The Kidney and Hypertension in Diabetes Mellitus

Second Edition

EDITED BY
CARL ERIK MOGENSEN

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EDITED BY

CARL ERIK MOGENSEN
Medical Department M
(Diabetes & Endocrinology)
Aarhus Kommunehospital
University Hospitals in Aarhus
Aarhus C, Denmark

Editorial secretary

ANETTE ANDERSEN

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This book is dedicated to **Knud Lundbæk**, distinguished diabetologist, my friend and mentor, and a great inspiration for all of us. He is now, over the age of 80 years, strongly engaged in exciting and penetrating new studies in the field of sinology, his new science.

CEM

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SOME KEYS TO THE LITERATURE

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CONTRIBUTING AUTHORS

Elias V. Balaskas, MD
University of Toronto
Division of Nephrology
Toronto, Ontario
CANADA

Hans-Jacob Bangstad, MD
Barneavd.
Aker sykehus
0514 Oslo 5
NORGE

Staffan Björck, MD
Njurmottagningen
Sahlgrenska sjukhuset
S-413 45 Göteborg
SVERIGE

Knut Borch-Johnsen, MD
Befokningsundersøgelserne
Amtssygehuset i Glostrup
DK-2600 Glostrup
DENMARK

Inge Bjørn Brekke, MD
Rikshospitalet
Medicinsk afdeling
0027 Oslo 1
NORGE

C. Andrew Combs, MD
The Good Samaritan Hospital
2425 Samaritan Drive
San Jose, CA 95124
USA

Mark E. Cooper, MD
Department of Medicine
Heidelberg Repatriation Hospitals
West Heidelberg VIC 3081
AUSTRALIA

Maximilian de Courten, MD
Medizinische Universitätspoliklinik
Inselspital Bern
CH-3010 Bern
SWITZERLAND

Indra D. Daniels, MD
Department of Medicine
State University of New York
Health Science Center at
Brooklyn
NY 11203-2098
USA

Ralph A. DeFronzo, MD
University of Texas Health
Science Center
7703 Floyd Curl Drive
San Antonio, Texas 78231
USA

Garabed Eknoyan, MD
Renal Section
Department of Medicine
Baylor College of Medicine
Houston, Texas 77030-34
USA

Bo Feldt-Rasmussen, MD
Nefro-Endokrinologisk afd. P 2132
Rigshospitalet
DK-2100 København Ø
DENMARK

Paola Fioretto, MD
Department of Internal Medicine
University of Padova
35128 Padova
ITALY

Allan Flyvbjerg, MD
Medical Department M
Institute of Experimental Clinical
Research
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Eli. A. Friedman, MD
Department of Medicine
State University of New York
Health Science Center at
Brooklyn
NY 11203-2098
USA

Rijk O.B. Gans, MD
Department of Internal Medicine
Free University Hospital
1081 HV Amsterdam
THE NETHERLANDS

Ana Grenfell, MD MRCP
The Jeffrey Kelson Diabetic Centre
Central Middlesex Hospital
NHS Trust
London NW10 7NS
UNITED KINGDOM

Klavs Würgler Hansen, MD
Medical Department M
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Ryuichi Kikkawa, MD
The Third Department of Medicine
Shiga University of Medical Science
Seta, Otsu, Shiga 520-21
JAPAN

Priscilla Kincaid-Smith, MD
Department of Pathology
The University of Melbourne
Victoria 3052
AUSTRALIA

Allan Kofoed-Enevoldsen, MD
Hillerød Centralsygehus
DK-3400 Hillerød
DENMARK

William C. Knowler, MD, Dr.P.H.
Diabetes and Arthritis Epidemiology Section
National Institute of Diabetes and Digestive and Kidney Diseases
Phoenix, Arizona 85014
USA

Ruggero Mangili, MD
Istituto di Ricovero e Cura a Carattere Scientifico
Cattedra di Clinica Medica Generale
20132 Milano
ITALY

Diane L. Manninen, MD
Battelle Center for Public Health Research and Evaluation
Seattle Washington
USA

Michel Marre, MD
Unite de Diabetologie
Centre Hospitalier Regional et Universitaire d'Angers
CHR-49033 Angers Cedex 01
FRANCE

Margrethe Mau Pedersen, MD
Medical Department M
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Carl Erik Mogensen, MD
Medical Department M
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Henrik Bindesbøl Mortensen, MD
Børneafdelingen L
Københavns Amts Sygehus
DK-2600 Glostrup
DENMARK

Søren Nielsen, MD
Medical Department M
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Gudrun Nyberg, MD
Transplant Division
Department of Surgery
Sahlgrenska University Hospital
S-413 45 Göteborg
SWEDEN

James A. O'Hare, MD FRCPI MRCP
Regional General Hospital
Dooradoyle, Limerick
IRELAND

Steen Olsen, MD
Patologisk Institut
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

David J. Pettitt, MD
Department of Healthy & Human Services
National Institute of Diabetes and Digestive and Kidney Diseases
Phoenix, Arizona 85014
USA

Per Løgstrup Poulsen, MD
Medical Department M
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Anthony E.G. Raine, D. Phil FRCP
Department of Nephrology
The Royal Hospital of St. Bartholomew
London EC1A 7BE
UNITED KINGDOM

Eberhard Ritz, MD
Sektion Nephrologie
Klinikum der Universität Heidelberg
6900 Heidelberg 1
GERMANY

D.J.F. Rowe, MD
Southampton General Hospital
Tremona Road
Southampton S09 4XY
UNITED KINGDOM

Peter T. Sawicki, MD
Medizinische Einrichtungen der Heinrich-Heine Universität
Abteilung für Ernährung und Stoffwechsel
W-4000 Düsseldorf 1
GERMANY

Erwin D. Schleicher, MD
Institut für Diabetesforschung
8 München 40
Kölner Platz 1
GERMANY

Anita Schmitz, MD
Medical Department M
Aarhus Kommunehospital
DK-8000 Aarhus C
DENMARK

Coen D.A. Stehouwer, MD
Department of Internal Medicine
Free University Hospital
1081 HV Amsterdam
THE NETHERLANDS

Roberto Trevisan, MD
Instituto di Medicina Clinica
Cattedra Malattie del Ricambio
Università di Padova
Divisione Malattie del Ricambio
35128 Padova
ITALY

René Vejlsgaard, MD
Klinisk Mikrobiologisk afdeling, lokal 3856
Amtssygehuset i Herlev
DK-2730 Herlev
DENMARK

Jiten P. Vora, MD
Department of Medicine
Royal Liverpool University Hospital
Liverpool L7 8XP
UNITED KINGDOM

James D. Walker, MD
Department of Endocrinology
St. Bartholomew's Hospital
London EC1A 7BE
UNITED KINGDOM

Ping H. Wang, MD
Joslin Diabetes Center
One Joslin Place
Boston, MA 02215
USA

PREFACE, first edition

The first sporadic observations describing renal abnormalities in diabetes were published late in the 19th century, but systematic studies of the kidney in diabetes started only half a century ago after the paper by Cambier in 1934 and the much more famous study by Kimmelstiel and Wilson in 1936. These authors described two distinct features of renal involvement in diabetes: early hyperfiltration and late nephropathy. Diabetic nephropathy is, despite half a century of studies, still a very pertinent problem, renal disease in diabetes now being a very common cause of end-stage renal failure in Europe and North America and probably throughout the world. It is a very important part of the generalized vascular disease found in long-term diabetes as described by Knud Lundbæk in his monograph *Long-term Diabetes* in 1953, published by Munksgaard, Copenhagen.

Surprisingly, there has not been a comprehensive volume describing all aspects of renal involvement in diabetes, and the time is now ripe for such a volume summarizing the very considerable research activity within this field during the last decade and especially during the last few years.

This book attempts to cover practically all aspects of renal involvement in diabetes. It is written by colleagues who are themselves active in the many fields of

medical research covered in this volume: epidemiology, physiology and pathophysiology, laboratory methodology, and renal pathology. New studies deal with the diagnosis and treatment of both incipient and overt nephropathy by metabolic, antihypertensive, and dietary invention. Considerable progress has been made in the management of end-stage renal failure and also in the management and treatment of nephropathy in the pregnant diabetic woman. Diabetic nephropathy is a worldwide problem, but it is more clearly defined in Europe and North America where facilities for the diagnosis and treatment of diabetes and its complications are readily available. Much more work needs to be done in other parts of the world, as it appears from this book.

It is hoped that we now have a handbook for the kidney and hypertension in diabetes and that further progress can be made in clinical work in diagnosing and treating diabetic patients. Much more work still needs to be done regarding patient education with respect to complications. Many diabetics have now been trained to take part in the management of their metabolic control; they should also be trained to take part in the follow-up and treatment of complications.

This volume also underlines the considerable need for future research. So far, research in this field has been carried out in relatively few countries and centers in the world. The editor is sure that this volume will also stimulate further advancement in clinical science within the field of diabetic renal disease.

In 1952, the book *Diabetic Glomerulosclerosis, The Specific Renal Disease in Diabetes Mellitus*, by Harold Rifkin and coworkers, published by Charles C. Thomas, Springfield, Illinois, USA, summarized all current knowledge on the diabetic kidney in about 100 short pages, including many case histories. Much more space is needed now and the many disciplines involved will undoubtedly attract many readers.

Carl Erik Mogensen

PREFACE, second edition

The sum of clinical problems caused by diabetic renal disease has been steadily increasing since the first edition of this book was published in 1988. Indeed, it is now estimated that throughout the world about 100,000 diabetic individuals are receiving treatment for end-stage renal failure. Obviously, this means a burden with respect to human suffering, disease and premature mortality, but additionally these treatment programmes are extremely costly, so costly that in many areas resources are not available for this kind of care. It is therefore clear, that every efforts should be made to prevent or postpone the development of end-stage disease.

The years since the first edition appeared we have seen a tremendous progress in research activities. Importantly, this also includes improvement in the treatment programmes to prevent end-stage renal failure. Thus it has become clear that the diabetic kidney is extremely pressure-sensitive, responding to effective antihypertensive treatment by retarded progression of disease. Some agents may be more beneficial in this respect than other, although the effective blood pressure reduction per se is crucial throughout the stages of diabetic renal disease. However, the prime cause of diabetic renal disease is related to poor metabolic control and it is now documented beyond doubt that good metabolic control is able to postpone or perhaps

even prevent the development of renal disease. However, in many individuals we are not able to provide such a quality of control that will prevent complications, and therefore non-glycaemic intervention remains important. Maybe in the future non-glycaemic intervention will become the most important research area in diabetic nephropathy.

With respect to the exact mechanisms behind poor metabolic control and development of renal disease, much information is now being gained. It is likely that a combination of genetic predisposition and metabolic and haemodynamic abnormalities explain the progression to renal disease, seen in about 30% of the diabetic individuals. Much of this development probably relates to modifiable genetic factors, such as blood pressure elevation or haemodynamic aberrations. However, mechanisms related to the response to hyperglycaemia are also of clear importance as is the possibility that these metabolic or haemodynamic pathway may be inhibited.

This volume review older data as well as the progress seen within the research of diabetic nephropathy over the last five years and provides a state of the art of the development. However, we are still far from the main goal, which is the abolition of end-stage renal disease in diabetic individuals. Obviously, much work still needs to be done and one of the intentions of this book is to stimulate further research in this area where so many sub-disciplines of medical science are involved from the extremes of genetic and molecular biology to clinical and pharmacological research trials.

Carl Erik Mogensen

1. DEFINITION OF DIABETIC RENAL DISEASE IN INSULIN-DEPENDENT DIABETES MELLITUS BASED ON RENAL FUNCTION TESTS

CARL ERIK MOGENSEN

Defining renal disease and renal involvement in diabetes appeared not to be an easy task, mainly because of the wide range of changes seen. The different degree of abnormalities, often with the same duration of disease, seemingly same quality of long-term metabolic control, and the same type of diabetes, may according to older literature indeed be striking [1-3]. However, with better techniques and more well-defined patients [4] much more consistency is found, as reviewed in this volume.

The main criteria for a suitable system of definition are outlined in table 1-1: (a) the parameters should have strong prognostic or predictive power with respect to progression of disease, (b) clear pathophysiologic relevance, (c) relation to structural or ultrastructural abnormalities, and (d), because of the generalized disease process of complications, the system should be related to other microvascular and also macrovascular lesions of diabetes. It should also be treatment-orientated.

During the last ten years, a diagnostic system has been elaborated [5,6] that seems to fulfil the criteria indicated above. This system was mainly worked out on the basis of the predictive power of urinary albumin excretion (UAE) as well as

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Table 1-1. Definition of diabetic renal disease

	Hyper-filtration	Micro-albuminuria	Clinical proteinuria	Structural lesions
Predictive power	Yes	Strong	Strong	Still unknown
Relationship to patho-physiology	Likely	Yes	Yes	Not defined
Relationship to structural damage	Not clearly	Clearly in IDDM	Yes	
Associated with other vascular lesions	?	Yes	Yes	Likely

knowledge of the pathophysiology of renal changes in diabetes. Structural changes appear still to be secondary elements in the system, although microalbuminuria clearly correlate to structural lesions [6,7]. The »subclinical« level of increased albumin excretion is termed microalbuminuria [8]. So far this system is mainly relevant to insulin-dependent patients, but can also to some extent be used in non-insulin-dependent diabetes [Chapter 2].

1. LONGITUDINAL AND FOLLOW-UP STUDIES IN INSULIN-DEPENDENT DIABETICS

Three centers documented the predictive power of raised UAE [8-11] as summarized in table 1-2. If UAE is above a certain limit, excretion rate tends to increase with time and spontaneous reversal occurs only in relatively few patients. The exact level above which albumin excretion rate tends to rise with time is not clearly defined [6], but even patients with upper-normal level tends to progress [12]. The level is likely to vary with methods of urine collection (table 1-2), e.g. the critical level of albumin excretion rate was 30 μg/min in a study using overnight urine collection procedure, 70 μg/min in a study using 24-h urine collection, and as low as 15 μg/min in another study using short-term collection during the daytime in hospital. Usually albuminuria is lower during night (lower blood pressure (BP) and recumbency), than during the day. The procedure of urine collection seems to be more important than the method used for measuring albumin, but duration of follow-up is also likely to be of significance.

The risk for future clinical nephropathy over the next decade is markedly higher ($\approx$80%) in the presence of microalbuminuria, compared with patients with a completely normal excretion rate ($\approx$5%). Thus it is now possible to identify, early

Table 1-2. Summary of studies of development of overt diabetic nephropathy, based on early microalbuminuria (M)

	London[a]	Copenhagen[b]	Aarhus[c]
Female/male	22/44	42/29	0/43
Follow-up (%)	75%	100%	98%
Mean age at screening (years)	40(17-60)	30(13-50)	25(18-31)
Mean duration of diabetes at screening (years)	10(1-41)	12(2-36)	12(7-20)
Follow-up period (years)	14	Mean 6	Mean 10
Proposed discrimination value	30 μg/min	70 μg/min	15 μg/min
Development of DN[d] above discrimination value	7/8	7/7	12/14
Development of overt DN below discrimination value	2/55	3/64	0/29
Urine sample	Overnight	24-h	Short-term at hospital
Number of urine samples	≥1	≥3	≥3
Methods	RIA	Radial immune diffusion	RIA
Prolonged follow-up (≈20 years)	M related to mortality and cardiovascular renal disease [22]	Not done	M clearly related to mortality, overt renal disease and ESRF[e] [6]

[a]From Viberti, et al. [8]
[b]From Mathiesen et al. [11]
[c]From Mogensen [10]
[d]DN, diabetic nephropathy
[e]ESRF = End-Stage-Renal-Failure

in the course of diabetes, patients prone to the development of overt renal disease. Longitudinal studies in patients with microalbuminuria have revealed a rather slow rate of progression, as measured by yearly increase in UAE. In recent longitudinal studies, the yearly percentage increase in albumin excretion on conventional insulin treatment was around 15%-20% [13,14]. the yearly increase rate in albumin excretion rate was related to BP elevation [13,14] as well as metabolic control during the observation period [14].

The recognition of the ability of microalbuminuria to predict future diabetic nephropathy (DN) leads to the definition of a new stage in the development of renal disease in diabetics, namely, incipient DN [5]. Obvious, effective antihypertensive treatment as well as intensified diabetes treatment reduces microalbuminuria or risk of development of microalbuminuria [6,14,15]. This is likely to change also long-term prognosis [Chapters 33 and 34].

2. URINARY ALBUMIN EXCRETION IN YOUNG NORMAL SUBJECTS AND PROCEDURE OF URINE COLLECTION

In one study, the UAE measured in 24-h samples in 23 normal men and 20 normal women (aged 22-40 years) averaged 4.7 $\pm$ 4.7 μg/min (SD) (range, 2.6-12.6) and 4.3 $\pm$ 4.8 (range, 1.1-21.9), respectively [16]. The day-to-day variation in UAE of 24 normal subjects, estimated as the coefficient of variance of 24-h samples, was 31.3%. The mean UAE at rest (short-term collections over several hours, or overnight n = 180) was similar (5.8 $\pm$ 1.4 μg/min). Similar values have been obtained by other authors, but usually overnight excretion rates are somewhat lower than day-time values, even at complete rest: median daytime UAE: 6.2 μg/min; overnight 3.7 μg/min for men, and similar values for women. There is not very precise correlation between UAE and urinary albumin creatinine ratio or albumin concentration as seen in figure 1-1 [E. Vestbo et al., personal communication]. Higher values for UAE are recorded in some elderly non-diabetic individuals in population studies [17].

Because the UAE varies with posture [18] and with exercise [19] and after heavy water drinking [20], evaluation should be carried out only on urine collected under very standardized conditions. Each of the following procedures is considered acceptable: (a) overnight (approximately 8-h) urine collection, (b) short-term collections over one or several hours in the laboratory or clinic, (c) a 24-h collection, and (d) an early morning urine sample using albumin concentration or possibly corrected for urine flow by creatinine measurements, using albumin creatinine ratio (mainly for screening purposes). Because the coefficient of variance in UAE is between 30%-45%, at least three urine collections are recommended [21].

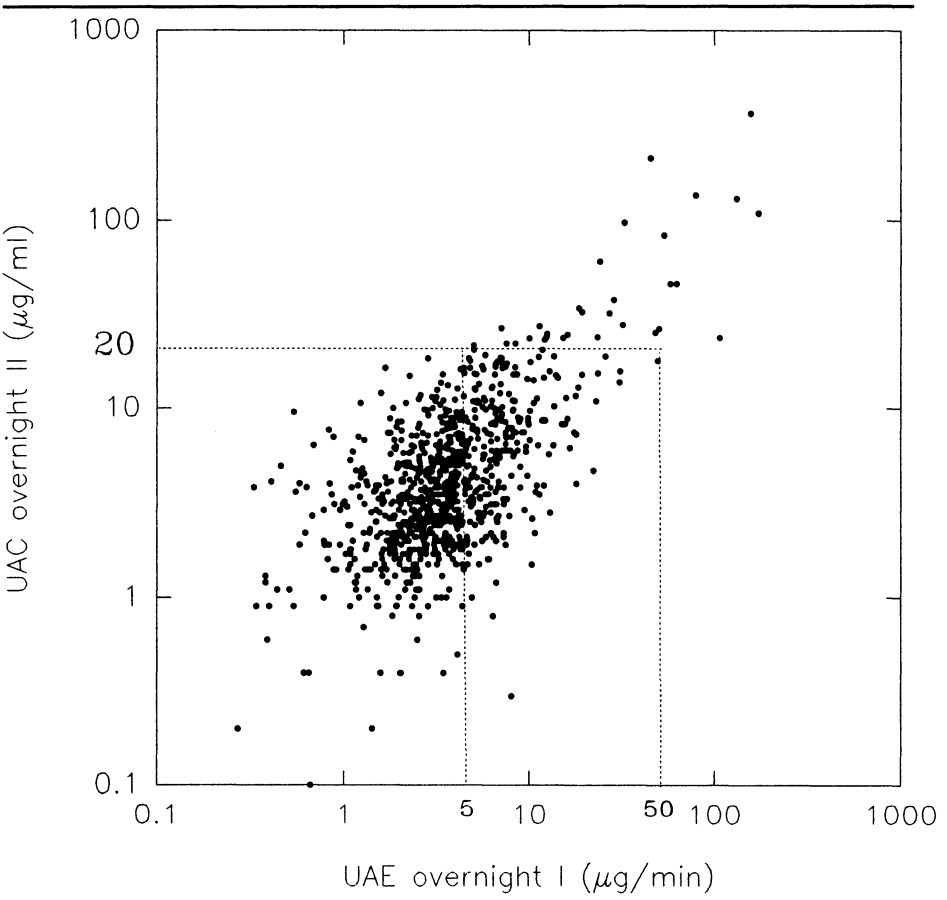

Figure 1-1. Relationship between UAE overnight I and UAC overnight II. Spearmans R = 0.53). (E. Vestbo with permission).

Studies among diabetics should always include measurements in healthy controls with exactly the same procedure.

3. CRITERIA FOR DIAGNOSING MICROALBUMINURIA AND INCIPIENT DIABETIC NEPHROPATHY IN INSULIN-DEPENDENT PATIENTS

It has recently been proposed that more firm criteria should be applied, both in research projects and in the clinical setting. The following criteria have been proposed for insulin-dependent patients [21], and subsequently used in many studies.

Microalbuminuria is present when UAE is greater than 20 μg/min and less than or equal to 200 μg/min. BP should always be carefully recorded by several measurements. Patients should be peaceful conditions while collecting urine.

Incipient diabetic nephropathy is suspected when microalbuminuria is found in two out of three urine samples, preferably collected over a period of 6 months. Urine should be sterile in non-ketotic patients and other causes of increased excretion rate should be excluded. If duration of diabetes is less than 6 years, other causes should especially be considered. Urine collection during the typical diabetes control of the individual patient is recommended.

Overt diabetic nephropathy is suspected when UAE rate is greater than 200 μg/min (macroalbuminuria) in at least two out of three urine samples collected within 6 months. Urine samples should be sterile in non-ketotic patients and other causes of increased UAE rate should again be excluded.

Dipsticks for urinary protein should not be applied in the classification of renal disease in diabetes according to this proposal. The dipstick procedure is useful, however, in clinical laboratories, and new screening tests, e.g. the Micral-test® are very useful in screening for microalbuminuria [Chapter 9].

