcome, and patient satisfaction is complex and the clinical outcome does not always directly correlate with the subjective outcome.
- We should inform patients of complications as soon as possible, maintain their trust, and try to reassure them.

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