4. A NEW CLASSIFICATION SYSTEM

Knowledge of the predictive power of microalbuminuria for renal disease in diabetes, and the description of glomerular hyperfiltration and hypertrophy in diabetes present already at diagnosis, have underlined the need for redefinition of renal involvement in diabetes and DN. A redefinition is most easily achieved by defining new stages in the development of renal changes. These stages, as well as their main characteristics, and outlined in table 1-3. The following stages can be defined:

1. *Glomerular hyperfunction and hypertrophy stage* present at diagnosis. It should be mentioned that certain features in this stage will also accompany diabetes of longer duration when metabolic control is not completely perfect.
2. *The silent stage with normal albumin excretion*, but with structural lesions being present. This stage may last many years; in fact, most patients will continue in this stage throughout their lifetime. Occasionally, in stress situations, e.g. during episodes of very poor metabolic control or during moderate exercise, albumin excretion rate may increase, but this is a readily reversible phenomenon. Transition to stage 3 is seen in about 4% of cases per year, associated with poor metabolic control, and high level of normoalbuminuria [12,23].
3. *Incipient diabetic nephropathy* is characterized by persistent and with long observation period usually increasing microalbuminuria, Patients with microalbuminuria have a very high risk of subsequent development of overt DN.

Table 1-3. Microalbuminuria and diabetic nephropathy stages in diabetic renal involvement and nephropathy (DN)

Stage	Designation	Main characteristics	Main structural changes	GFR (ml/min)	UAE	Blood pressure	Suggested main pathophysiologic change
Stage I	Hyperfunction/hypertrophy[a]	Glomerular hyperfiltration	Glomerular hypertrophy	≈150	May be increased	N	Glomerular volume pressure increase
Stage II	Normoalbuminuria	Normal UAE	Increasing basal membrane (bm) thickness	Hyperfiltration[a]	N (high in stress situations)	N	Changes as indicated above but quite variable
Transition from II→III	Transition phase	High normal UAE	Not known	Hyperfiltration	Increasing	Increasing	Somewhat poor metabolic control
Stage III	Incipient DN, microalbuminuria	Elevated UAE	UAE correlated to structural damage	Still high GFR	20→200 μg/min	Elevated compared to stage II	Advancing glomerular lesions. Permeability defect not located
Stage IV	Overt DN	Clinical proteinuria or UAE >200 μg/min	Advanced structural damage	"Normal" to advanced reduction	>200 μg/min	Often frank hypertension Increase by ≈5% yearly	High rate of glomerular closure advancing and severe mesangial expansion.

[a]Changes present probably in all states when control imperfect and in stage II marker of future nephropathy (if GFR >150 ml/min)

Scheme is valid in the "untreated situation". BP reduction often reduces albuminuria (Proteinuria → Microalbuminuria → Normoalbuminuria)

However, intervention (e.g. optimized metabolic control as well as antihypertensive treatment) may certainly change the so-called natural history, reversing functional and maybe even stabilizing structural changes.

4. *Overt diabetic nephropathy* is characterized by proteinuria, hypertension and subsequent fall in glomerular filtration rate (GFR). A decrease in incidence may be seen now [24].
   Beta-2-microglobulin excretion starts to increase in the stage of overt DN, at UAE of around 1000 μg/min [13]. Dextran clearance is according to older as well as most recent study only abnormal with advanced proteinuria [5,25].
5. *End-stage-renal-failure* (ESRF). This entity is now the most common cause of uraemia in the US, and very common also elsewhere. Treatment options are also discussed in the final chapters of the book. Recently scepticisms has been expressed about combined pancreas-kidney transplantation, which with the exception of selected patients, may be regarded as experimental medicine [26].

Systematic screening for early renal involvement is clearly advisable in the diabetes clinic, e.g. by annual measurement of albuminuria in all ranges, or possibly at each visit; more frequent monitoring should be done if UAE is elevated.

4.1 The traditional clinical definition of diabetic nephropathy

The clinical definition can also, as by tradition, be based on measurement of total protein excretion over three 24-h periods. If mean excretion rate is more than 0.5 g over 25 h, DN is likely in a patient with more than 8-10 years' of diabetes, especially with the presence of retinopathy. This level corresponds approximately to >200 μg/min in UAE.

With a non-typical course, e.g. short duration of diabetes in patients without retinopathy or rapid progression of disease (e.g. great fall in GFR, very rapid increase in proteinuria, or sudden onset of proteinuria) - renal biopsy would be appropriate in order to diagnose non-diabetic renal disorders. Measurement of total proteinuria is now usually being replaced by measurement specifically for albuminuria.

4.2. Abnormalities associated with microalbuminuria

Several abnormalities have been documented in patients with incipient DN.

1. During the stages of incipient DN, the GFR is most often elevated above normal [4]. As microalbuminuria progresses to proteinuria, GFR returns to the »normal« range, which is in fact usually abnormally low IDDM-patients. Patients who enter the stage of clinical proteinuria exhibit gradual decreases in both GFR and renal plasma flow (RPF).

2. Several groups have recognized that elevated BP is an early accompaniment of incipient DN; the magnitude of the elevation is in the range of 10%-15% above values in control subjects and normoalbuminuric diabetics [27, Chapter 24].
3. Diabetic retinopathy is more advanced in patients with microalbuminuria than in patients with silent stage II disease [28]. Importantly, patients at risk for proliferative diabetic retinopathy can be identified on the basis of microalbuminuria [29].
4. Transcapillary escape rate of albumin is increased in incipient DN [30], and plasma lipid abnormalities may be found.
5. A multitude of other features of vascular, cardiac and neurological damage is seen in these patients [31]. Plasma prorenin may also be associated to microalbuminuria both its significance is still not clearly defined [32].

At the time of diagnosis of microalbuminuria or incipient DN, HbA_{1c} is often elevated by in mean by 10%-20% compared to normoalbuminuric diabetics [4]. Patients with microalbuminuria are obviously likely to have been in poorer control also during many years earlier in the course of diabetes [12,23,24].

5. PROBLEMS RELATED TO DIAGNOSING DIABETIC NEPHROPATHY ON THE BASIS OF URINARY ALBUMIN EXCRETION

There are a number of other causes of raised UAE rate in diabetic patients. UAE may increase during very poor metabolic control [21], and it may also be slightly increased at the time of clinical diagnosis [18]. Such elevations are usually readily reversible. Urinary tract infection may also be present and may cause some elevation of UAE [17]. Other vascular diseases such as essential hypertension and cardiac failure should also be considered [33]. Moderate exercise causes increases in UAE more readily in diabetics than in non-diabetics and is thus a confounding factor [19]. Exercise-induced increases in UAE have not been documented to predict either incipient or overt nephropathy. It has also been shown that UAE increases temporarily (less than one hour) after drinking large amounts of water, e.g. 1 litre [20]. Therefore, urine flow and UAE should be stable sometime after the start of water drinking (2 h are advisable) when evaluating patients during, e.g. renal clearance procedures [4].

A special problem regarding interpretation of data is borderline increase of UAE. Some patients do show an excretion rate of around 15-30 μg/min and classification may be difficult during a short observation period. The risk of progression is, however, high [12,34].

6. PROGRESSION OF CHANGES

It is important to note that progression of nephropathy in the incipient phase is rather slow: yearly mean increase rate in UAE is around 15%-20%. GFR probably starts to decline late in this stage. Progression is more rapid in overt nephropathy without treatment and GFR declines at a mean value of 12 ml/min/year [35,36]. To have clinical relevance, studies of the spontaneous course as well as studies on the effect of intervention should be sufficiently long, e.g. at least 2-3 years or even longer. A given treatment modality may also be difficult to sustain for a prolonged period without any other intervention: e.g. can optimized insulin treatment be given without considering BP elevation? Of course the final end point would be prevention of development of ESRF. In any patients under study, however, development of renal failure would last one or more decades. Therefore ESRF is not really a feasible test parameter. Increasing albuminuria and especially fall in GFR are satisfactory intermediate end-points

7. GLOMERULAR FILTRATION RATE IN THE DEFINITION OF DIABETIC NEPHROPATHY

An isolated GFR is not a very appropriate parameter to use in the definition of DN. Both metabolic control and structural lesions have a profound effect on GFR. A low GFR (e.g. 110 ml/min), accompanied by totally normal UAE ($\approx$4 μg/min), certainly indicates an excellent prognosis. A similar low GFR may be found in patients with even marked proteinuria. Such a patient is likely to have experienced a decline in GFR, e.g. from 170 to 110 ml/min.

When optimizing metabolic control, GFR usually falls, as does an even borderline elevated UAE, whereas a completely normal UAE does not change. Progression of structural lesions also results in reduction of GFR, but in this case UAE increases considerably.

Importantly, hyperfiltration in well-defined patients with and without microalbuminuria carries a much poorer prognosis [10,37]. In the follow-up of patients, it is extremely important to *monitor* GFR along with UAE, but the definition of DN should be based upon UAE (in patients without antihypertensive treatment and in their usual glycaemic control).

The coefficient of variance in GFR measurements using a constant infusion technique with 3-6 periods may vary according to the degree of renal involvement or vascular and neuropathic damage in general. In normoalbuminuric and microalbuminuric patients, the coefficient is low, on the order of 5%-8% [4]. In some situations it is not possible to use a constant infusion technique in patients with advanced nephropathy because of voiding problems. Six or more collection periods are usually advisable in such patients and, if the coefficient of variance is high

(>15%), this procedure for measuring GFR simply cannot be used. Single-shot measurement of GFR, e.g. using [Cr]EDTA clearance, is then clearly advisable [38,39].

Several more detailed reviews on different aspects of microalbuminuria and diabetic renal disease is available elsewhere [31-49].

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2. ALBUMINURIA AND RENAL DISEASE IN NIDDM-PATIENTS

ANITA SCHMITZ

The multitude of reports on the unequivocal importance of microalbuminuria in predicting diabetic complications in insulin-dependent diabetes (IDDM), have during recent years been succeeded by an increasing number of studies on patients with non-insulin-dependent diabetes (NIDDM). It has hence become clear, that the course of complications and the implication of microalbuminuria differ in several respects between the two types of diabetes [1-3].

The rather high prevalence of microalbuminuria and proteinuria in NIDDM is conspicuous, being 20-40% and 5-15% [4-8] respectively. This pertain also to newly or recently diagnosed patients [4,8-13], though at that point elevated albuminuria is reversible to some degree [12,14,15]. On the other hand, the incidence of renal impairment is of a low order of magnitude [4,16]. Due however to the large number of patients with NIDDM, renal failure constitutes an important health care problem also in these patients [17-19]. The association of diabetes and increased mortality is well established, but the poorer prognosis in NIDDM is due mainly to disabilities caused by large-vessel disease.

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

In 1984 Jarrett et al. [20] and Mogensen [21] both reported that microalbuminuria is a predictor of increased mortality in NIDDM.

1. MICROALBUMINURIA, AN IMPORTANT RISK MARKER: A 10-YEAR FOLLOW-UP STUDY OF 416 NON-INSULIN-DEPENDENT DIABETICS

We investigated the prognostic influence of microalbuminuria, also in relation to other possible risk factors in a 10-year follow-up study [5] of 416 non-insulin-dependent patients with urinary albumin concentration (UAC) ≤ 200 μg/ml ($\approx$ the upper limit of microalbuminuria) [22]. UAC was measured in first morning urine samples by radioimmunoassay [23] at each outpatient attendance during one year. Measurements were done on the total outpatient population and inclusion criteria were: age 50-75 years, age at diagnosis ≥ 45 years, and treatment managed without insulin for a period of at least 2 years. Clinical data are presented in table 2-1; 15 μg/ml was chosen as the upper limit of strictly normal UAC, and the patients were divided into three categories accordingly (UAC ≤ 15 μg/ml, 15 μg/ml $<$ UAC ≤ 40 μg/ml, and 40μg/ml $<$ UAC ≤ 200 μg/ml). Weight recorded during all visits (until death or end of follow-up), was related to »ideal« and treatment modality was recorded as the most »severe« (insulin > tablets > diet) during the 10-year period, since treatment modality often changes over time.

It appears that the only significant differences between the groups were higher level of plasma glucose ($r=0.17$, $p<0.001$) and serum creatinine ($r=0.26$, $p<0.001$) in patients with elevated UAC. Blood pressure (BP) was similar and hypertensive (BP >160 mmHg systolic or >95 mmHg diastolic, $n=255$) and normotensive ($n=161$) patients had mean UAC values of 11.0 μg/ml $\times/\div$ 2.8 and 9.3 μg/ml $\times/\div$ 2.8 respectively. Frequency of retinopathy tended to be higher in the groups with microalbuminuria, but the difference was not significant.

After 10 years 219 patients had died. The prognostic influence of the variables listed in table 2-1 was first evaluated separately using a log rank test. Age and UAC had highly significant influence on the survival ($p<0.00005$ for both variables). Known diabetes duration also had significant prognostic influence ($p=0.0006$), and serum creatinine was close to reaching significance ($p=0.07$). The remaining variables had no significant influence on survival. By Cox regression analyses age, UAC, diabetes duration, and serum creatinine were the only significant independent prognostic variables.

Figure 2-1 presents the survival curves for the three UAC levels after correction for the other independent prognostic variables. Even a minor increase in UAC, i.e. 16-40 μg/ml, predicts significantly reduced survival probability. A further increase in albuminuria i.e. 41-200 μg/ml, was associated with a worse prognosis. The hazard ratios in the groups with elevated UAC relative to those with UAC ≤ 15

Table 2-1. Clinical data

	Urinary albumin concentration (μg/ml)			
	≤15 *n* = 290	>15-≤40 *n* = 72	>40-≤200 *n* = 54	
Age	65.6 ± 6.5	66.9 ± 5.7	67.2 ± 5.0	NS[e]
(years)	50 - 75	50 - 75	54 - 75	
Age at diagnosis	59.4 ± 7.2	59.8 ± 6.6	59.8 ± 6.9	NS
(years)	45 - 75	47 - 74	46 - 71	
Known diabetes duration	6.2 ± 4.9	7.1 ± 5.4	7.5 ± 5.2	NS
(years)	0 - 23	0 - 22	1 - 21	
Systolic blood pressure	159 ± 23	162 ± 23	166 ± 26	NS
(mmHg)	113 - 250	108 - 210	110 - 231	
Diastolic blood pressure	91 ± 12	92 ± 14	94 ± 12	NS
(mmHg)	60 - 130	60 - 134	70 - 128	
Fasting plasma glucose	8.8 ± 2.1	9.5 ± 2.6	9.6 ± 2.5	$p = 0.005$
(mmol/liter)	4.6 - 15.8	4.4 - 15.8	6.1 - 17.6	
Fasting plasma glucose	8.7 ± 1.6	9.3 ± 1.9	9.3 ± 1.8	$p = 0.002$
(all visits) (mmol/liter)	5.3 - 14.1	6.4 - 13.6	5.8 - 16.3	
Relative weight	111 ± 18	114 ± 22	111 ± 16	NS
(all visits) (%)	73 - 207	76 - 231	82 - 163	
Serum creatinine	0.9 ×/÷ 1.2	1.0 ×/÷ 1.3	1.1 ×/÷ 1.4	$p = 0.000$
(mg%)[a]	0.6 - 2.8	0.6 - 3.1	0.7 - 3.3	
Sex (M/F)[b]	126/164	35/37	23/31	NS
Retinopathy (N/B/P)[c]	238/42/0	51/16/0	43/10/0	NS
Treatment (D/T/I)[d]	33/201/56	8/44/20	5/34/15	NS

[a]Geometric mean ×/÷ tolerance factor.
[b]M/F, male/female.
[c]N/B/P, normal/background/proliferative.
[d]D/T/I, diet/tablet/insulin.
[e]NS, not significant

μg/ml were 1.65 (p=0.003) and 2.41 (p=0.000002) respectively. No further increase in mortality was detected in patients with UAC >200 μg/ml [5]. Causes of death were obtained from autopsy reports when available, otherwise from medical records. Fifty-six per cent died from acute myocardial infarction, cardiac insufficiency, or stroke, whereas only a total of 2.3% of deaths were caused by uraemia. These cases tended however to be increasingly frequent through the three albuminuria groups (0.8, 2.1 and 7.5% respectively). The major predictive power of microalbuminuria for mortality has later been confirmed [24,25] and recently a very similar relative risk was found in a population based study in diabetics (NIDDM) [26]. Any explanation for this association between elevated urinary

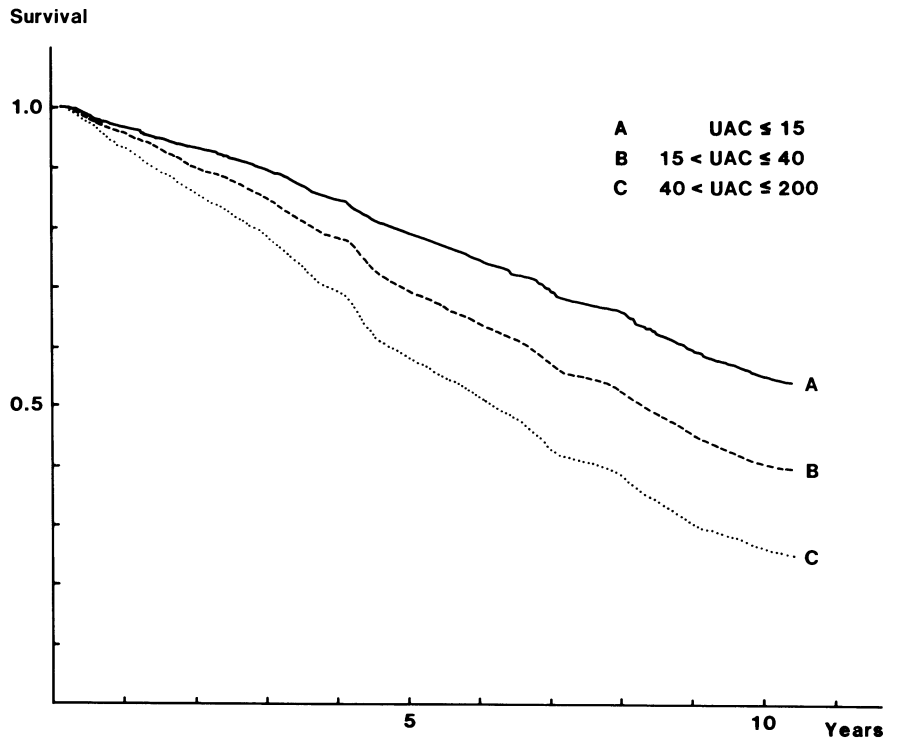

Figure 2-1. Survival curves for the three UAC groups, after correction for the other independent significant prognostic variables; age, known diabetes duration and serum creatinine. N=407, (subjects with missing value(s) excluded).

albumin excretion and cardiovascular disease and death has so far not emerged. The frequency of albuminuria versus the relative rareness of renal failure [4,5,26] appears somewhat paradoxical. Microalbuminuria is seen in 17% of a population of elderly non-diabetic subjects [8], but albumin excretion is normal in those who are healthy [27], and is thus not caused by age per se. Albuminuria in non-insulin-dependent patients is predominantly of glomerular origin [28], but the exact mechanism behind increased escape of albumin is not known in either type of diabetes [29-31]. Increased albuminuria is associated with both coronary heart disease, cardiac failure (even minor degrees of left ventricular dysfunction), as well as peripheral vascular disease [3,10,32-35]. A number of cardiovascular risk factors have been linked also with albuminuria, such as lipoprotein abnormalities,

hyperinsulinaemia and markers of endothelial dysfunction as well as hypertension. It is predominantly systolic BP (also isolated systolic hypertension), that carries the risk [3,31,36-42]. None of these factors, however either alone or in combination have been able to »explain« the increased cardiovascular mortality in patients (of either type of diabetes) with microalbuminuria [3,31,36].

2. ALBUMINURIA AND GLOMERULAR STRUCTURE

Diabetic glomerulopathy does develop in non-insulin-dependent diabetes [43,44]. Information concerning the relationship between quantitative glomerular morphology and clinical renal parameters is however scarce in NIDDM.

We studied the possible relation between urinary albumin excretion and glomerular structure [45] in 19 patients, who had died within 18 months after UAC had been measured. The mean period from last measurement of UAC until death was 9 months. The study was performed on autopsy kidney tissue in patients without other known renal disease. They were aged 76 years (59-89), (mean, (range)), known diabetes duration was 11 years (2-24), and UAC was 29.7 μg/ml $\times/\div$ 5.5 (1.4-710). Autopsy kidney tissue from 19 consecutive sex-and age-matched non-diabetics without known renal disease was sampled for control.

A quantitative light-microscopic study of glomeruli was performed on periodic-acid-Schiff (P.A.S.) stained sections. The classic diabetic glomerulopathy is characterized by increased amounts of basement membrane and mesangial matrix (P.A.S.-positive) in the glomerular tuft (Chapter 14). The volume of P.A.S. - positive material as per cent of tuft volume (defined as the minimal convex circumscribed polygon), was estimated by point counting, and it was significantly increased in the group of diabetics. In this series there was no correlation between the quantitative structural parameters obtained and UAC, figure 2-2. Notably, a high UAC was not necessarily associated with advanced glomerulopathy. On the other hand, a few additional cases dying with uraemia showed severe glomerulopathy. In a later light- and electron microscopic study of biopsies from 20 NIDDM patients with proteinuria [46], the degree of glomerulopathy was estimated by measurement of basement membrane thickness, mesangial and matrix volume fractions (i.e volume per glomerular volume), and frequency of glomerular occlusion. Patients were aged 55 years (37-67), known diabetes duration was 8 years (1-19), urinary albumin excretion (UAE) 1.5 g/24h (0.3-8.7) and glomerular filtration rate (GFR) 90 ml/min/1.73 m^2 (24-146). Data were compared with previous data on 22 IDDM patients aged 35 years (24-47), diabetes duration 20 years (12-31), UAE 1.4 g/24h (0.3-7.9) and GFR 57 ml/min/1.73 m^2 (16-104). Reference was made to 13 (age 51 years (21-68)) non-diabetic living renal transplant donors. There was a striking variation in the severity of glomerulopathy among NIDDM patients, and some

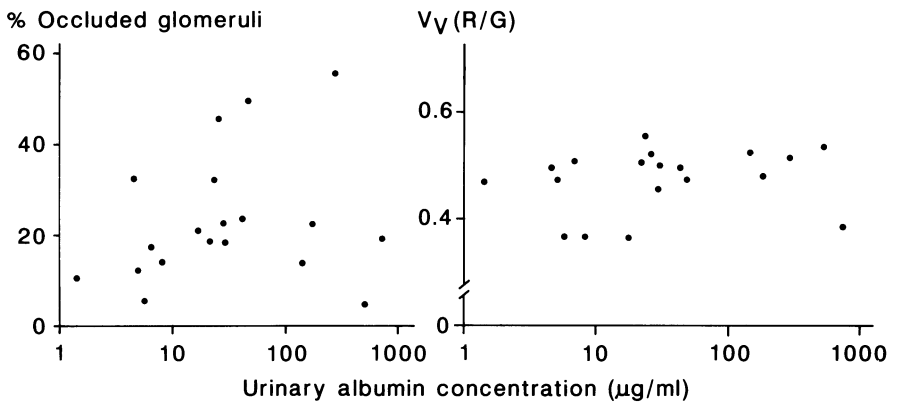

Figure 2-2. Relationship between urinary albumin concentration (µg/ml) and frequency of glomerular occlusion (left panel) and volume fraction of P. A. S. positive material in the glomerular tuft (Vv(R/G)) in 19 NIDDM patients. Data obtained from light-microscopic studies on autopsy kidneys. Reproduced with permission from the American Diabetes Association, Inc. [45].

proteinuric patients exhibited structural parameters within the normal range, figures 2-3 and 2-4. When retinopathy was taken into account, patients with this complication all showed a glomerulopathy index (index is a calculated expression of the sum of changes in peripheral basement membrane and mesangium) above normal. In those without retinopathy approximately half had a normal glomerular structure. Notably, GFR was rather well preserved in NIDDM compared with the younger IDDM patients, with the same degree of proteinuria. Kidney function was however definitely associated with the structure, as an inverse correlation obtained between severity of glomerulopathy (index) and current glomerular filtration rate. Also the structural index correlated with ensuing rate of decline in GFR ($r=0.84$). Interestingly , also in this study no clear association between the structural quantities and albuminuria was seen, and in three different studies around 60% of NIDDM patients with proteinuria had no retinopathy [5-7], quite different from findings in IDDM.

These observations imply, that albuminuria has also causes other than diabetic glomerulopathy. Renal diseases unrelated to diabetic nephropathy may contribute [47,48]. As remarked above, coronary and other large vessel diseases appear also to be involved. Noticeable in this context, is the relation between systolic blood pressure and albumin excretion, which is demonstrated in several studies [3,5,6,9,-26,39,49], whereas the relation to diastolic pressure is modest. Systolic hypertension expresses reduced vascular compliance, rather than »real« hypertension. Both

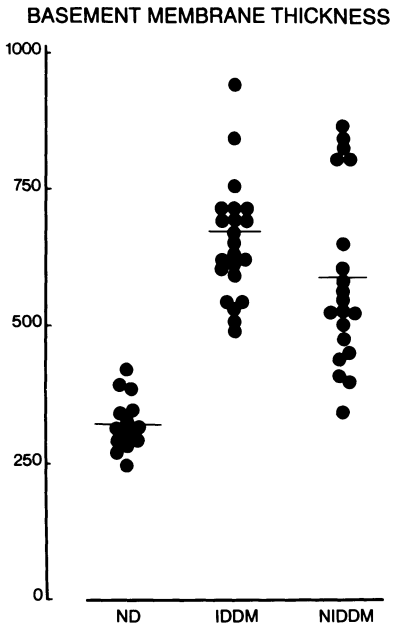

Figure 2-3. Basement membrane thickness in non-diabetic kidney transplant donors (ND) and IDDM and NIDDM patients with proteinuria. Data obtained from electron-microscopic studies on kidney biopsies.

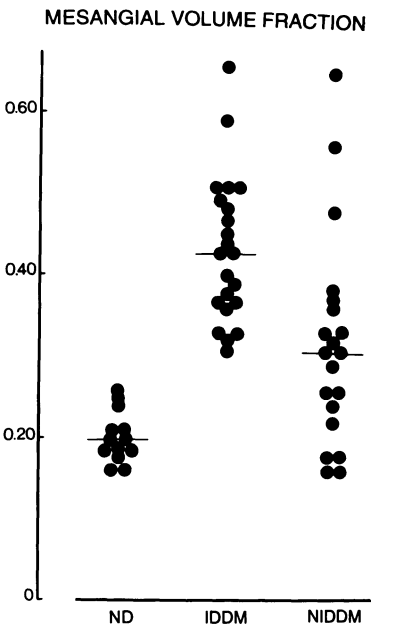

Figure 2-4. Mesangial volume per glomerulus (defined as the minimal convex polygon). See legend to figure 2-3.

systolic BP and albuminuria are related to coronary heart disease [3,50] in both NIDDM and non-diabetic subjects. Albuminuria may thus express widespread vascular disease [3,31].

3. ALBUMINURIA AND FUTURE RENAL FUNCTIONAL DETERIORATION

In IDDM microalbuminuria heralds progression to overt nephropathy in more than 80% of cases within a decade, with relentless decline in kidney function [1,51]. Microalbuminuria in NIDDM obviously also progresses to overt proteinuria, but overall does so at a slower rate, around 20% over a decade [51]. In a population based study, the cumulative risk for renal failure 10 years after the appearance of proteinuria, was reported to be 11% [52] far less than in IDDM. As also described in the former sections, albuminuria is not as closely linked with microvascular

complications in NIDDM as it is in IDDM, and discrepant progression of microalbuminuria to overt nephropathy disable the notion »incipient nephropathy« [1,27] in NIDDM. Elevated UAE is associated both with nephropathy and large-vessel disease, and it is possible that even less severe renal changes may aggravate the latter. (For further on the clinical course of renal function see Chapter 11).

4. PERSPECTIVES FOR INTERVENTION

There are no longer any doubts that microalbuminuria is a major independent marker of a poor prognosis. Obviously, reducing albuminuria would be a goal for the distressed physician. Whereas it now in several studies has been documented, that albuminuria can be reduced by antihypertensive treatment and optimised glycaemic control [3,27,49,53,54], studies so far have not demonstrated any improvement in health or survival. One very recent long-term study [55] however indicates, that antihypertensive treatment may retard the decline in kidney function at least in younger NIDDM patients.

The predominant problem in intervention is that the cause(s) of albuminuria and the mechanism behind the relations to cardiovascular diseases and risk factors remain largely unknown.

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3. FAMILIAL FACTORS IN DIABETIC NEPHROPATHY

DAVID J. PETTITT and WILLIAM C. KNOWLER

Reports of nephropathy developing in some patients with apparently well controlled diabetes and not developing in some patients even after years of severe hyperglycemia lead to the conclusion, expressed by several researchers [1-5], that some individuals are and others are not predisposed to the development of diabetic renal disease. If this predisposition is genetic, there must be an interaction between the genes and the environment, and it is often impossible to differentiate between genetic inheritance and the effect of a common environment shared by family members. This chapter reviews some of the data which indicate that there are familial differences in the predisposition to the development of diabetic renal disease.

1. RACIAL DIFFERENCES IN PREVALENCE OF RENAL DISEASE

Diabetic nephropathy has been reported at different rates in different racial groups, and several inter-racial comparisons have been made [6-10]. Rostand et al. [6] and Cowie et al. [9] have both reported higher rates of end-stage renal disease in American Blacks than Whites, and Pugh et al. [7] reported higher rates of end-stage

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

renal disease in Mexican Americans than in Non-Hispanic Whites. Diabetes duration, which is a strong risk factor for end-stage renal disease, may account for some of the racial differences in these studies. However, with diabetes duration accounted for, Haffner et al. [8] found higher rates of proteinuria among Mexican Americans, and there have been several reports of very high rates of renal disease among the Pima Indians [11-14], a population which has high rates of type 2 diabetes and which has participated in a longitudinal study of diabetes and its complications [15,16]. The incidence of end-stage renal disease in Pima Indians was similar to that in subjects with type 1 diabetes in Boston, Massachusetts [11], but almost four times as high as in Caucasians with type 2 diabetes in Rochester, Minnesota [14].

The reasons for inter-population differences in rates of renal disease are unclear. Rostand [10] has argued that barriers to medical care for Black and Mexican Americans may impede early detection, and therefore control, of microalbuminuria and hypertension with a consequent adverse effect on the prevalence of renal disease. However, the cost, one of the major barriers to medical care, is not a factor for the Pima Indians, who have access to free medical care by providers who are well aware of the high risk of diabetic renal disease in this population. Thus, cost of medical care cannot be the only reason for racial differences. However, other aspects of access to medical care, such as transportation or cultural barriers, could be important.

Genes predisposing to renal disease might well exist at different rates in different races resulting in differences in susceptibility. Thus, if renal disease is genetic its prevalence would be expected to be different in different races. However, finding different rates in different races is consistent not only with genetic inheritance but also with differing environmental exposures or with differences in competing causes of death.

2. SIBLINGS OF AFFECTED INDIVIDUALS

Seaquist et al. [17] reported evidence for the familial clustering of nephropathy among diabetic siblings of diabetic probands recruited from either the University of Minnesota kidney transplant registry or from a family diabetes study. Nephropathy was found among 83% of the diabetic siblings of diabetic probands with nephropathy but among only 17% of siblings of probands without nephropathy (figure 3-1). Furthermore, 41% of the siblings of probands with nephropathy had end-stage renal disease. Clustering of diabetic nephropathy among siblings was confirmed by Borch-Johnsen et al. [18]. These data, which are consistent with the hypothesis that genetic heredity is a major determinant of diabetic nephropathy, are also consistent with the

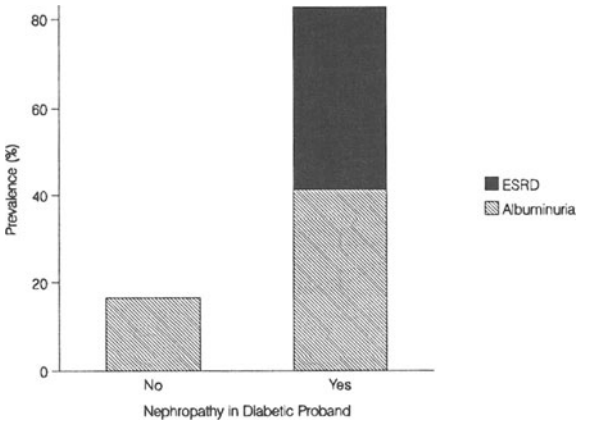

Figure 3-1. Prevalence of albuminuria and end-stage renal disease (ESRD) in diabetic siblings of diabetic probands with or without nephropathy. Adapted from Seaquist et al. [17].

hypothesis that an environmental factor or factors shared by siblings is responsible for the development of nephropathy in some families.

3. OFFSPRING OF AFFECTED INDIVIDUALS

Proteinuria and elevated serum creatinine concentrations were studied in Pima Indian families with diabetes in two generations [19]. Proteinuria occurred among 14% of the diabetic offspring of diabetic parents if neither parent had proteinuria, 23% if one parent had proteinuria, and 46% if both parents had diabetes with proteinuria (figure 3-2). The familial occurrence of an elevated creatinine was limited to male offspring, among whom 11.7% had a high creatinine if the parent had a high creatinine but only 1.5% did so if the diabetic parent had a normal creatinine. These data demonstrated that proteinuria and elevated creatinine aggregate in Pima families and suggest that the susceptibility to renal disease is inherited independently of the diabetes. As with the sibling concordance described above, the inheritance could be a shared environment, but since the environments of parents and of their children are very likely to differ more than those of siblings, a genetic inheritance is a strong possibility.

More recent data from the Pima Indians have shown that diabetic nephropathy in parents is a risk factor for the development of diabetes in the offspring [20]. The prevalence of diabetes at 25 to 34 years of age was 46% among the offspring of two diabetic parents if one had proteinuria and only 18% if neither had proteinuria. Corresponding rates among subjects with one diabetic and one non-diabetic parent

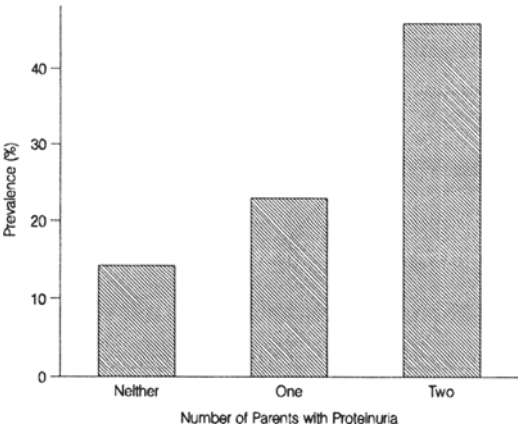

Figure 3-2. Prevalence of proteinuria by number of parents with proteinuria, adjusted for age, sex, blood pressure, diabetes duration and glucose concentration. Adapted from Pettitt et al. [19].

were 29% if the diabetic parent had proteinuria and 11% if not. Thus, multiple loci or homozygosity at a single locus may determine susceptibility to both diabetes and renal disease. In other words, parents with diabetes and renal disease may have a higher genetic load which increases the risk of diabetes in the offspring as well as increasing the risk of nephropathy once the diabetes develops.

4. FAMILIAL HYPERTENSION AND RENAL DISEASE

The frequent association of renal disease with hypertension has led to the examination of blood pressure in non-diabetic family members of persons with diabetes and in individuals thought to be at high risk of developing diabetes in the future. Viberti et al. found that both systolic and diastolic blood pressures were significantly higher in the parents of diabetic subjects with proteinuria than in the parents of diabetic subjects without proteinuria [21]. The difference between the mean blood pressures averaged 15 mmHg. Similarly, Krolewski et al. [22] reported that the risk of nephropathy among subjects with type 1 diabetes was three times as high in those having a parent with a history of hypertension as in those whose parents had no such history. Beatty et al. [23] have recently found more insulin resistance as well as higher blood pressures in the offspring of hypertensive than of normotensive parents. These offspring, therefore, are presumably at increased risk of developing diabetes. Since they already have significantly higher blood pressures, they may be at particular risk of renal disease if they do develop diabetes.

Sodium-lithium countertransport activity in red cells, a genetically transmitted trait, has been found in some studies to be abnormal in subjects at risk of essential hypertension [24-27]. Rates of countertransport activity have been found to be higher in diabetic subjects with renal disease than in those with diabetes alone [22,28]. Kelleher et al. [29] reported more hypertension among the siblings of hypertensive than of normotensive subjects with type 1 diabetes. However, hypertension among siblings of subjects with type 2 diabetes was more prevalent than among siblings of subjects with type 1 diabetes and was not related to hypertension in the diabetic proband. Given the association between hypertension and nephropathy, it is reasonable to assume that these hypertensive diabetic patients may be at risk for developing nephropathy, or may already have some nephropathy, and the hypertensive siblings might be at risk themselves if they were to develop diabetes.

Among Pima Indians, higher mean blood pressure measured at least one year prior to the onset of diabetes predicted an abnormal urinary excretion of albumin determined after the diagnosis of diabetes [30]. Thus, the hypertension so often associated with diabetic nephropathy cross-sectionally does not appear to be entirely a result of the renal disease. This hypertension, which appears to be familial in several studies, may precede and contribute to the renal disease seen after several years of diabetes in some subjects.

5. GENETIC MARKERS

The possibility of genetic causes for diabetic microvascular complications has stimulated the search for a disease gene or for linkage between the disease and a genetic marker. Several reports of associations between markers and retinopathy have been encouraging [31,32], but the findings of associations with renal disease have been mixed [31,33,34]. Among patients with type 1 diabetes, Barbosa [31] found similar frequencies of HLA-A and HLA-B antigens, but Christy et al. [33] found a different distribution of HLA/DR markers in those with and in those without nephropathy. Walton et al. [34], in a very small sample, also found no evidence of an HLA association with nephropathy. Mijovic's [35] findings suggest that microangiopathy (not limited to renal disease) was influenced by genes in linkage disequilibrium with both the major histocompatibility complex and the Gm loci.

Reviews of the subject by Barbosa and Saner [36] and by Barnett and Pyke [37] have both concluded that there is no convincing evidence that genetic factors play a role in the pathogenesis of diabetic renal disease. Twin studies, which have suggested a genetic component in the pathogenesis of retinopathy, have had too few twin pairs to provide any evidence for the genetics of nephropathy [37].

6. MODIFICATION OF DISEASE

Environmental factors, most of which probably remain unknown, which influence the development or progression of renal disease in subjects with diabetes are likely to be shared with other family members resulting in concordance of renal disease. Therapeutic manipulations of several factors have been shown to alter the course of diabetic renal disease in individuals, but it will take family studies to see if the response to therapies is also genetic or influenced by other environmental factors.

Various treatments, which will be discussed in detail in subsequent chapters, may alter the familial aggregation of renal disease. Reichard et al. [38] showed that intensive insulin therapy in type 1 diabetes can reduce the development of microvascular complications including diabetic kidney disease. Similar results were reported by the Diabetes Control and Complications Trial [39].

Dietary protein may induce glomerular hyperfiltration [40], and beneficial effects of dietary protein restriction have been described [41-44]. As the renal effects differ with different types of protein [45], familial aggregation of renal disease may be due to a common diet rather than to genetics. Likewise, the beneficial effects of protein restriction may differ in different families depending, not only on genetic differences, but also on the type and the amount of protein consumed before the intervention.

Treatment of hypertension in subjects with diabetic nephropathy has been found to retard the progression of the renal disease [46], especially with the use of drugs which inhibit angiotensin converting enzyme [47]. Recently, in several randomized trials, angiotensin converting enzyme inhibitors have been shown to slow the progression of renal disease and reduce mortality in subjects with proteinuria, regardless of hypertension [48-50].

In summary, much of the intriguing information regarding the familial occurrence of diabetic renal disease suggests a genetic component for this disorder but is also consistent with environmental effects. The epidemiology of renal disease is complicated by the fact that several forms of therapy currently employed to treat hyperglycemia, proteinuria and hypertension can alter the progression of renal disease and may, in some cases, even prevent its development. Selective prevention of renal disease will likely alter the familial aggregation of the disease. If there are important genes providing susceptibility to renal disease or influencing the response to treatment, even if the contribution is small, their identification could increase the clinician's knowledge about the risk for a given patient and help identify those for whom intensive therapy may be most beneficial.

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4. HYPERTENSION, CARDIOVASCULAR DISEASE, DIABETES MELLITUS, AND DIABETIC NEPHROPATHY: ROLE OF INSULIN RESISTANCE

ANNA SOLINI and RALPH A. DEFRONZO

HYPERTENSION AND DIABETES

Essential hypertension (blood pressure > 160/95 mmHg) is a common disorder that affects approximately 15-20% of Caucasian populations [1]. If a blood pressure greater than 140/90 mmHg is used as the cut off value, then 40-45% of the general population would be considered to have essential hypertension [1]. In nonwhite populations the incidence of essential hypertension is even higher. A number of factors including obesity, physical inactivity, age, dyslipidemia, glucose intolerance, smoking, and positive family history all have been linked to an increased incidence of essential hypertension. It is noteworthy that each one of these factors has been shown to be associated with the presence of insulin resistance [2-8]. Conversely, weight loss [9] and enhanced physical activity [10] have been shown to improve insulin sensitivity and to lower blood pressure. Over the last decade there has accumulated a large body of evidence which implicates insulin resistance and its compensatory hyperinsulinemia as the central feature of a tightly interwoven

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Table 4-1. Insulin resistance syndrome

Hypertension
Dyslipidemia
Impaired glucose tolerance
Diabetes mellitus
Obesity
Atherosclerotic cardiovascular disease
Microalbuminuria
Aging

metabolic-cardiovascular web (table 4-1), and several excellent review of the ***Insulin Resistance Syndrome*** have been published recently [11-14].

In individuals with diabetes mellitus the incidence of hypertension is significantly increased. However, the pattern of hypertension differs quite markedly in non-insulin dependent diabetes mellitus (NIDDM) and in insulin dependent diabetes mellitus (IDDM) (table 4-2). In IDDM hypertension is absent at the time of initial diagnosis [15,16] and remains normal for approximately 10 years after the onset of diabetes (table 4-2). The blood pressure begins to rise at about the time of onset of microalbuminuria [16,17] and characteristically involves both the systolic and diastolic levels (table 4-2). Despite the absence of any increase in blood pressure during the initial ten years after the onset of IDDM, there are progressive histologic changes at the level of the kidney. In contrast, in NIDDM it is not uncommon for hypertension to be present at the time of diagnosis of diabetes [15,16] (table 4-2). There is a progressive increase in the blood pressure with age (figure 4-1) and with increasing degree of obesity [18]. In these respects the rise in blood pressure most closely reflects the pattern that is seen in patients with essential hypertension. The systolic blood pressure also rises disproportionately more than the diastolic blood (table 4-2), suggesting that decreased vascular compliance (i.e. atherosclerosis), rather than intrinsic renal disease, plays a major role in the development of hypertension.

In NIDDM it is now recognized that hypertension rarely occurs as an isolated feature. Rather, it occurs in association with a cluster of metabolic and cardiovascular features (atherosclerotic cardiovascular disease, dyslipidemia, obesity, ageing, microalbuminuria) that collectively have been referred to as the ***Insulin Resistance Syndrome*** (table 4-1) [11-14]. Until recently, it had been considered that IDDM was not part of this metabolic-cardiovascular cluster, but recent studies by Viberti et al. [19] have indicated that the 40% of type I diabetics who progress to end stage renal failure are characterized by insulin resistance, accelerated atherosclerosis, and dyslipidemia [19]. Microalbuminuria, an indicator of early renal disease, also has

Table 4-2. Characteristics of hypertension in IDDM and NIDDM

Type I (insulin dependent) diabetes mellitus
1. Hypertension is absent at time of diagnosis
2. Development of hypertension correlates closely with the onset of renal disease
3. Systolic and diastolic blood pressure increase proportionately
4. Hypertension markedly accelerates progression of renal disease
Type II (non-insulin dependent) diabetes mellitus
1. Hypertension is common at time of diagnosis
2. Hypertension correlates closely with degree of obesity and advancing age
3. Systolic blood pressure increases more than diastolic
4. Hypertension correlates poorly with presence of renal disease

been shown to be associated with insulin resistance in both IDDM and NIDDM [19,20]. Thus, in both type I and type II diabetes mellitus, but especially in the latter [20], microalbuminuria is a predictor of death from cardiovascular disease. This has led to the »Steno« hypothesis that microalbuminuria reflects widespread vascular disease [21] and, in this context, is closely related to the insulin resistance syndrome.

HYPERTENSION, HYPERINSULINEMIA, AND INSULIN RESISTANCE

A number of epidemiologic studies have demonstrated a close association between hyperinsulinemia and hypertension [11-14]. From the prospective standpoint results from the San Antonio Heart Study have shown that the fasting plasma insulin concentration predicts the later development of both hypertension and NIDDM [22]. Since hyperinsulinemia usually indicates underlying insulin resistance [6,23], these observations suggest the presence of a link between impaired insulin action and hypertension. Using the euglycemic insulin clamp technique and the insulin suppression test, a number of investigators have shown that both obese [24] and lean [25-29] individuals are characterized by insulin resistance. Moreover, a close association exists between these verity of insulin resistance and the elevation in blood pressure (figure 4-2). From the metabolic standpoint the insulin resistance primarily involves the glycogen synthetic pathway [25] and occurs in muscle [28,29]. Thus, the insulin resistance of essential hypertension closely resembles that observed in obesity and NIDDM [6,23]. Because of these similarities, it has been suggested that the same underlying metabolic and molecular mechanism contribute to the insulin resistance in all three of these common »metabolic« disorders [11].

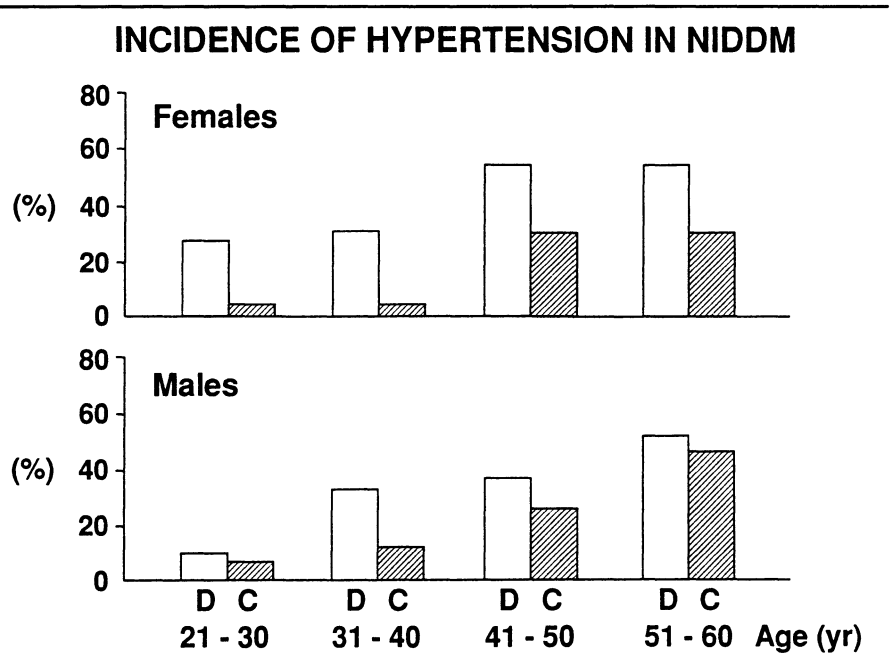

Figure 4-1. Age-related incidence of hypertension in non-insulin dependent diabetic (D) and non-diabetic control (C) subjects. Reproduced from reference #1 with permission.

If insulin resistance and/or hyperinsulinemia were indeed responsible for the development of hypertension, one would expect to observe an increase in blood pressure during chronic insulin infusion. Indeed, Brand et al. [30] in rats have shown that chronic sustained physiologic hyperinsulinemia created by continuous intravenous insulin infusion leads to the development of sustained hypertension within three days and that the hypertension is reversible following cessation of the insulin infusion (figure 4-3). Somewhat paradoxically, the same investigators failed to observe a rise in blood pressure in dogs during chronic insulin infusion [31]. It is noteworthy, however, that hyperinsulinemia was associated with the development of insulin resistance in rats [30], but actually enhanced insulin sensitivity in the dog [31]. These results suggest that the presence of insulin resistance may be needed for the hypertensive effect of insulin to fully manifest itself.

A number of clinical observations provide further support for the link between hyperinsulinemia and hypertension. Thus, when NIDD patients are started on insulin, there is a rather consistent rise in blood pressure [32]. Conversely, withdrawal of insulin in type II diabetic individuals is associated with a decrease in

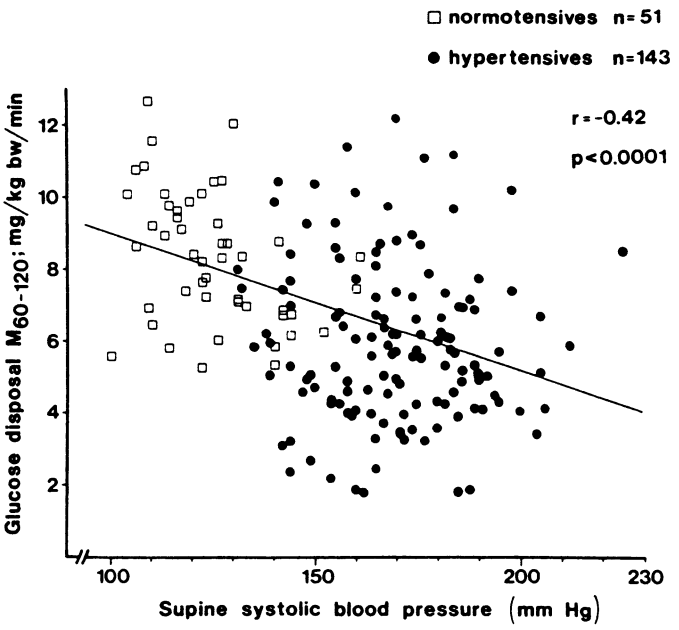

Figure 4-2. Relationship between systolic blood pressure and insulin mediated glucose disposal during the last hour of a euglycaemic insulin clamp in control (open squares) and hypertensive (solid circles) patients. Reproduced from reference #26 with permission.

blood pressure [33]. Most impressive are the recent findings of Landin et al. [34] who demonstrated that treatment of hypertensive nondiabetic individuals with metformin, an insulin sensitizer, reduced the blood pressure by 38/20 mmHg in association with a decline in fasting insulin and C-peptide concentrations and an improvement in insulin sensitivity.

PATHOGENESIS OF HYPERTENSION IN HYPERINSULINEMIC STATES

It generally is believed that hyperinsulinemia is responsible for the development of hypertension since: (i) there is a well established association between the plasma insulin concentration and systemic blood pressure, (ii) insulin infusion in rats leads to the development of hypertension; (iii) a number of well defined biochemical and physiologic mechanisms have been described whereby insulin can elevate the blood pressure (see below). However, not all epidemiologic studies have shown an association between the plasma insulin concentration and blood pressure in Caucasian populations [35]. This raises the possibility that it is the insulin resistance

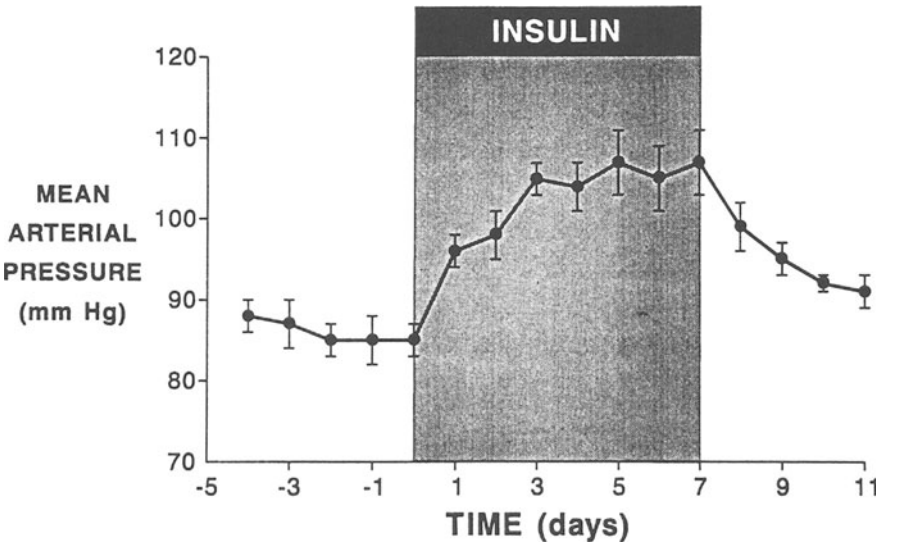

Figure 4-3. Effect of chronic, sustained insulin infusion, while maintaining euglycaemia, on mean arterial blood pressure in rats. Reproduced from reference #30 with permission.

per se, by causing a shift from glucose to lipid metabolism [36] or by some as of yet undefined mechanism, which is responsible - either alone or inconcert with hyperinsulinemia - for the development of hypertension. In the following section we shall review a number of mechanisms via which insulin per se can lead to the development of hypertension.

1. Hyperinsulinemia and sodium retention

Studies in both man [37,38] and animals [39], have shown that insulin is a potent antinatriuretic hormone when administered either acutely [37,39] or chronically [38] to cause physiologic hyperinsulinemia (50-100 μU/ml). The antinatriuretic effect of insulin results from a direct action of the hormone on the renal tubule [40], as well as via indirect effects mediated through stimulation of the sympathetic nervous system [41], augmentation of angiotensin II - mediated aldosterone section [40], and inhibition of the action of atrial nutriuretic peptide [42]. It is well established that the total body sodium content and, in particular, the sodium concentration, in vascular smooth muscle cells, are increased in both NIDD and IDD patients with hypertension [43,44]. An increase in the intracellular sodium concentration in vascular smooth muscle cells sensitizes these cells to the pressor effects of angiotensin II and norepinephrine [43,44]. Consistent with this, diuretic treatment

in diabetic subjects induces a natriuresis, desensitizes the vasculature to the pressor effects of angiotensin II and norepinephrine, and decreases the blood pressure [43,44].

2. Hyperinsulinemia and the sympathetic nervous system

Infusion of insulin, while maintaining euglycemia, increases the plasma norepinephrine concentration in a dose dependent fashion [41] and increases norepinephrine turnover in muscle, liver, and adipose tissue [45,46]. Stimulation of the SNS can increase the blood pressure via a number of mechanisms including increased cardiac output, augmented cardiopulmonary blood volume, enhanced arteriolar vascular resistance and renal sodium retention [47]. Moreover, SNS activation is a potent antagonist to insulin action [48] and thus provides a self-perpetuating stimulus that closes the feedback loop between resistance and hypertension [11].

3. Atrial natriuretic peptide

Circulating levels of atrial natriuretic peptide (ANP) are increased in diabetic man and animals, both in the presence and absence of hypertension, and the ability of saline-induced volume expansion to suppress ANP secretion is impaired in diabetic subjects [42,49,50]. Trevisan, Nosadini and colleagues [40,42,50] have shown that in IDD patients hyperinsulinemia provides a chronic stimulus for the release of ANP and this leads to a down regulation of ANP receptors and/or the intracellular ANP signaling mechanism.

4. Insulin and cation transport systems

Insulin affects a number of key ion pumps that regulate intracellular sodium, potassium, and calcium concentrations, cell volume, cell pH, and cell growth [11]. An alteration in any of these ion pumps could lead to the development of hypertension. As discussed previously, a primary defect in insulin action in muscle will lead to a compensatory increase in insulin secretion by the pancreatic beta cells [11,23]. The resultant hyperinsulinemia will lead to a stimulation of the Na^+-H^+ exchanger [51-53], leading to the intracellular accumulation of Na^+ in exchange for H^+. The increased intracellular sodium concentration, in turn, will sensitize the vascular smooth muscle cells to the pressor effects of norepinephrine, angiotensin II, and sodium chloride loading [43,44]. In addition, enhanced Na^+-H^+ exchange will increase the intracellular pH, a known stimulator of protein synthesis and cell proliferation [54]. This will result in the characteristic arteriolar hypertrophy that represents the characteristic histologic feature of essential hypertension. Consistent with this sequence of events, increased intracellular sodium is a characteristic finding in individuals with essential hypertension [8,11,54-56]. Increased Na^+-Li^+

countertransport activity has been reported in erythrocytes of hypertensive versus normotensive insulin dependent diabetic subjects [57]. An association between insulin resistance, hypertension, diabetic nephropathy and increased Na^+-Li^+ countertransport activity also has been demonstrated in insulin dependent diabetics, as well as in their normotensive relatives [19,58]. Of even greater interest, enhanced Na^+-Li^+ pump activity has been shown to be associated with the entire cluster of disorders (hypertension, dyslipidemia, diabetes, obesity, atherosclerotic cardiovascular disease, microalbuminuria), including diabetic nephropathy, that comprise the ***Insulin Resistance Syndrome*** [19,58].

Insulin also stimulated the Ca^{++}-ATPase pump in a variety of tissues, including muscle, and the vasodilatory action of the hormone is closely correlated with the efflux of calcium from vascular smooth muscle cells [59,60]. In vivo and in vitro studies [61,62] have shown that in insulin resistant man and animals the ability of insulin to activate the CA^{++}-ATPase pump and to enhance the extrusion of calcium out of cells is impaired. This may have important pathophysiologic implications with regard to the development of hypertension and diabetic nephropathy, as well as to the perpetuation of insulin resistance. When insulin is infused acutely, there is no consistent change in blood pressure or muscle blood flow despite activation of the SNS [41,45,46]. The failure of blood pressure to rise despite SNS stimulation results from the simultaneous direct vasodilatory effect of insulin on blood vessels [63], which is mediated via activation of the CA^{++}-ATPase pump [59,60]. In insulin resistant states the ability of insulin to activate the Ca^{++}-ATPase pump is impaired [61,62], and the vasodilatory effect of the hormone is lost. This results in unopposed SNS stimulation and vasoconstriction. Moreover, if a similar scenario of events were to occur in the efferent arteriole in the kidney, this would lead to an increase in intraglomerular pressure, an important pathogenic factor in the development of diabetic nephropathy. Lastly, intracellular calcium is an important second messenger for insulin action [64]. Impaired activity of the Ca^{++}-ATPase pump would lead to an accumulation of intracellular free calcium and this would further exacerbate the insulin resistance with regard to glucose metabolism.

Insulin also stimulated the Na^+-K^+ ATPase pump, which is the primary regulator of the intracellular potassium concentration [65]. Importantly, a reduction in intracellular potassium content is closely correlated with increased blood pressure in individuals with essential hypertension [66], and dietary potassium supplementation, with restoration of normokalemia and repletion of intracellular potassium content, has been shown to reduce both systolic and diastolic blood pressure [66]. Patients with essential hypertension are characterized by increased intracellular sodium and decreased intracellular potassium concentrations [66,67]. If the Na^+-K^+ ATPase pump were to be resistant to the action of insulin in patients with essential

hypertension and NIDDM, this would explain the development of hypertension in these two clinical disorders, as well as the abnormalities in intracellular electrolyte composition.

INSULIN RESISTANCE, HYPERINSULINEMIA, AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Three large prospective studies have demonstrated that hyperinsulinemia both fasting and postprandial, is an independent risk factor for coronary artery disease (CAD) in non-diabetic individuals [68-70] and a similar association has been shown in prospective studies carried out in NIDD individuals [69,71]. Much experimental evidence, from both in vitro and in vivo studies have shown that insulin promotes the development of atherosclerotic lesions and these data recently have been reviewed by Stout [72]. In a classic study Cruz et al. [73] demonstrated that chronic, low dose insulin infusion into one femoral artery of the dog caused marked intimal and medial proliferation and the accumulation of cholesterol and fatty acids on the insulin-infused side but was without effect on the contralateral femoral artery or any other blood vessel in the body. Conversely, if cholesterol fed rabbits are made diabetic with alloxan the markedly accelerated rate of atherosclerosis is prevented; insulin replacement in diabetic rabbits returns the rate of atherosclerosis to its previous high level [74]. These elegant, but simple studies [73,74] provide strong evidence for the pathogenic role of insulin in the atherogenic process. However, it is important to note that hyperinsulinemia almost always reflects the presence of underlying insulin resistance [11,23]. If this were indeed, true, one would expect patients with CAD to be resistant to the action of insulin. Using the euglycemic insulin clamp technique, we recently have shown that individuals with angiographically documented CAD are markedly insulin resistant compared to those without any significant stenoses of the major coronary vessels [75].

The direct atherogenic effect of insulin on arteriol blood vessels [72-74], as well as insulin-related alterations in the plasma lipid profile [5,11,13] and blood pressure [11,13,25-27,30] are likely to explain the accelerated rate of atherogenesis in NIDDM and the lack of correlation between elevated plasma glucose levels and macrovascular complications. Interestingly, these same atherosclerotic changes in the renal vessels may protect the kidney of NIDD patients from the transmission of elevated systemic blood pressure to the glomerulus and may prevent the characteristic hyperfiltration/increased intraglomerular pressure that plays an important pathogenic role in the development of diabetic nephropathy.

It also is important to recognize that accelerated atherosclerosis occurs with increased frequency in IDDM as well. However, macrovascular complications appear to be a characteristic feature of the type I diabetic patients with proteinuria

and renal insufficiency [76]. The recent observations by Trevisan, Fioretto and colleagues [19,58] that cardiac and renal disease are associated with the same clustering of cardiovascular risk factors that comprise the insulin resistance syndrome suggest that the same pathogenic mechanisms may be responsible for macrovascular (stroke and myocardial infarction) and microvascular (nephropathy) disease in both IDDM and NIDDM.

SUMMARY

The observation that ***Insulin Resistance*** represents a ***Syndrome*** characterized by hypertension, dyslipidemia, glucose intolerance, microalbuminuria, and atherosclerotic cardiovascular disease (table 4-1) has particular relevance to NIDD patients who typically manifest the complete metabolic and cardiovascular cluster [11-14,22]. However, the recent demonstration that the ***Insulin Resistance Syndrome*** exists in IDD patients as well and is associated with renal and cardiac hypertrophy, proteinuria and renal insufficiency, as well as high Na^+-H^+ + countertransport activity [19,50,58], raises the intriguing possibility that insulin resistance/-hyperinsulinemia, either directly or indirectly by altering renal hemodynamics, but stimulating mesangial hyperplasia and renal hypertrophy, by causing systemic hypertension, by promoting renal arteriolar atherosclerosis, or by altering renal cellular metabolism and/or electrolyte composition, may play an important role in the development of diabetic nephropathy in both IDD and NIDD patients [77].

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5. DIABETES, HYPERTENSION, AND KIDNEY DISEASE IN THE PIMA INDIANS COMPARED WITH OTHER POPULATIONS

WILLIAM C. KNOWLER, ROBERT G. NELSON and DAVID J. PETTITT

Hypertension and kidney disease are well-known concomitants of both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). Hypertension, kidney disease, and diabetes are associated with each other, but the nature of the associations varies between populations, and the causal interpretations, especially regarding hypertension and diabetic nephropathy, are controversial. The complications of diabetes have been studied extensively among the Pima Indians of Arizona, U.S.A. In this chapter, we describe the epidemiology of diabetic renal disease and its relationship with hypertension in the Pima Indians in comparison with other populations.

1. THE PIMA INDIAN DIABETES STUDY

The Pima Indians have the world's highest reported incidence and prevalence of diabetes [1]. Since 1965, this population of about 5000 people has participated in a longitudinal epidemiologic study of diabetes and its complications [2]. At each examination, conducted at about two-year intervals, an oral glucose tolerance test

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is performed and classified according to the World Health Organization criteria [3]. Throughout the study, urine samples with at least a trace of protein on dipstick have been assayed for total protein and the urine protein-to-creatinine ratio used as an estimate of the 24-hour protein excretion [4]. Since 1982, the urine samples have been assayed for albumin with a nephelometric immunoassay using a monospecific antiserum to human albumin, and a urine albumin-to-creatinine ratio used as an estimate of the urinary albumin excretion rate [5]. Blood pressure is measured at each examination after the patient has been at rest in the supine position [6].

Pima Indians develop only NIDDM (or type 2 diabetes) [7] which is like NIDDM in other populations except that it develops at younger ages [1,2]. Diabetic complications also develop at rates similar to those of other populations. The prevalence of diabetes in Pima Indians is almost 13 times as high as in the mostly white population of Rochester, Minnesota [1]. Over one-third of Pima Indians aged 35-44 years have diabetes, and many cases develop before the age of 25 years [2]. In contrast to populations in which NIDDM usually develops later in life, many Pima Indians have diabetes of sufficient duration for nephropathy to develop.

2. THE COURSE OF DIABETIC NEPHROPATHY IN PIMA INDIANS

Abnormally elevated albuminuria is a characteristic early sign of diabetic nephropathy. In a cross-sectional study of albuminuria in Pima Indians ≥ 15 years of age, abnormal albuminuria was defined by a urine albumin(mg)-to-creatinine(g) ratio ≥ 30 [5]. A level of 30-299 mg/g corresponds approximately to the definition of incipient nephropathy of Mogensen et al. [8]. Abnormal albuminuria was found in 8% of those with normal glucose tolerance, 15% of those with impaired glucose tolerance, and 47% of those with diabetes [5]. The prevalence was also related to the duration of diabetes, varying from 29% within five years of diagnosis to 86% after 20 years of diabetes. The high prevalence in diabetes and the relationship with diabetes duration suggest that albuminuria is a complication of diabetes, but there is also a substantial prevalence in those with normal or impaired glucose tolerance, indicating that diabetes is not the sole cause of abnormal albuminuria in this population. Abnormal albuminuria often leads to more serious renal disease. Among diabetic Pimas, the degree of albuminuria over the range of values below 300 mg/g predicts the subsequent incidence of overt nephropathy, defined by albuminuria of ≥ 300 mg/g, which is usually detectable by dipstick [9].

The onset of NIDDM in Pima Indians is characterized not only by an increased prevalence of abnormal albuminuria, but also, on average, by an elevated glomerular filtration rate and a modest size-selective abnormality of the glomerular capillary wall [10]. Whether these factors influence the development of overt diabetic renal disease remains to be determined.

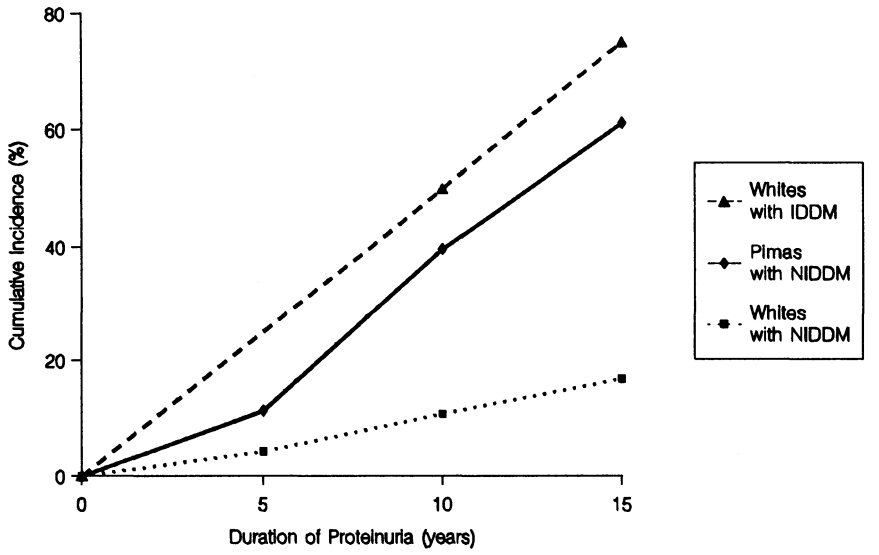

Figure 5-1. Cumulative incidence of end stage renal disease by duration of proteinuria. Adapted from Nelson et al. [11], Krolewski et al. [12], & Humphrey et al. [13].

In diabetic persons, the onset of clinical proteinuria, defined by the urinary excretion of at least 500 mg protein per day, heralds a progressive decline of renal function that often leads to end-stage renal disease (ESRD) [11]. Figure 5-1 shows the cumulative incidence of ESRD as a function of the duration of proteinuria in Pima Indians and, using similar definitions of proteinuria, in whites with IDDM [12] or NIDDM [13]. Coronary heart disease is a frequent cause of death in older persons with diabetes and proteinuria and may, in part, account for the lower incidence of ESRD in whites with NIDDM. Due to the relatively young age at onset of NIDDM in Pima Indians and their lower death rate from coronary heart disease [14], the cumulative incidence of ESRD in this population more closely resembles that of whites with IDDM than those with NIDDM.

When expressed as a function of duration of diabetes, the cumulative incidence of ESRD is also nearly identical in the Pimas with NIDDM and the whites with IDDM [15]. Other studies comparing persons with IDDM and NIDDM in the same populations have concluded that the duration-specific risk of ESRD is similar in the two types of diabetes [13,16].

Autopsy studies indicate that intercapillary glomerular sclerosis, typical of diabetic nephropathy in other ethnic groups, is the predominant renal disease in the

Pimas [17], although other glomerular lesions were found in some nondiabetic Pimas [18]. The incidence of ESRD is also very high among other American Indians [reviewed in 19], but diabetes is apparently not responsible for as great a proportion of cases of ESRD in some of the other American Indian tribes.

Familial aggregation of diabetic nephropathy in Pima Indians [20] and in other populations suggests that susceptibility to this disease may be genetically transmitted, as reviewed in Chapter 3. Other factors, including duration of diabetes, blood pressure, level of glycemia, and pharmacologic treatment of diabetes are associated with the development of renal disease in Pima Indians [4,11,15].

Nearly all of the excess mortality associated with diabetes in this population occurs in persons with clinically detectable proteinuria, and the age-sex-adjusted death rate in diabetic subjects without proteinuria is no greater than the rate in nondiabetic subjects [21]. Thus, proteinuria is a marker not only for diabetic renal disease, but identifies those with NIDDM who are at increased risk for a number of macro- and microvascular complications and for death. Similar findings have been observed in persons with IDDM and suggest a common underlying cause for albuminuria and the other associated diabetic complications, both renal and extrarenal [22].

3. RELATIONSHIP OF BLOOD PRESSURE WITH DIABETES AND KIDNEY DISEASE

The relationships of blood pressure with glucose tolerance, hyperinsulinemia, and insulin resistance have been examined in many populations. A difficulty in examining these relationships is that many drugs used in treating high blood pressure may also affect insulin resistance or glycemia. Thus, correlations of these variables are difficult to interpret if studies include subjects taking antihypertensive drugs; yet if such subjects are excluded, the associations might be underestimated because of exclusion of those with the most severe hypertension. One approach is to divide blood pressure into two categories, hypertension or not, and include those treated with antihypertensive drugs as hypertensive regardless of their measured blood pressure.

Blood pressure (or hypertension) is related to glucose tolerance in the Pima population. The age-sex-adjusted prevalence rates of hypertension (systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 95 mmHg, or receiving antihypertensive drugs) among Pima Indians with normal glucose tolerance, impaired glucose tolerance, or diabetes were 7%, 13%, and 20%, respectively (figure 5-2), an almost three-fold difference [6]. Similarly, as continuous variables, blood pressure and two-hour plasma glucose concentrations were correlated among subjects who were not treated with either antihypertensive or hypoglycemic drugs. It has

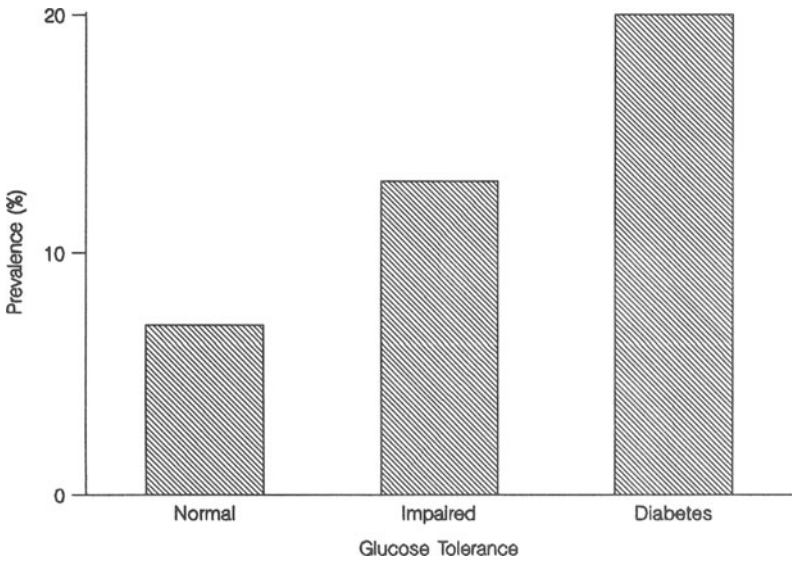

Figure 5-2. Age-sex-adjusted prevalence of hypertension in Pima Indians with normal glucose tolerance, impaired glucose tolerance or diabetes. Adapted from Saad et al. [6].

been proposed that this relationship, also observed in other populations, is explained by hyperinsulinemia, as serum insulin concentrations tend to be higher in persons with impaired glucose tolerance and in some persons with diabetes than in those with normal glucose tolerance. Yet in the Pimas blood pressure has a much stronger correlation with plasma glucose than with serum insulin concentrations, and the partial correlation of blood pressure with fasting insulin, controlled for age, sex, BMI, and glucose, is practically zero [6]. Thus the relationship, at least among the Pimas, is primarily with glucose, and the correlation with insulin may be secondary.

In addition to studies of blood pressure and serum insulin concentrations, the correlation of blood pressure with insulin resistance was assessed by the euglycemic clamp. In a study of three racial groups, among nondiabetic, normotensive subjects not taking any medicines, blood pressure and insulin resistance were correlated only among whites, but not among blacks or Pima Indians [23]. While this study confirmed previous reports of a correlation of blood pressure with insulin resistance in whites, it suggests that such a relationship is race-specific, and hence may not indicate that insulin resistance is an important or consistent cause of hypertension.

Although blood pressure and plasma glucose concentrations are correlated and the prevalence of hypertension is related to 2-hr glucose, even among nondiabetic

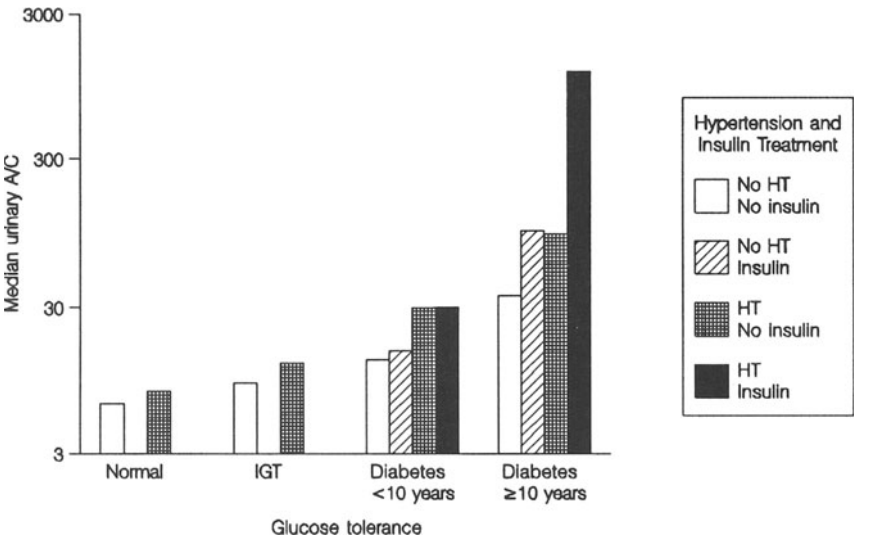

Figure 5-3. Median urinary albumin (mg)-to-creatinine(g) ratio by glucose tolerance, diabetes duration, insulin treatment, and hypertension (HT). IGT = impaired glucose tolerance.

subjects, hyperglycemia is not the only factor of importance for blood pressure in diabetes. Blood pressure and kidney disease are clearly related, although the causes of this relationship are not clear and have been extensively debated, with some arguing that the elevated blood pressure in diabetes is only secondary to diabetic nephropathy [22,24], and others that elevated blood pressure due to a genetic predisposition contributes to the development of diabetic nephropathy [25,26].

Among 2414 Pima Indians ≥25 years of age, albuminuria, expressed as the median urinary albumin(mg)-to-creatinine(g) ratio of subjects in each group, is related to glucose tolerance, hypertension, and treatment of diabetes with insulin (figure 5-3). The median albumin-to-creatinine ratio was higher with progressively worse glucose tolerance or longer duration of diabetes, and among diabetic patients was higher in those treated with insulin. In each of these groups defined by glucose and duration of diabetes, those with hypertension had greater albuminuria. The associations of each of these variables with albuminuria were highly significant, but the causal directions underlying them have not been determined. The relationship with insulin treatment is similar to the relationship of insulin treatment with many complications of diabetes [4,5,14,27,28] and might reflect more severe NIDDM (i.e.

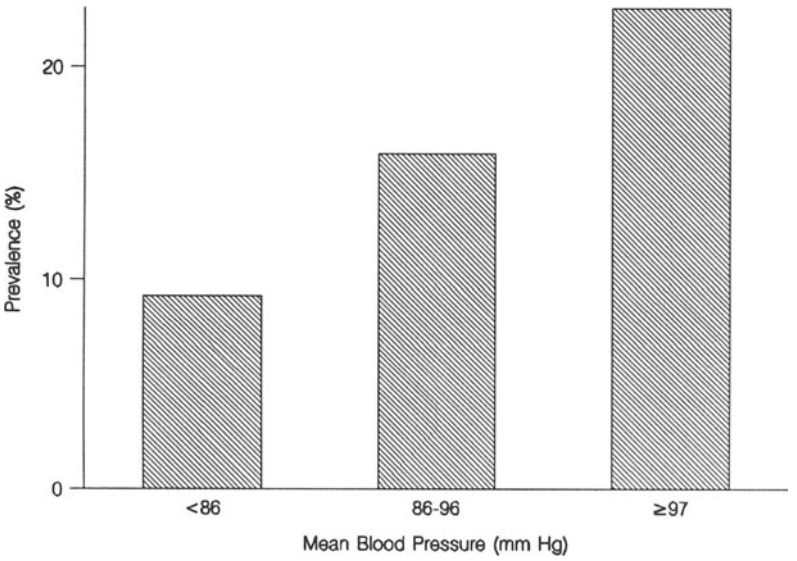

Figure 5-4. Prevalence of abnormal albumin excretion (albumin(mg)-to-creatinine(g) ratio ≥100) after the diagnosis of diabetes by prediabetic blood pressure. Adapted from Nelson et al. [29].

those with greater hyperglycemia or more complications have a greater need for insulin treatment).

The relationship between blood pressure and renal disease, however, is problematic since elevated blood pressure may be either a cause or a consequence of renal disease, or it may be both. In the Pima Indians, higher blood pressure *before* the onset of diabetes confers a greater risk of renal disease *after* diabetes develops (figure 5-4). This suggests that blood pressure may indeed contribute to the initiation of diabetic nephropathy [29]. Alternatively, higher pre-diabetic blood pressure may be an early manifestation of an underlying susceptibility to renal disease which is manifested only in the presence of diabetes or may be a risk factor for diabetes [30].

4. CONCLUSIONS

Hypertension and kidney disease are common complications of diabetes in the Pima Indians, as they are in other populations, and patients with these conditions have a particularly bad prognosis. Almost all of the excess mortality in diabetic Pimas is associated with proteinuria. Albuminuria is associated with hypertension, insulin treatment, and duration of diabetes. The higher prevalence of abnormal albumin

excretion in diabetic subjects who had higher blood pressures before the onset of diabetes suggests that the hypertension of diabetes is not entirely secondary to diabetic nephropathy, but that higher blood pressure contributes to this complication.

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6. ECONOMIC EVALUATIONS OF STRATEGIES FOR PREVENTING RENAL DISEASE IN NON-INSULIN DEPENDENT DIABETES MELLITUS

DIANE L. MANNINEN, ERIK J. DASBACH, FREDERICK B. DONG, RONALD E. AUBERT, STEVEN M. TEUTSCH and WILLIAM H. HERMAN

1. INTRODUCTION

Recent clinical trials such as the Stockholm Diabetes Intervention Study (SDIS) and the Diabetes Control and Complications Trial (DCCT) have demonstrated that intensive glycaemic control can slow the development and delay the progression of renal disease in persons with insulin dependent diabetes mellitus (IDDM) [1,2]. In addition, clinical studies suggest that treatment of patients with microalbuminuria and clinical nephropathy with angiotensin-converting enzyme (ACE) inhibitors and other antihypertensive agents [3-8] or with a low protein diet [9-12] can slow progression to end-stage renal disease. However, few studies have demonstrated the efficacy of such interventions in persons with non-insulin dependent diabetes mellitus (NIDDM).

Given the cost of these trials and the limited resources available for biomedical research, it is reasonable to ask whether investing in such a trial is worthwhile and which type of intervention(s) should be evaluated [13-16]. A useful methodology for answering these questions is to conduct an economic evaluation. The purpose of this

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chapter is to describe the data necessary and the data available for conducting such an economic evaluation.

2. OVERVIEW OF THE ECONOMIC EVALUATION

An economic evaluation assesses the cost to achieve a given health effect for a given set of alternatives. For example, an economic evaluation can be used to evaluate treatments aimed at preventing or delaying the onset of diabetic nephropathy and end-stage renal disease (ESRD) among NIDDM patients. In evaluating the economics of a proposed clinical trial, one must consider the costs of conducting the clinical trial, as well as the costs and benefits associated with incorporating the medical treatment into clinical practice.

The costs of preventing ESRD include screening and intervention. The benefits include quality of life improvements and gains in life expectancy. Given that costs are incurred and benefits are realized at different times, a model of how the disease progresses is necessary for estimating the occurrence of these events.

3. DISEASE MODEL

Two recent studies have developed models to assess the cost-effectiveness of screening and early treatment of nephropathy in IDDM patients by comparing the cost and effectiveness of current standard diabetes treatment with the early treatment of patients with ACE inhibitors [17,18]. The model developed by Borch-Johnsen and associates [18] simulates the progression of renal complications in a hypothetical cohort of newly diagnosed IDDM patients from onset of diabetes through microalbuminuria, diabetic nephropathy, and renal failure. Siegel et al. [17] present a similar model; however, in this model microalbuminuria is divided into two levels: microalbuminuria and significant microalbuminuria. The stages used in these two models are shown in Table 6-1.

Modelling the natural progression of the disease involves forecasting the proportion of people who move from one stage to the next (e.g. from normoalbuminuria to microalbuminuria, from microalbuminuria to diabetic nephropathy, from nephropathy to ESRD), as well as the length of time spent in each stage. In addition, the disease progression is affected by the mortality rate because death is a competing risk. The probability of making a transition from one disease stage to another may vary with duration in the stage and/or age. The probabilities may also vary with respect to other characteristics such as gender or race. One approach is to compute annual transition probabilities based on an estimate of the time spent in each disease stage using a log-normal distribution. Annual transition probabilities can then be estimated based on (1) the percentage of patients who make the transition

Table 6-1. Stages of Diabetic Nephropathy in Patients with Insulin Dependent Diabetes Mellitus

Five Stage Model[1]		Four Stage Model[2]	
Stage of Disease Progression	Urinary Albumin Excretion Rate	Stage of Disease Progression	Urinary Albumin Excretion Rate
Normoalbuminuria	<20 μg/min	Normoalbuminuria	<20 μg/min
Microalbuminuria	20-99 μg/min	Microalbuminuria	20-200 μg/min
Significant Microalbuminuria	100-299 μg/min	Diabetic nephropathy	≥200 μg/min
Overt proteinuria	≥300 μg/min		
Renal failure	-	Renal failure	-

[1]Siegel, et al. [17].
[2]Borch-Johnsen et al. [18].

to the disease stage; (2) the average transition time; and (3) the variation in the transition time among those who make the transition.

Given the similarity in the disease progression between IDDM and NIDDM, it is possible to model disease progression among NIDDM patients utilizing the same general model structure. However, the NIDDM model may differ from the IDDM model in two respects. First, the models of disease progression developed for IDDM patients have been developed using the characteristics of a white population. Since the prevalence of NIDDM is particularly high among certain minority populations in the U.S. (e.g., Native Americans, African-Americans, Hispanics) [19-25], it may be desirable to incorporate race as a factor in modelling the progression of renal disease in NIDDM patients.

Second, modelling disease progression in NIDDM is complicated by the fact that true duration of diabetes is unknown for many NIDDM patients. Among IDDM patients, duration of disease can be measured from diabetes diagnosis. Among NIDDM patients there is often a considerable lag between disease onset and diagnosis. Based on two population-based groups of NIDDM patients in the United States and Australia, Harris and associates estimate that onset of NIDDM may occur 9 to 12 years prior to clinical diagnosis [26]. In a population based study of Rochester, Minnesota, approximately 10 percent of NIDDM patients had persistent proteinuria at the time of diabetes diagnosis [27]. While the NIDDM model will also

begin at disease diagnosis, the model should assume a proportion of NIDDM patients have microalbuminuria or clinical nephropathy at the time of diagnosis.

The disease model requires considerable data. In particular, the model requires: (1) age, sex, and race specific mortality rates for each disease stage, (2) the annual probability of moving from one disease stage to the next in the absence of a screening and treatment program, and (3) the effect of various treatments on annual probabilities of moving from one disease stage to the next. Possible sources of these data include published clinical studies, existing databases, and expert opinion.

Data regarding mortality rates for patients with ESRD in the U.S. are reported by the U.S. Renal Data System [28]. However, mortality rates for persons with diabetes with microalbuminuria or clinical nephropathy are not readily available. Data must be derived from clinical studies reporting increased mortality among persons with diabetes with microalbuminuria and clinical nephropathy.

Transition probabilities of progressing from one stage of nephropathy to the next can be derived from epidemiologic studies, which typically report the cumulative incidence of microalbuminuria or diabetic nephropathy as a function of time since disease onset. Data from observational studies reflect current standards of care in that community. Data from clinical studies can be used to make assumptions regarding the impact of a particular intervention on the annual probabilities of progressing from one disease stage to the next. Unfortunately, these data may be limited to studies of small samples at a single clinic or hospital. Occasionally, the results of large multi-center trials may be available. Since more data are available about the natural progression of IDDM than NIDDM, it may be necessary to assume that the disease progression is similar.

In the absence of published data, it may be necessary to rely on expert opinion. For example, existing data sources may be inadequate to assess the effect of various screening and treatment programs on the annual probability of developing diabetic nephropathy. Therefore, one can attempt to achieve consensus among clinical experts regarding these probabilities.

4. COSTS

An economic evaluation requires an estimation of the annual costs associated with care for each disease stage. At a minimum, this includes the direct costs of medical care (e.g., outpatient services, hospitalizations, laboratory and diagnostic tests, dialysis treatments, medical equipment and supplies, home health care services, medications, and long-term care). Direct costs may also include nonmedical services (e.g., transportation, costs of housekeeping services). Indirect costs--for example, loss of work, disability payments--may also be included an economic evaluation.

It is possible to conduct an economic evaluation from a variety of perspectives--from the points of view of the patient, public and private payers, or society. From the patient point of view, costs would include those costs not covered by public and private payers, plus the cost of other out-of-pocket expenses incurred because of illness (including time missed from work). Costs from the point of view of the payer would include only those charges allowed by the payer. Adopting a societal perspective would involve considering total net costs incurred by the various components of society. While a societal perspective is regarded as preferable for most economic evaluations, it is often interesting to conduct an economic evaluation from more than one point of view.

An economic evaluation will compare the costs associated with a standard treatment protocol and the costs associated with an experimental treatment protocol that includes various screening strategies and interventions aimed at delaying or preventing the onset of disease. The model requires an estimation of treatment costs for each disease stage, including the costs associated with the treatment of end-stage renal disease for those patients who develop renal failure. Screening and intervention costs will consist of: (1) costs associated with screening for microalbuminuria; (2) costs incurred in establishing a definitive diagnosis for those with both true positive and false positive screening tests; (3) medical costs associated with intensified treatment, including the costs of treating possible side-effects of the intervention; and (4) the costs associated with the treatment of end-stage renal disease for those patients who develop renal failure. Typically, the screening and intervention costs occur early, while cost savings may not occur for a number of years. To express the present value of health effects occurring in the future, it is necessary to apply a discount rate.

Data for estimating the costs of various screening and prevention programs can be obtained from a number of sources. Public and private payers may represent a source of cost and utilization data. In the United States, for example, the Health Care Financing Administration routinely reports data on the treatment costs of patients with end-stage renal disease [29]. A summary of Medicare program expenditures for diabetic patients with end-stage renal disease is presented in Table 6-2. Screening and treatment costs associated with delaying the onset of renal failure are more difficult to obtain (see Table 6-3). In these cases it may be necessary to estimate the amount of medical care utilized and to estimate the cost of the care from published data sources. To supplement the information available through published sources, it may be necessary to elicit information from a panel of clinical experts (for example, regarding what constitutes routine care for each disease stage).

Table 6-2. Average medicare program expenditures for patients with diabetic end stage renal disease, by treatment modality: United States, 1990[1]

Treatment modality	Number of Persons[2]	Expenditures per person (U.S. dollars)					
		Inpatient	Outpatient	Physician/ supplier	Other	Total	Annualized
Dialysis patients	27,350 (173)	$15,998	$11,747	$8,390	$544	$36,676	$49,040
Transplant patients							
First year	717 (350)	61,689	9,382	11,627	478	83,176	86,741
Subsequent years with functioning graft	5,193 (347)	7,336	1,046	2,706	370	11,458	12,052
Graft failure	223 (315)	29,226	8,089	10,510	518	48,343	56,016

[1]Expenditures were calculated only for persons who had at least one full year of Medicare entitlement prior to the observation year. Thus, any patients for whom Medicare was a secondary payer were not included.
[2]Average number of days of Medicare coverage shown in parentheses.

Source: Health Care Financing Administration [29]

Table 6-3. Surveillance and intervention costs

Treatment	Cost (U.S. dollars)[1]
Screening tests[1]	
Albustix (per test)	$0.50
Urinanalysis (per test)	3.17
Other diagnostic procedures[2]	
Renal ultrasound (per test)	99.68
Antihypertensive treatment[3]	
Enalapril (per year)	259.00
Hydrochlorothiazide (per year)	22.00
Lasix (per year)	113.00

[1]Health Care Financing Administration [30]
[2]Medicare Fee Schedule [31]
[3]Siegel, et al. [17]

5. EFFECTIVENESS

The effectiveness of a particular treatment can be defined in terms of the improvements in the health status of a patient population as a result of the therapy. A particular treatment may delay disease, in which case one can measure effectiveness in terms of number of cases averted. Or, a treatment may save lives, in which case one can measure effectiveness in terms of the number of deaths prevented or years of life saved. The economic evaluation may show an actual cost savings of a particular screening and prevention program. Alternatively, if the cost of a particular screening and prevention program exceeds the cost of treatment without the program, the difference in costs can be divided by the incremental increase in disease free years or average life expectancy to estimate the cost per additional disease free year or year of life gained.

While extending life expectancy is an important outcome, it may also be important to consider the quality of the additional years gained under alternative programs. The quality adjusted life year (QALY) is a measure that weights life expectancy by the quality of life expected [32-33]. Table 6-4 shows some weights reported in the literature for patients with ESRD [34-36]. Health utilities generally range between 1.0 (excellent health) and 0.0 (death).

Table 6-4. Health state utilities from studies reported in the literature

Health state	Utility	Std. dev.	Rater	Method
end-stage renal disease[1]				
home dialysis	0.40	0.26	197 members of general population	time trade-off
hospital dialysis	0.32	0.42		
end-stage renal disease[2]				
transplant	0.84	0.24	103 patients with end-stage renal disease	time trade-off
hospital haemodialysis	0.43	0.26		
home haemodialysis	0.49	0.23		
continuous ambulatory peritoneal dialysis	0.56	0.29		
end-stage renal disease[3]				
recombinant human erythropoietin trial		not reported	120 patients receiving haemodialysis	time trade-off
placebo	0.42			
low dose	0.51			
high dose	0.58			

[1]Sackett and Torrance [33]
[2]Churchill et al. [34]
[3]Canadian Erythropoietin Study Group [35]

6. SENSITIVITY ANALYSIS

Often there is uncertainty regarding key variables in an economic evaluation. For example, information may not be available concerning the effect of an intervention on disease progression or various treatment costs may be unknown. Sensitivity analysis allows one to change the values of key variables in the model and to examine the effect on the results of the analysis. Sensitivity analysis can be used to

identify those data elements that are more important than others in determining the cost-effectiveness of a treatment program. For example, the analysis might show that the conclusions vary more as a function of the epidemiological data regarding the natural disease progression than with the level of effectiveness of a particular intervention. These findings would be valuable in deciding whether or not to invest in research focused on new interventions.

7. CONCLUSIONS

In recent years there has been a growing concern on the part of employers, public and private insurers, and consumers regarding increasing health care costs. It is no longer sufficient to demonstrate the safety and efficacy of a new treatment. It is also important to show that the particular treatment is cost-effective.

Before embarking on an expensive clinical trial focusing on the prevention of renal complications among NIDDM patients, an economic evaluation such as that described above may provide valuable input into the design of the trial. Given the lack of good epidemiologic data on NIDDM, it may be necessary to make assumptions regarding the model of the disease progression in NIDDM based upon what is known about the disease progression in IDDM. This economic evaluation can be used to evaluate various screening and intervention programs among NIDDM patients and to identify those that are most likely to be cost-effective among this group of patients. Such an economic evaluation may also be useful in identifying specific data that are not readily available that should be collected as part of the trial.

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7. INCIDENCE OF NEPHROPATHY IN INSULIN-DEPENDENT DIABETES MELLITUS AS RELATED TO MORTALITY AND COST-BENEFIT OF EARLY INTERVENTION

KNUT BORCH-JOHNSEN

Development of clinical diabetic nephropathy in IDDM-patients is associated with high excess mortality as well as with generalized vascular lesions and impairment in the cardiovascular risk profile of the individual. It therefore indicates a poor prognosis of the patient.

Improved metabolic control, in combination with other factors, has led to a gradual decrease in the incidence of diabetic nephropathy in most countries. Furthermore, anti-hypertensive treatment of patients with nephropathy has improved the prognosis of these patients by postponing or preventing end stage renal failure. Finally, early detection of at-risk individuals by sensitive measurement of the urinary albumin excretion rate is now a routine procedure, and at present intervention trials including IDDM-patients with microalbuminuria are ongoing.

The decreasing incidence of diabetic nephropathy, the improved treatment of patients with nephropathy and the possibilities for early detection and intervention for microalbuminuria will probably further improve the prognosis of future IDDM-patients. What can be expected in the future, to what extent will the mortality

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decrease and what will be the cost-effectiveness of screening and intervention? These are some of the questions addressed in this chapter.

1. MORTALITY AND PROTEINURIA

Studies from different parts of the world consistently show, that IDDM-patients have an excess mortality compared with the non-diabetic population. The excess mortality varies with age and diabetes duration [1], and also shows considerable variation between countries [2]. As shown in table 7-1, the distribution of causes of death varies according to diabetes duration. While acute, metabolic complications and infections dominates in patients with short diabetes duration, diabetic nephropathy and cardio-vascular diseases account for 70-80% of all deaths in patients with longer diabetes duration.

In 1972 Watkins et al suggested, that development of proteinuria was a strong prognostic marker in diabetes, and probably even stronger than grading of nephropathy on the basis of histo-pathological findings [3]. In our study of excess mortality in 1030 IDDM patients followed for 30 to 50 years we found [4], (figure 7-1) that the very high excess mortality of IDDM-patients was found only in patients who developed persistent proteinuria (clinical diabetic nephropathy), while patients not developing clinical nephropathy had a low and rather constant excess mortality. This study also showed, that the most likely way of improving the prognosis of IDDM-patients would be to prevent development of diabetic nephropathy.

2. DECREASING EXCESS MORTALITY AND DIABETIC NEPHROPATHY

In a study of the relative mortality of IDDM-patients in Denmark during the period from 1930 to 1981 we found [5] that the excess mortality decreased by nearly 40%. The study included nearly three thousand patients diagnosed before the age of 31 years, diagnosed during the period 1933 to 1972 and admitted to the Steno Memorial Hospital (Steno Diabetes Centre). All patients were followed up from their first admission to the hospital until death, emigration or January 1st 1982. The major decrease in the excess mortality took place in patients diagnosed from 1940 to 1955, but a constant and gradual decline was found over the entire period. As discussed above, the excess mortality in IDDM-patients is predominantly due to development of diabetic nephropathy. Thus the most likely explanation of this decreasing excess mortality would be a decreasing incidence of diabetic nephropathy. This hypothesis was confirmed when studying the incidence of clinical nephropathy in the same cohort [6], as the incidence of nephropathy decreased by nearly 50% during the 50 years observation period. The decreasing incidence of nephropathy was not a consequence of introduction of anti-hypertensive treatment, as the major part of the decrease took place during the period from 1940 to 1965 [6]. These results are in

Table 7-1. Cause of death according to diabetes duration in a cohort of 2,900 Danish IDDM-patients diagnosed 1932-1972, before the age of 31 years.

Cause of Death	Diabetes Duration		
	0-15 years (n=124)	16-30 years (n=513)	>30 years (n=199)
Vascular			
Acute Myocardial Infarction	9%	17%	36%
Other Cardiovascular	4%	3%	11%
Cerebrovascular	2%	4%	10%
Diabetic Nephropathy	17%	52%	15%
Ketoacidosis	18%	2%	3%
Hypoglycaemia	6%	3%	2%
Diabetes NOD	2%	1%	1%
Infections	14%	5%	10%
Suicide	8%	3%	3%
Cancer	2%	3%	4%
Other	19%	7%	9%

accordance with data from the Joslin Clinic in USA [7] where the incidence of diabetic nephropathy was 1.9 times higher in patients diagnosed in 1939 than in patients diagnosed in 1949 or 1959. Our studies therefore confirmed that the most effective way of improving the prognosis of IDDM-patients was by preventing development of diabetic nephropathy. In our studies of the excess mortality as related to nephropathy we used the classical definition of nephropathy (table 7-2). Thus patients with nephropathy had a urinary protein excretion of 0.5 g/24 h in at least 3 consecutive samples. During the last 10 to 15 years, measurement of urinary albumin excretion rates at much lower levels have been possible, and it has been shown, that patients with microalbuminuria (30 to 300 mg/24 hours) are at high risk of developing diabetic nephropathy [8-10], and thus also at higher risk of dying. Diabetic nephropathy and microalbuminuria are both associated with atherogenic changes in the lipid-profile, rheological factors and increasing blood pressure [11,12] and it is likely, that even microalbuminuria may be associated to clinical vascular disease. The Steno Hypothesis [13], suggesting common pathogenetic mechanisms behind several of these changes, is discussed in detail in Chapter 20. The question,

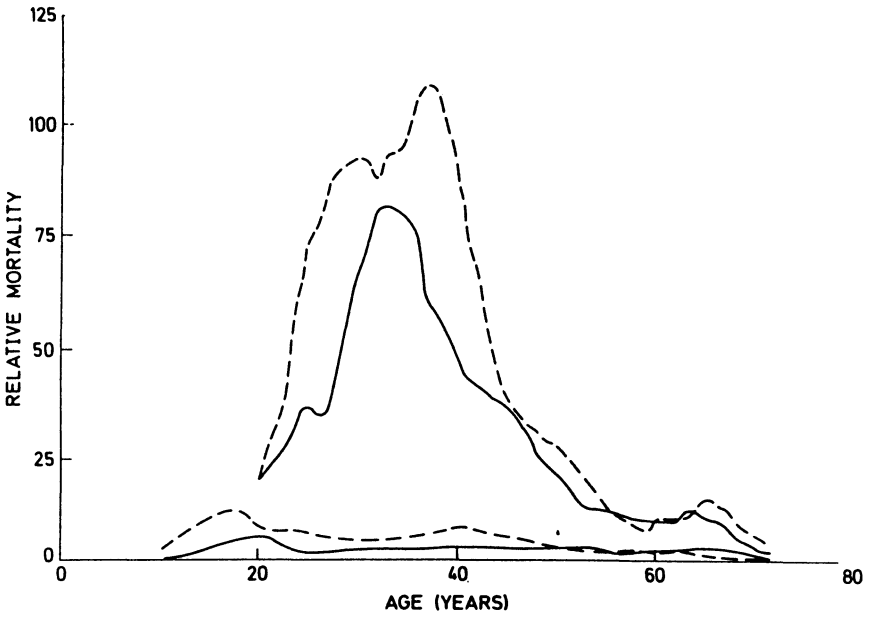

Figure 7-1. Age adjusted relative mortality of IDDM-patients with proteinuria (upper curves) and without proteinuira (lower curves) in a cohort of 1003 Danish IDDM-patients: --- Women, ¯ Men. (Reproduced with permission from Diabetologia and Springer Verlag [4]).

however, is whether microalbuminuria per se is associated with excess mortality in IDDM-patients.

3. MORTALITY AND MICROALBUMINURIA

In non-insulin dependent diabetic patients [14,15] as well as in non-diabetic individuals [16,17] microalbuminuria is associated with a marked excess mortality. In IDDM-patients the excess mortality in patients with microalbuminuria has not been thoroughly studied. In a recent study by Messent et al it was found [18], that when IDDM patients with microalbuminuria were followed for more than twenty years, this group of patients had a significant excess mortality. Among the 8 patients with microalbuminuria originally included in the study 5 died. However, all deceased patients had developed clinical nephropathy and were no longer microalbuminuric at the time of death. Among the three surviving patients, one developed renal failure while two remained microalbuminuric throughout the observation period. Thus, it is still unknown whether microalbuminuria in it self is associated

Table 7-2. Definitions of microalbuminuria, proteinuria and diabetic nephropathy.

Stage	Urinary Albumin Excretion Rate	
	mg/24h	μg/min
Normoalbuminuria	<30	<20
Microalbuminuria	30-300	20-200
Proteinuria or Clinical Nephropathy	>300 *	>200

*or more than 0.5 g protein per 24 hours.

with an excess mortality in IDDM-patients, or whether it is so only because it is a predictor of clinical nephropathy.

This question is highly relevant, as recent studies have shown that anti-hypertensive treatment of IDDM-patients with microalbuminuria may delay or prevent progression to diabetic nephropathy, and it must therefore be assumed, that it will prevent some of these patients from developing End Stage Renal Failure and uraemia. The generalized vascular lesions [12] and changes in the atherogenic profile [11] that characterize patients with microalbuminuria may, however, lead to death from vascular disease, even in the absence of clinical nephropathy and end stage renal failure. Thus it is possible that intervention by anti-hypertensive treatment and strict metabolic control may not be able to bring mortality-rates down to the same level as that of normo-albuminuric IDDM-patients, but the controlled clinical trials have been so small and running for so short periods of time [19-21] that an evaluation of this has been impossible so far.

4. PROSPECTS FOR PREVENTION

For unknown reasons the incidence of diabetic nephropathy decreased by nearly 50% when comparing patients diagnosed in the 1930's with patients diagnosed after 1950. The general assumption is, that this decrease was due to improved metabolic control, facilitated by changes in the attitude of health care professionals as well as of the diabetic patients, and facilitated by the easier access to methods for home monitoring - first of urinary, and later also of blood glucose. It should, however, be kept in mind that, despite the effect of near-normalization of blood-glucose levels [22], the most dramatic changes took place before the introduction of stix-methods for urinary and blood glucose, and long before the introduction of antihypertensive treatment.

Microalbuminuria develops in 30 to 50% of all IDDM-patients. It is rarely seen before 5 years of diabetes duration, but thereafter the prevalence increases with increasing diabetes duration [23]. Once microalbuminuria develops, the excretion rate will gradually increase in most patients, and from the very few studies of the

natural history of microalbuminuria it may be calculated [24] that the annual increase rate in UAER is approximately 15 to 20%, but with considerable inter-individual variation. This increase rate can, however, apparently be altered and decreased by strict metabolic control and antihypertensive treatment.

Recent studies have shown that strict metabolic control - most easily obtained by insulin pumps or multiple injection regiments - can postpone or prevent progression from microalbuminuria to overt nephropathy [22], and - as discussed further in Chapter 33 - it may also be important in primary prevention. With the world wide rapidly increasing access to devices for home monitoring, insulin »pen«-devices, and with the gradually changing attitude among professionals as well as among diabetic patients, it is likely that improvements in metabolic regulation can be obtained with a concomitant decrease in the risk of developing diabetic nephropathy. Importantly, the DCCT has confirmed European studies (Chapter 1).

With the introduction of antihypertensive treatment the prognosis improved for patients with nephropathy [25,26], a result which is true also in clinical practice, outside the frame of a controlled clinical trial [27]. Short term trials in IDDM--patients with microalbuminuria (reviewed in Chapter 27) give considerable hope that this may also be the case in the microalbuminuric stage. It is still premature to recommend antihypertensive treatment for all cases of microalbuminuria, but real long-term controlled clinical trials should be encouraged, evaluating harder end-points as development of persistent proteinuria, falling GFR and eventually death. These trials should also be encouraged to meticulously record and analyze non-fatal cardiac and vascular events as well as changes in the cardio-vascular risk factors.

Further clinical trials are necessary for several reasons. One being that the trials so far have been running for to short periods of time to evaluate any hard end-points. Secondly, the trials so far have not included estimations of costs and benefits related to the intervention. Thirdly, none of the trials so far have focused on the potential for prevention of cardio-vascular disease in the patients with microalbuminuria. Before large scale intervention is being planned, the economical aspects including the costs of screening and intervention should be weighted against the potential savings for the patient (economical as well as in quality of life) and for the society.

4.1 Screening, intervention and cost-benefit

As trials aiming at early intervention in the microalbuminuric stage are relatively small and few, it is difficult to estimate the cost effectiveness of different regiments for screening for and early intervention in microalbuminuria. On the other hand, treatment of end stage renal failure with dialysis or renal transplantation is so

expensive (costs approximately 25 to 40.000 US $ per year) [28], that if intervention programmes are effective, then they are also likely to be cost-beneficial. Furthermore, screening for microalbuminuria is becoming increasingly simple, fast and cheap with the availability of methods described in detail in Chapter 9.

Two independent groups have tried to estimate the likely cost-benefit and cost effectiveness of different regimens for screening and intervention. In the study of Siegel et al [29], the authors compared the likely costs and savings related to 4 different programmes: 1: No screening for microalbuminuria or proteinuria, antihypertensive treatment at BP 140/90, 2: Screening for proteinuria (0.5 g/24h) and ACE-inhibitor treatment in case of proteinuria, 3: Screening for microalbuminuria, treatment with ACE-inhibitor if UAER 100 g/min and 4: Screening for microalbuminuria and ACE-inhibitor if UAER 20 g/min. The authors used previously published epidemiological data regarding the natural history of diabetic nephropathy to estimate the time of progression from normo-to microalbuminuria, from microalbuminuria to proteinuria and from proteinuria to end stage renal failure. They then assumed two different potential effects of antihypertensive treatment, 50% increase in progression-time (called conservative estimate) and 75% increased progression-time (called optimistic estimate).

The second study [30], used a rather similar design including annual testing for microalbuminuria in all IDDM-patients from 5 to 30 years of diabetes duration. Antihypertensive treatment using an ACE-inhibitor would be initiated in all patients with microalbuminuria (30 mg/24h). The study used data from a previously published Danish epidemiological study [31] of the incidence of nephropathy and the mortality in patients with and without proteinuria to estimate mortality rates and transmission-times without intervention. Based on the results from controlled clinical trials [19-22] they estimated that the increase rate in UAER could be decreased by 33 or 67 per cent.

Both studies conclude, that if antihypertensive treatment can lower the annual increase rate in UAER in microalbuminuric patients, then screening- and intervention programmes will save money for the providers of the health care system. In our own study, we found [30] that even when taking discounting into consideration, a treatment-effect of the antihypertensive treatment of 8 to 12% would be sufficient to out-balance costs and savings. In patients with nephropathy, antihypertensive treatment has been shown to decrease the decline-rate in GFR and to decrease the mortality rates by 67% [26,27]. If this was the case also in patients with microalbuminuria, then screening and intervention for microalbuminuria would increase the median life-expectancy of IDDM-patients by more than 10 years, and the life-time risk of developing end stage renal failure would decrease by more than 60%.

In conclusion, these two studies both indicate that screening and early intervention may be beneficial. It must, however, be remembered, that both studies are based on assumptions as long term intervention trials are lacking. These studies can not by them selves serve as arguments for routine intervention, but they point at the urgent need for large scale, very long term trials of early antihypertensive treatment, and they both indicate that these trials would have a very high likelihood of success.

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8. MEASUREMENT OF ALBUMIN AND OTHER URINARY PROTEINS IN LOW CONCENTRATION IN DIABETES MELLITUS: TECHNIQUES AND CLINICAL SIGNIFICANCE

D.J.F. ROWE and W. GATLING

MICROALBUMINURIA

Independent clinical studies have indicated that urinary albumin excretion increased above normal but below the level of detection by Albustix (»microalbuminuria«) predict accurately the development of clinical nephropathy and end-stage renal failure in adults with insulin-dependent diabetes (IDD) [1-3].

Following these studies, measurement of urinary albumin has been used to investigate changes in renal function in children with IDD [4-6], in non-insulin dependent diabetic subjects [7,8], in non-diabetics with heart failure and/or hypertension [9,10] and in pregnancy [11]. The measurement may also predict mortality as well as morbidity from non-renal causes [7,8,12,13].

The clinical significance of the excretion of other urinary proteins has also been investigated. Conclusions that the excretion of B2-microglobulin was not increased in early diabetic renal disease have been shown to be flawed due to the instability of this protein in urine under normal collection conditions [14].

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Does microalbuminuria predict progression of renal disease?

Recent studies have challenged the belief that microalbuminuria is a strong predictor of progression to diabetic nephropathy.

In adult IDD with duration of diabetes >15 years there was only limited evidence of progression of microalbuminuria to clinical nephropathy (5/18 subjects) or of progression of clinical nephropathy to end-stage renal failure over a 10 year follow-up [15].

Young insulin dependent and adult insulin-requiring diabetic subjects showed no significant change in urinary albumin/creatinine ratio (ACR) in random samples over a 5 year follow-up, nor was there any consistent change in ACR in those subjects with microalbuminuria (20% and 28% of the respective clinic populations) (figure 8-1) [16].

Histological studies have demonstrated that structural abnormalities in glomerular basement membrane thickness and in mesangial volume are present in some diabetic patients without apparent abnormalities in urinary albumin excretion [17]. The relationship between the pathological features and functional abnormalities in diabetic renal disease have always been difficult to correlate. All diabetic patients with duration over 10 years have histological features of kidney disease yet only a proportion of these will have functional abnormalities such as increased protein excretion.

Other urinary proteins

The excretion of many enzymes and small-molecular weight proteins is increased early in the diabetic process, in many cases independent of the excretion of albumin.

Conclusions that the excretion of B2-microglobulin was not increased in early diabetic renal disease were flawed due to the instability of this protein in normally acid urine. This was shown by Bernard [14] and confirmed independently by Watts et al. [18]. These workers measured B2-microglobulin and retinol-binding protein (RBP), which are both considered to reflect changes in renal tubular function, in non-diabetic and diabetic subjects. A weak correlation was shown between the excretion of the two proteins accompanied by a lower mass excretion of B2-microglobulin. The experiment was repeated after *in vivo* alkalinization prior to urine collection. The correlation between the proteins increased to $r=0.8$ and the mass excretion of B2-microglobulin increased to equivalence with that of RBP. The excretion of RBP did not increase significantly after alkalinization.

The excretion of enzymes such as n-acetyl B-D-glucosaminidase (NAG), gamma-glutamyl transferase and alkaline phosphatase and other proteins such as a1-microglobulin, RBP, immunoglobulin light chains and transferrin may be increased early in the diabetic process and independent of the excretion of albumin [4,20-

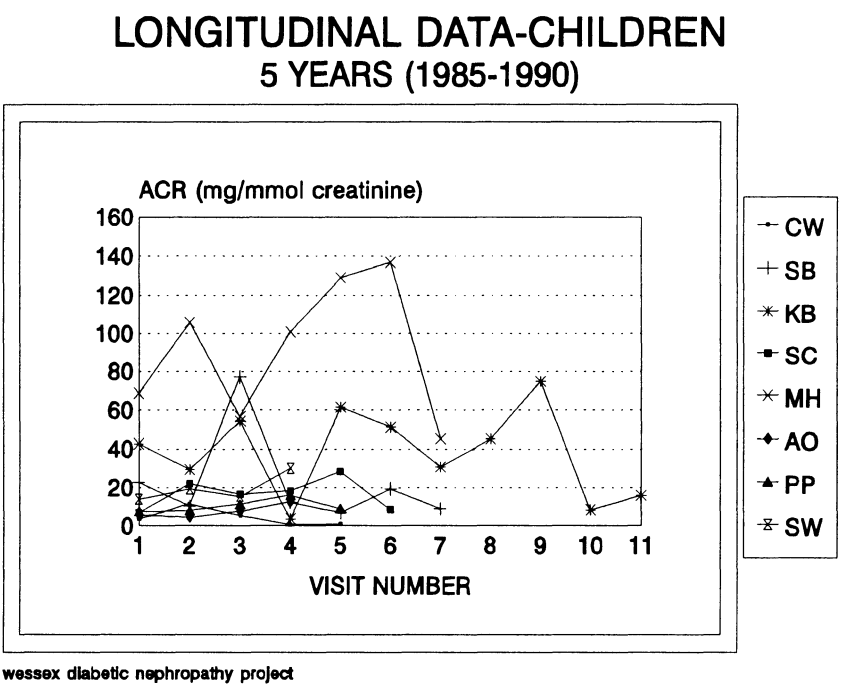

Figure 8-1. Longitudinal data from individual patients over 5 years follow-up.

29,31]. One study demonstrated that the excretion of a1-microglobulin and gamma light chains was significantly increased and correlated with HbA1 in young people with IDD without significant change in the excretion of albumin [22]. Pontuch also showed a correlation between RBP excretion and HbA1c but not with albumin excretion [20]. Others showed a correlation between RBP excretion and albumin but not HbA1 [30]. Neither study could relate RBP to duration of disease. Elsewhere, the excretion of NAG and RBP correlated with albumin excretion and with HbA1c [4]. Holm and others showed the increased excretion of RBP in IDD with no correlation to HbA1, fructosamine or urinary albumin [23,24].

The excretion of NAG has been shown to be the most sensitive tubular function marker in terms of increased excretion in diabetic subjects [27]. No study has yet shown a predictive value for tubular markers indicating progression of renal disease although none of them have been studied for as long as albumin.

Tubular markers and glycemic control

The increased excretion of these markers may be related particularly to changes in acute glycaemic control. In 1985, Miltenyi showed that NAG excretion was increased in diabetic children with ketoacidosis and glycosuria compared to well-controlled diabetic children and non-diabetic subjects. Excretion of the enzyme decreased with the establishment of diabetic control over eight days. However, NAG excretion continued to remain higher than in the non-diabetic controls suggesting than an abnormality in tubular function persisted [31].

One study has demonstrated the increased excretion of RBP in response to acute glucose and insulin infusion in subjects undergoing euglycaemic clamping [32]. There was no clamping of blood glucose in the non-diabetic controls in this study and the results could not be confirmed by others [33]. In a third study, acute hyperglycemia was shown to increase the excretion of albumin and of B2-microglobulin but not of kappa light-chains in normal subjects [25]. RBP excretion has also been shown to be increased in chronic heart disease [10].

Physiological variability in the excretion of these tubular proteins occurs as for albumin. Thus, normal volunteers show an acute increase in the excretion of tubular proteins in response to exercise and in the day-to day variability of pre-exercise samples [34].

METHODS FOR MEASUREMENT OF SPECIFIC URINARY PROTEINS

Albumin

Immunoassay techniques for the measurement of urinary albumin have been reviewed [35-37]. Approximately 70% of UK health service laboratories use immunoturbidimetry, approximately 20% use immunonephelometry and the remainder of laboratories a mixture of radio- or enzyme-immunoassays. Commercial kits for urinary albumin measurement are available although in-house methods are easy to establish and maintain. Overall, the between-laboratory agreement of the different assay types is similar; results from the UK External Quality Assessment Scheme for urinary albumin are shown in figure 8-2.

Immunoturbidimetry lacks the sensitivity to detect reliably normal albumin excretion which is frequently less than 5 mg/L. It is therefore less suitable than the more sensitive immunoassays for use in research applications. The more sensitive methods require assay desensitisation or sample dilution before use.

»Tubular« proteins

High sensitivity immunoassays using ELISA [4], RIA [30] and latex-agglutination [14] methods have been described for the detection of proteins such as RBP and B2-

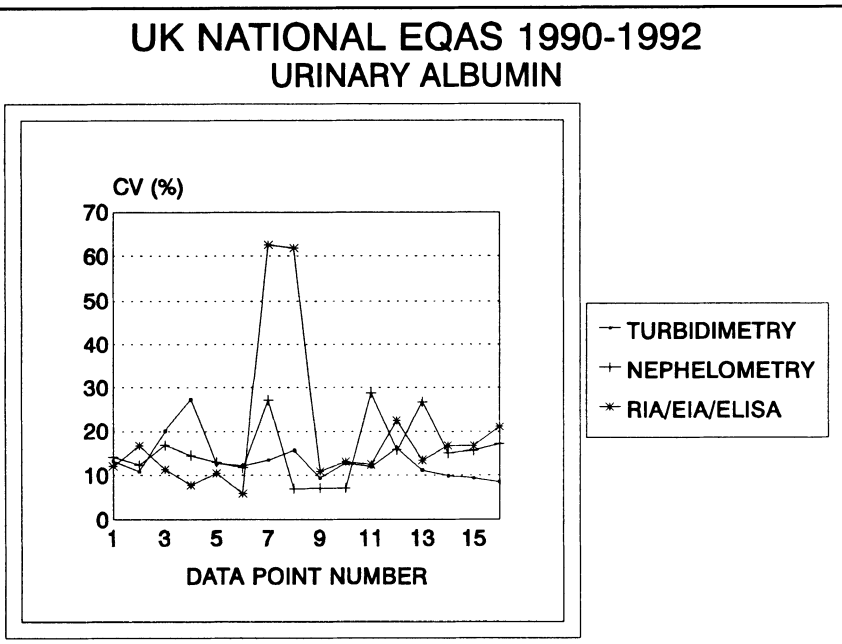

Figure 8-2. United Kingdom National External Quality Assurance data.

microglobulin into the normal range. Most methods for the analysis of NAG use p--nitrophenyl-N-acetyl-B-D-glucosamide as substrate [4,26]. Such enzyme methods are easily automated on modern laboratory analyzers.

Type of urine sample

Storage at -20°C appears to result in losses of albumin from urine and from standard solutions. Two studies have investigated the loss of albumin following storage for 2 months, 6 months and 2 years at -20°C and have shown variable but marked losses of 28 and 39% and 27 and 50% at 6 months and at 2 years for albumin/creatinine (ACR) and NAG/creatinine ratios respectively [19,38]. Creatinine concentration also decreased over 2 years. Urine can be stored at +4° for at least 7 days before analysis and for longer if sodium azide is added as preservative [37]. There is little deterioration in RBP levels in urine samples stored at -20°C for 12 months (unpublished observations).

Clinic »stix« testing

Several dipstick and tablet screening methods have been developed for the detection of microalbuminuria in clinics and are reviewed elsewhere in this book. They may provide a useful screen but positive cases need to be followed up by quantitative measurement of urinary albumin in the laboratory and by correction of the concentration by time or by creatinine concentration.

Which urine sample to screen for microalbuminuria?

Gatling assessed the ability of an overnight ACR, an overnight albumin concentration or a random ACR to predict a timed overnight albumin excretion rate (AER) of >30 μg/min. An overnight ACR was found to be the optimal screening test. A random ACR >3 mg/mmol had only 12% predictive value for AER >30 μg/min [39].

Marshall has recommended an early morning sample as being the best compromise to predict a »gold standard« overnight AER or ACR [40]. She reported sensitivity and specificity between 82-100% and between 74-100% respectively from several independent studies depending on the cutoffs set for ACR and for microalbuminuria. The data for random clinic samples indicated sensitivities between 56-100% and specificities between 81-96% respectively. She suggested that if early morning ACR was <3.5 mg/mmol then the patient be considered normal and be rescreened annually. If >10 mg/mmol then active treatment is indicated. If 3.6-10 mg/mmol then the patient be rescreened at the next clinic visit. Others have argued that there may be unacceptable delay clinically with a cutoff of 3.5 mg/mmol and annual retesting. They recommend a lower cutoff of 2 mg/mmol in this situation and consideration of active treatment for patients in the 3.6-10 mg/mmol group [39]. Both authors suggest that attempts to assess microalbuminuria on the basis of concentration alone are not valid. Kouri concluded that the false positive and false negative rates incurred with testing random clinic samples were unacceptable clinically and placed unnecessary work upon hospital laboratories [41]. Bouhanick however, stated that a single random clinic sample uncorrected for creatinine or for time could predict persistent microalbuminuria or clinical proteinuria in 24 hour samples (sensitivity 83%, specificity 82%, positive predictive value 69%, concordance 80%) [42]. Importantly there are differences between men and women in ACR because of lower excretion of creatinine in women ($\approx 50\%$ higher in men). This produce a higher ratio in women [43].

There is no long-term study available to suggest that strictly normoalbuminuric patients (at baseline) with exercise-induced microalbuminuria progress more readily than patients with only small response in albuminuria to exercise.

Variability of urinary albumin

Variability in assay methods is relatively small in comparison to physiological variation. This creates major difficulties in the interpretation of changes in urinary albumin excretion in adult and juvenile diabetics and non-diabetics. Urinary albumin excretion may fluctuate by more than 100% and indicates the need to average multiple measurements on an individual before deciding on intervention. In addition, upright posture and exercise may both increase the excretion of albumin [44]. These factors may explain the variability in reference ranges between 24-hour, overnight and random daytime samples [45]. A recent study showed very limited loss of albumin by different types of storages of 7 days (4° or 20°) to 6 month (-20°) [46].

CONCLUSIONS

Techniques for the measurement of urinary albumin are routine in many laboratories. The type of technique should be dictated by the sensitivity required for the population under study.

Storage of urine samples deep-frozen may result in variable losses of albumin and of NAG. RBP appears to be stable at -20°C for at least 6 months.

Measurement of an albumin/creatinine ratio on an early morning sample is recommended for screening purposes.

Multiple samples are needed to confirm persistent microalbuminuria.

Excretion of tubular proteins may reflect changes in acute glycaemic control more clearly than that of albumin.

No studies have yet shown a relation between tubular proteinuria and progression of renal disease.

B2-microglobulin measurement should only be used as a marker of renal tubular function after prior alkalinization of the subject.

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9. OFFICE TESTS FOR MICROALBUMINURIA

PER LØGSTRUP POULSEN

INTRODUCTION

Microalbuminuria defined as an increase in urinary albumin excretion rate to the range 20-200 μg/min not only predicts later development of nephropathy in diabetic subjects [1-4] but may also guide the detection or prediction of other complications e.g. proliferative retinopathy [5,6]. In addition, microalbuminuria is also strongly associated with cardiovascular risk factors and coronary heart disease in diabetic as well as non-diabetic patients [7,8].

The clinical usefulness of the versatile and strong predictive power of microalbuminuria has been further augmented as it has now been shown that effective intervention modalities exist. Several studies have shown that antihypertensive treatment of normotensive (-- maybe certainly a debatable concept) microalbuminuric IDDM patients reduces urinary albumin excretion rate considerably and probably postpones or prevents clinical nephropathy [9-12].

Furthermore, it is now established that achievement of good glycemic control has similar beneficial effects [13-15 and the DCCT as described in Chapters 33,34].

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The strong predictive power in combination with effective treatment modalities clearly indicates that screening for microalbuminuria should be an essential part of the care for IDDM patients [16].

THE INTRA-INDIVIDUAL VARIATION OF URINARY ALBUMIN EXCRETION - SCREENING AS A CONTINUOUS PROCESS

There is considerable intra-individual variation in urinary albumin excretion, up to 40-50% [17] or even greater when measuring albumin concentrations or albumin:creatinine ratios under routine clinical conditions [18]. Thus, several samples should be taken in order to avoid misclassification of patients and screening should be a continuous process.

There is now a consensus e.g. in the St. Vincent document that persons with IDDM should be screened at least once every year and more often if microalbuminuria is detected. As the prevalence of microalbuminuria is very low before five years diabetes duration [19] annual screening could be initiated at this point.

HOW TO SCREEN - TIMED COLLECTIONS OR ALBUMIN CONCENTRATION ?

Timed urinary collections (24 h or overnight) remains the 'gold standard'. However, they are cumbersome to the patient, and in repeated large scale screening this may become a significant problem [20]. In one large study a patient compliance of only 59% was reported [21]. It should be emphasized that these figures are obtained under study conditions and that compliance may well turn out to be further reduced with repeated screening in clinical practice.

Aggravating this problem is the fact that diabetic nephropathy is often seen in 'non attenders' to diabetic care [22] who presumably have even less patience with cumbersome screening tests.

In addition, timed urinary collections are subject to collection errors or timing errors which can make the interpretation of results difficult, though creatinine concentration measurements and calculation of albumin:creatinine ratio may be helpful.

In order to assure good compliance it is crucial that screening procedures are acceptable to the patients.

OFFICE TEST: ADVANTAGES AND DISADVANTAGES

In general, office tests for detecting abnormal albuminuria should be simple in use, robust, quick, inexpensive and have sufficient specificity and sensibility. Several tests have now been evaluated [23-32]. They all share the advantage of bringing the result of test closer to the patient. It is possible to get the result before the patient

Table 9-1. Nycocard U-Albumin®

# patients	Cut-off	Sensitivity	Specificity	Predictive value of positive test	Predictive value of negative test
134	>20 mg/l	100%	70%	79%	98%
	>40 mg/l	100%	82%	71%	100%

leaves the outpatient clinic or the general practitioner. On the basis of the result, immediately action can be taken, whether it is arrangement of annual rescreening (negative test) or in the case of a positive test e.g. arrange collection of timed urinary samples to assess urinary albumin excretion rate.

Several office tests seem to fulfil the requirements of adequate sensitivity, specificity and reproducibility. However, it should be noted, that all the tests are critically dependent on correct handling. Thus, training in the use of the stick must have high priority and continuous monitoring of results is recommendable.

As to costs analysis regarding quantitative lab methods vs. semiquantitative office tests the result will depend on the local organization of the health system: If a majority of diabetic patients are seen in large outpatients clinics automated laboratory procedures (e.g. turbimetric methods) can be set up permitting a large number of samples to be processed in a minimum of time, at a very low cost -- probably below the price of the office tests. If, on the other hand, the care for diabetic patients is mainly in the hands of general practitioners costs of sending the samples to the laboratory should be taken into account and economy may point towards office tests.

A SURVEY OVER SOME OF THE OFFICE TESTS

As there have been reports of interference with non-protein components in tests using bromphenol based colorimetry resulting in a high number of false positives [33,34] antibody based screening methods should confer an advantage, and two such test are described in the following.

Nycocard U-Albumin® (Nycomed Pharma AS, Oslo, Norway) is a three-drop test based on a solid phase enzyme-linked immunosorbent assay (ELISA). The test kit includes a test card containing immobilized antibodies on a porous membrane and conjugate (albumin-specific antibodies conjugated with microsized colloidal gold). The albumin molecules in the sample are trapped on the membrane-bound antibodies and subsequently bind the coloured conjugated antibodies. Excess coloured conjugate is removed with a washing solution, and the colour intensity (proportional to the

Table 9-2. Micral-Test®

	# patients	Cut-off	Prevalence of samples over cut-off	Sensitivity	Specificity	Predictive value of positive test	Predictive value of negative test
Bangstad [27]	186	>20 mg/l	28%	92%	82%	67%	97%
Jury [28]	184	>30 mg/l	35%	91%	98%	96%	95%
Agard [31]	117	>20 mg/l	35%	88%	97%	95%	94%
Marshall [30]	112	>20 mg/l	30%	100%	91%	83%	100%
Poulsen [29] Lab technician	239	>20 mg/l	34%	91%	85%	76%	95%
Poulsen [29] Trained nurses	269	>20 mg/l	34%	84%	96%	76%	97%
Poulsen [29] General Practioners	563	>20 mg/l	35%	66%	92%	81%	83%

albumin concentration) on the sample is evaluated using a colour card. The colour development in the Nycocard U-Albumin® test is stable and can be read at any time once the procedure is completed. Results (G. Scott, personal communication) are summarized in table 9-1.

Another antibody based semiquantitative tests, Micral-Test® (Boehringer Mannheim Germany) is a test-strip based on a specific immunocapture technique in which the colour reaction is mediated by an antibody bound enzyme. The white fleece of the test strip, serving as a reservoir, is dipped into the urine for 5 seconds to a level just beneath the blue test zone, and then laid down horizontally. The absorbed urine enters a zone on the strip that contains a soluble antibody-enzyme conjugate that specifically binds to urinary albumin. Excess conjugate is retained in a separation zone that contains immobilized human albumin so that only the conjugated immunicomplex is mobile and can pass through the matrix with the fluid flow and reach the reaction zone. Here, the enzyme beta galactosidase reacts with a substrate to produce a red dye, the intensity of which, after five minutes, is directly related to the albumin content of the urine. The Micral-Test® yields semi-quantitative results reflected by five colour blocks on the vial label.

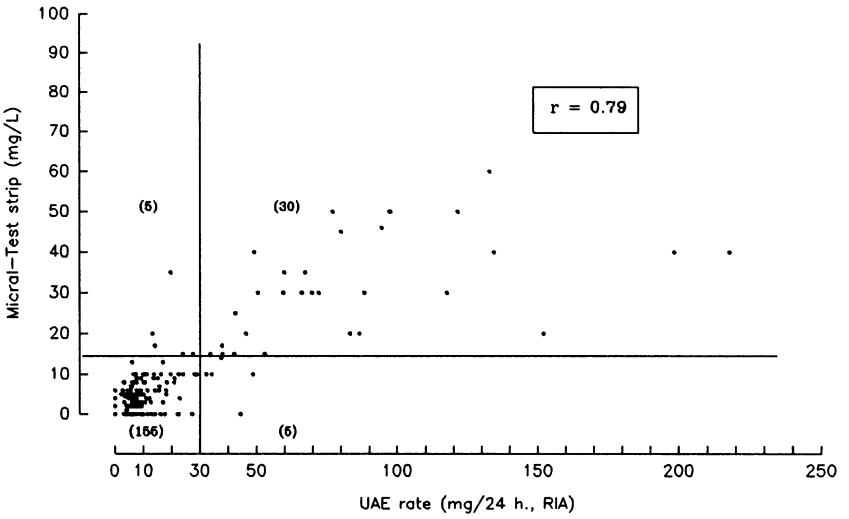

Figure 9-1. 195 Micral-Test® sticks read by trained nurses and the corresponding 24 h. UAE rates. Horizontal line discriminates positive and negative sticks, vertical line discriminates normo- vs microalbuminuria. Figures in parentheses indicates number of samples. (With permission from reference 29).

The test strip has been evaluated by several authors [27-32] and results are summarized in table 9-2.

In our own evaluation of the same dipstick test [29] we evaluated 1071 samples and included correlation with urinary albumin excretion rate as well as correlation with urinary albumin concentration. The dipstick was evaluated in three settings: **A.** 3 trained nurses testing samples from day-clinic diabetics, **B.** 1 laboratory technician testing not-hospitalized diabetics and **C.** 58 general practitioners also testing not-hospitalized diabetics. Results are given table 9-2 and figure 9-1.

We conclude that in the hands of trained nurses and laboratory technician the Micral-Test® showed good correlation with urinary albumin excretion and urinary albumin concentration and can be recommended as a screening tool. However, general practitioners obtained a lower sensitivity probably due to lack of experience and incorrect handling of the sticks leading to systematically errors. Training in the use of the stick must be encouraged since under such circumstances the results are satisfactory.

SUMMARY

Several reliable tests office tests for detecting microalbuminuria exist. Anti-body based screening methods confers an advantage in specificity compared to colorimetry methods based on bromphenol dye. Whether the tests are economically attractive will depend on the local organization of the health system. The tests are critically dependent on correct handling. Thus, training in the use of the tests is important and continuous monitoring of results is recommendable.

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10. RISK FACTOR FOR PROGRESSION OF MICROALBUMINURIA IN RELATIVELY YOUNG NIDDM-PATIENTS

RYUICHI KIKKAWA and MASAKAZU HANEDA

Microalbuminuria, which is defined as a minute increase in urinary albumin excretion rate in patients whose urine is Albustix-negative, is reported the most reliable predictor for the development of clinical diabetic nephropathy in IDDM [1,2]. Similarly to findings in IDDM, the pioneering work by Mogensen has clearly showed that, in NIDDM, the incidence of macroalbuminuria or of clinical proteinuria of a 9-year period is higher in those with microalbuminuria (22%) than in those with normoalbuminuria (5%) [3], although the predictive power of microalbuminuria appeared to be lower in patients with NIDDM. Since microalbuminuria can reportedly predict the risk of early mortality as well as of clinical proteinuria in subjects with NIDDM [3], it is important to identify the factor(s) responsible for the development and progression of microalbuminuria. Although it may be worthwhile to investigate the progression of microalbuminuria in relatively young subjects with NIDDM, who would be expected to live long enough to show the outcome of microalbuminuria perhaps by minimizing the influence of age-related

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

cardiovascular diseases, the mean age of such subjects studied is in the late 50s. In this chapter, we will summarize the data obtained in such patients with NIDDM.

1. MICROALBUMINURIA IN SUBJECTS WITH NIDDM

Cross-sectional studies show a prevalence of microalbuminuria of about 20-30% in non-proteinuric subjects with NIDDM [4-6]. Data on prevalence may vary with sex, age, ethnic origin, and duration of diabetes, as well as study design [7-9]. However, some subjects with NIDDM have microalbuminuria when the diabetes is diagnosed, and there is uncertainty as to the time of disease onset [10]. The clinical characteristics of such patients resemble those of patients with IDDM with microalbuminuria. The prevalence of advanced retinopathy and neuropathy is increased and the systolic blood pressure is elevated within the range of normal [4]. A significant association between the microalbuminuria with retinopathy and neuropathy in IDDM and NIDDM has been reported [6]. These findings suggest that the stage of microalbuminuria in NIDDM may represent a period of transition between the normoalbuminuric and the macroalbuminuric stage as previously described for patients with IDDM [11]. A longitudinal cohort study in a large group of subjects with NIDDM may clarify this issue.

2. PROGRESSION OF NORMOALBUMINURIA TO MICROALBUMINURIA

Only limited data are available concerning the progression from normoalbuminuria to microalbuminuria in patients with NIDDM. A report by Cooper et al. [12] from Melbourne showed that 9 subjects who were initially normoalbuminuric developed microalbuminuria over a mean period of 7 years. The total number of subjects who were initially normoalbuminuric was not well defined, however [12]. The longitudinal study by Haneda et al. [13] from Otsu also suggested that a substantial number of cases of normoalbuminuria develop microalbuminuria. In this study, 11 of the 34 initially normoalbuminuric subjects (32.4%) developed microalbuminuria within 5 years [13]. Since a previous study concerning 3 years of observation showed the rate of disease progression to be 19.5% [14], the rate of progression would be about 6.5% per year.

3. PROGRESSION OF MICROALBUMINURIA TO MACROALBUMINURIA

As mentioned, Mogensen showed the rate of progression from microalbuminuria to macroalbuminuria or to clinical proteinuria to be 22% in a 9-year period [3]. In the study by Haneda et al. [13], the rate of progression was faster, with 6 of the 18 initially microalbuminuric subjects (33.3%) becoming macroalbuminuria within 5 years [13]. The difference in the rates with disease progression between these two studies may be attributed to a difference in the age of the subjects studied. The

Table 10-1. Risk factors for progression of microalbuminuria in patients with NIDDM.

A. Strong association:
1. Poor glycemic control
2. High blood pressure
3. High rate of urinary albumin excretion
B. Possible association:
1. High plasma level of atrial natriuretic peptide
2. Renal endothelial dysfunction
3. High plasma level of prorenin
4. Abnormal lipid metabolism

higher mortality rate in Mogensen's study (59/76, 78%) vs. that in Haneda's study (4/18, 22%) could also be attributed to age differences. Although the exact rate of progression is not known, macroalbuminuria may develop earlier in patients with NIDDM than in those with IDDM after the diabetes is diagnosed [6]. The Melbourne study (Cooper et al. [12]) also observed a progression of microalbuminuria to macroalbuminuria, although the patients' ages and the precise rate were not described [12]. The estimate of the rate of progression of diabetic nephropathy in NIDDM can be inaccurate due to the high mortality rate in these patients. For example, in one study of 503 patients with NIDDM with normoalbuminuria as well as microalbuminuria [5], 265 of those patients died during the 10-year period of follow-up. Thus, that report could not accurately determine the rate of progression of microalbuminuria to macroalbuminuria, although the incidence of deaths due to uraemia was only 3%.

4. RISK FACTORS FOR PROGRESSION OF MICROALBUMINURIA

Results indicate that diabetic nephropathy in patients with NIDDM may progress from normoalbuminuria to microalbuminuria, and thence to macroalbuminuria. These stepwise progression may be influenced by the risk factors listed in table 10-1.

Hyperglycaemia, or the poor glycaemic control, probably accelerates the progression of diabetic nephropathy in both NIDDM and IDDM patients [15]. In the study by Haneda et al. [13], the normoalbuminuric NIDDM patients with poor glycaemic controls, who were evaluated by the mean glycated haemoglobin value, showed a significant increase in microalbuminuria compared with patients with better glycaemic control (table 10-2) [13]. In contrast, there was no significant difference in glycated haemoglobin values in the study by Cooper et al. [12] between the group showing progression (normo- to micro- or micro- to macroalbuminuria) and the group without progression. Since both studies were hospital-based, and evaluated a

Table 10-2. Mean values of hemoglobin A_1 (Hb A_1) and the mean blood pressure (MBP) in the first 3 years of the follow-up and the incidence of microalbuminuria (Reproduced with permission from J Diab Compl and Elsevier [13]).

Parameter		Incidence of micro-albuminuria	
Hb A_1	<9.5%	4/22 (18.2%)	
	>9.5%	7/12 (58.3%)	$p<0.05$
MBP	<95 mmHg	4/21 (19.0%)	
	>95 mmHg	7/13 (53.8%)	$p<0.05$

small number of selected NIDDM subjects, no definite conclusion on the role of hyperglycaemia as a factor leading to disease progression can be drawn. However, a population-based study by Ballard et al. [16] in Minnesota found hyperglycaemia to be a strong risk factor for the development of proteinuria in subjects with NIDDM. The stage of microalbuminuria was not evaluated in that study, however [16].

High blood pressure is another possible risk factor for the progression of microalbuminuria. A strong association between albuminuria and hypertension is typically reported [6,7], with only a few contradictory reports [17]. However, the influence of elevated blood pressure on the development of nephropathy in patients with NIDDM is not well documented. According to the 5-year follow-up study conducted by Haneda et al. [13], the development of microalbuminuria in NIDDM subjects who initially had normoalbuminuria increased significantly in the group having a mean blood pressure exceeding 95 mmHg during the first three years of observation (table 10-2) [13].

Similar results were obtained by Knowler et al. [18] in a study of the Pima Indians. That study supported the predictive power of the blood pressure that was determined before the onset of diabetes for the subsequent development of microalbuminuria [18]. Elevated blood pressure is also associated with the development of proteinuria in subjects with NIDDM [19,20]. Thus, hypertension or an elevated blood pressure may accelerate the progression of diabetic nephropathy at any stage of the disease. In addition to hypertension, a genetic predisposition to hypertension is thought to increase the risk of diabetic nephropathy in patients with IDDM [21,22]. However, such an association has not been observed in patients with NIDDM [23,24], although a genetic background may influence the development of diabetic nephropathy in such patients [25].

A high rate of urinary albumin excretion within the microalbuminuric range may predict an increased rate of progression rate of nephropathy in patients with NIDDM [13] as well as patients with IDDM [26]. The study by Haneda et al. [13] suggests

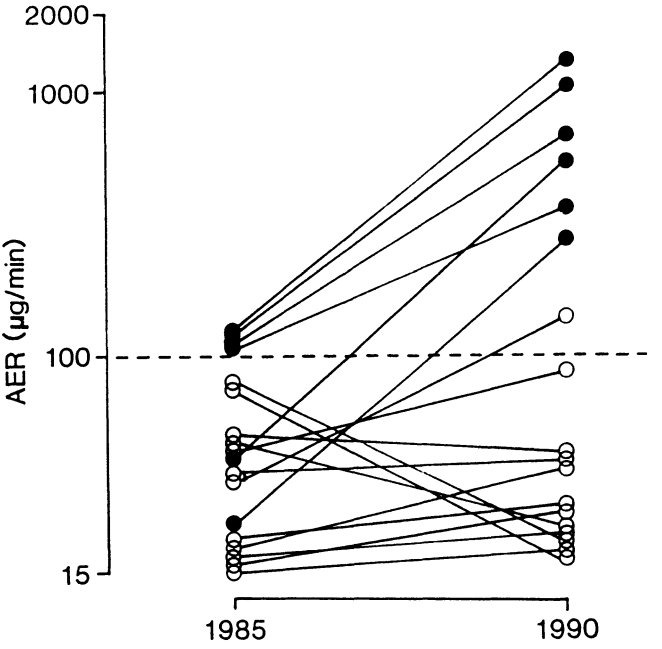

Figure 10-1. Urinary albumin excretion rates (AER) in patients who remained microalbuminuric (open circle, n=12) and in those who progressed to overt proteinuria (closed circle, n=6). (Reproduced with permission from J Diab Compl and Elsevier [13]).

that subjects with an albumin excretion rate (AER) exceeding 100 µg/min constitute a high risk group for overt nephropathy (figure 10-1).

Various other factors are thought to increase the risk of progression of microalbuminuria. For example, an increased level of plasma atrial natriuretic peptide (ANP) may influence the development of microalbuminuria, even in subjects with NIDDM [27]. A dysfunction of renal endothelial cells measured by the plasma level of von Willebrand Factor [28], and the elevation of the plasma levels of factor Xla-α_1-antitrypsin complex levels [29] may be involved. An elevation of plasma prorenin level has also been associated with an increase in albuminuria in both NIDDM and IDDM patients [6]. Abnormal lipid metabolism may be another risk factor. At this time, we lack longitudinal studies to evaluate the specific roles of these factors in predicting the likelihood of progression of microalbuminuria.

In conclusion, patients with NIDDM with poor glycaemic control, elevated blood pressure, and higher rates of urinary albumin excretion are at high risk for

progression of diabetic nephropathy. The role of other possible factors such as a genetic predisposition to hypertension, plasma prorenin levels and others remains to be confirmed. Additional studies are needed to clarify the specific risk factors for predicting the progression of diabetic nephropathy in patients with NIDDM.

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11. THE CLINICAL COURSE OF RENAL DISEASE IN CAUCASIAN NIDDM-PATIENTS

SØREN NIELSEN and ANITA SCHMITZ

Diabetic nephropathy is now the most prevalent cause of end-stage renal disease (ESRD) in the western world [1], accounting for approximately 30% of all patients entering end-stage renal failure programmes [2]. Albeit diabetes is the single most important cause of ESRD in the United States [3], the percentage of patients with diabetes requiring renal replacement therapy in the European population is somewhat lower [4], about 13%, leaving glomerulonephritis and renal vascular disease due to hypertension as the most frequent causes of ESRD [5]. Approximately one-half of the diabetes related ESRD occur in NIDDM patients [6,7].

Clinical monitoring of diabetic nephropathy primarily include consecutive determinations of the glomerular filtration rate (GFR), and in addition repeated measurements of the urinary albumin excretion rate (UAE) during 24 hours or in timed overnight collections should be implemented [8]. Even a minor abnormality, microalbuminuria, with UAE in the range of 20-200 $\mu g \cdot min^{-1}$ (i.e. dipstick-negative albuminuria), predicts an increased incidence of overt diabetic nephropathy [9] and cardiovascular mortality [9-11], and studies in the Pima Indians have clearly

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documented, that diabetic proteinuria (i.e. UAE > 200 $\mu g \cdot min^{-1}$) is associated with a poor prognosis in terms of survival [12].

For many years measurement of the plasma clearance of an intravenously injected, single-dose of ^{51}Cr-EDTA has been considered a reliable and reproducible method for routine determination of GFR, and superior to assessment of the endogenous creatinine clearance [13,14]. The coefficient of variation (CV) in an unselected group of patients with various renal disorders is 4.1% in patients with GFR $\geq$ 30 $ml \cdot min^{-1}$ and 11.6% in patients with a GFR < 30 $ml \cdot min^{-1}$ [14]. The reproducibility of GFR determinations in diabetic patients has recently been evaluated, showing a CV of the single-shot ^{51}Cr-EDTA procedure very much like that seen in the afore mentioned patients and similar to the constant ^{125}I-iothalamate infusion technique [15].

1. NEWLY DIAGNOSED NIDDM

Recent studies in caucasians have shown, that GFR is elevated 10-20% in newly diagnosed NIDDM patients [16,17]. Moreover, increases in renal plasma flow (RPF) [16] and kidney volume [17] were observed. By comparison to an age matched control group Vora et al. showed, that 45% exhibited a GFR above the mean + 2 SD (= 120 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) of the control subjects. Frank hyperfiltration (GFR > 140 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) was not observed by Schmitz et al. [17] in contrast to 16% in the study by Vora [16].

In a population based study [18] one hour creatinine clearance was not increased in 81 subjects with fasting hyperglycaemia (i.e. previously undiagnosed diabetes) as compared to healthy sex and age matched control subjects.

In other ethnic groups limited hyperfiltration has been described in Pima indians [19], whereas more pronounced increases in GFR has been found in Black Americans [20].

2. IMPACT OF INITIAL METABOLIC TREATMENT

A few years ago Schmitz et al. demonstrated that, improvement of glycaemic control during a 3 months period in 10 newly diagnosed NIDDM patients (mean(SD) age 59(5) years) reduced both GFR and kidney volume to normal values [17]. A concomitant decline in UAE, which correlated positively to the fall rate in GFR, was also seen. Recently, Vora et al. [21] investigated renal haemodynamics before and after 6 months of antidiabetic treatment in 76 newly presenting NIDDM patients with a mean(SD) age of 54(10) years. GFR and albuminuria declined significantly during treatment, whereas mean values of RPF and filtration fraction were stable. The fall rate in GFR was significantly, but not very precisely, correlated to reductions in HbA_{1c} and RPF, but not to changes in albuminuria, blood pressure or

lipids. Furthermore, the decline in GFR was more pronounced in younger patients with GFR levels above 120 ml • min^{-1} • 1.73 m^{-2} before treatment. Still, despite clear reductions during 6 months, GFR remained greater than 120 ml • min^{-1} • 1.73 m^{-2} in a considerable number (32%) of patients as compared to pretreatment level (45%).

3. ESTABLISHED NIDDM

Cross-sectional studies in caucasian patients with established NIDDM show, that GFR is well preserved in patients with uncomplicated NIDDM [22] as well as in microalbuminuric patients [23] (table 11-1). Glomerular hyperfiltration (i.e. GFR > mean+2 SD of a control group) has not been a consistent finding [18,22-24], but a few studies, including studies in other ethnic groups, have described high levels of GFR, in some of the patients (≈20%), especially in those with the shortest known diabetes duration [19,20,25].

4. LONGITUDINAL STUDIES

Two new prospective studies have evaluated the rate of decline in kidney function using the single shot ^{51}Cr-EDTA plasma clearance in NIDDM patients with different levels of albuminuria [26,27]. These studies merely describe the clinical course of renal involvement, not the natural history of diabetic nephropathy, since any drug therapy (e.g. antihypertensive therapy), which may influence renal function and albuminuria was continued (and adjusted) during the studies.

Normo- and microalbuminuria

A recent longitudinal study has confirmed, that NIDDM patients with normo- and microalbuminuria preserve intact renal function. During a 3.4 year follow-up of 37 patients (mean(SD) age 63(5) years, known diabetes duration 7(5) years) Nielsen et al. [26] found, that the average rate of decline in GFR in both normo- and microalbuminuric patients was similar to that reported in healthy, non-diabetic individuals (≈-1.0 ml • min^{-1} • 1.73 m^{-2}) [28]. However, the change in GFR varied considerably between individuals: from -13.5 to +4.3 (normoalbuminuria) and from -7.0 to +4.2 ml • min^{-1} • 1.73 m^{-2} per year (microalbuminuria). Univariate and multiple linear regression analysis revealed, that the fall rate of GFR was significantly related to the systolic blood pressure at baseline (figure 11-1), as well as the mean systolic blood pressure during the study. Moreover, this relation was maintained when the analysis was confined to the subgroup of patients (73%) without antihypertensive treatment. Conversely, the fall rate of GFR was not related to the level of albuminuria, metabolic parameters, or baseline GFR [26]. Plasma prorenin was not in our NIDDM patients found associated to microalbuminuria, nor did this parameter predicts progression (unpublished data).

Table 11-1. Glycaemic control, risk factors and kidney function in normo- and microalbuminuric NIDDM patients

	Normoalbuminuria	Microalbuminuria
Sex (male/female)	14/5	14/5
Age (years)	64±4.5	64.5±4.2
Diabetes duration (years)	7.3±5.6	8.4±6.8
Body mass index ($kg \cdot m^{-2}$)	27.1±3.2	28.2±3.7
Fasting p-glucose ($mmol \cdot l^{-1}$)	8.5±2.5	9.1±2.7
HbA_{1c} (%)	7.7±1.5	7.7±1.3
UAE ($\mu g \cdot min^{-1}$)	7.0×/÷1.6	61.7×/÷2.3
GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	94±13	91±20
Kidney volume ($ml \cdot 1.73\ m^{-2}$)	220±45	260±54*
Systolic blood pressure (mmHg)	154±17	164±22
Diastolic blood pressure (mmHg)	81±11	86±11
Retinopathy (N/B/P)	16/3/0	9/8/2*
Antidiabetic treatment (diet/oha)	6/13	4/15
Antihypertensive treatment (%)	21	37
Smokers/non-smokers	7/12	12/7

*$p < 0.05$
Values are: UAE: geometric mean ×/÷ antilog SD. Other: mean±SD or numbers.
Data obtained from reference 23.

A relation between the decline in renal function (estimated as the reciprocal creatinine level) and systolic blood pressure has also been noted in an Israeli study of somewhat younger (age 42(2) years, known diabetes duration<2 years), normotensive patients followed for 14 years [29].

Diabetic nephropathy

The clinical course of renal function in NIDDM patients with proteinuria has recently been evaluated by Gall and coworkers [27] in a 5.2 (range: 1.0-7.0) years

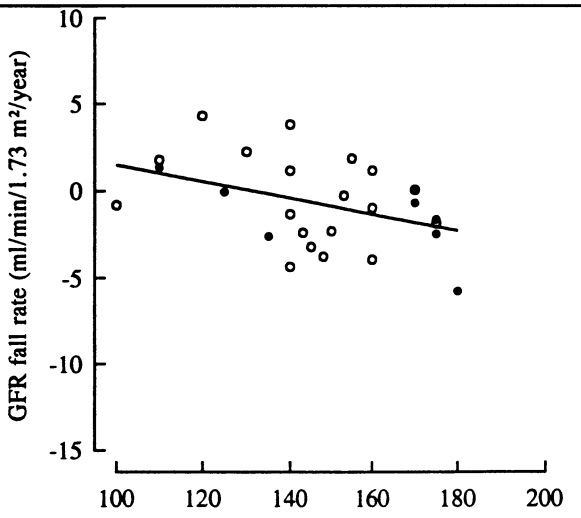

Figure 11-1.

prospective study of 26 patients (mean(SE) age 52(2) years, known diabetes duration 9(1) years), in whom a kidney biopsy showed diabetic glomerulosclerosis. An average of 7 (range: 3-10) GFR measurements were conducted in each patient. GFR decreased from 83 (range 24-146) to 58 (2-145) ml • min^{-1} • 1.73 m^{-2}, with a mean reduction of 5.7 ml • min^{-1} • 1.73 m^{-2} per year. Again, considerable interindividual variations were found, ranging from a decrease of 22.0 to an increase of 3.5 ml • min^{-1} • 1.73 m^{-2} per year. A concomitant increase in albuminuria from (geometric mean (range)) 1.2 (0.3-7.2) to 2.3 (0.4-8.0) g/24 h ($p < 0.001$) together with the mean systolic blood pressure, the mean blood pressure and baseline GFR correlated significantly to the rate of decline in GFR in a univariate analysis. No correlations were demonstrated between the fall rate of GFR and the mean dietary protein intake, mean total cholesterol, mean HDL-cholesterol or mean HbA_{1c} concentrations during the follow-up period. Stepwise multiple linear regression analysis revealed that the mean systolic blood pressure during the study was the only factor that significantly determined the rate of decline in kidney function. Although the blood pressure remained unaltered throughout the study (162/93 at entry versus 161/89 mmHg at exit) the prevalence of arterial hypertension was quite high as judged from the substantial number of patients requiring antihypertensive medication (62% at entry versus 81% at exit). The overall mortality was 27%. Three patients

died from uraemia and 4 patients from cardiovascular diseases. Two patients needed renal replacement therapy at the end of the study.

A few other studies have indicated, that high systolic blood pressure may be a major contributor to the progression of decline in kidney function. Baba et al. found, that the fall rate in GFR correlated to systolic blood pressure in proteinuric NIDDM patients with uncontrolled hypertension [30], and Stornello and coworkers reported that normotensive NIDDM patients with persistent proteinuria treated with placebo (or low dose Enalapril) during 12 months had stable GFR [31].

Thus, elevated systolic blood pressure is consistently posed as the most important factor promoting future decline in GFR in NIDDM patients. However, it is also clear, that the decline in renal function is negligible in patients with a systolic blood pressure below 150 mmHg [26] or a mean blood pressure about 95 mmHg in younger subjects [29]. Even in patients with systolic blood pressures above 150 mmHg the decline in GFR is quite slow, and end-stage renal failure may not be involved in the long-term prognosis of these patients. In patients with overt proteinuria, however, deterioration in kidney function is obviously accelerated in some patients and related to the systolic blood pressure [27].

5. INTERVENTION STUDIES

The list of abnormalities associated with NIDDM and abnormal albuminuria (e.g. obesity, sedentary lifestyle, hypertension, dyslipidaemia, haemostatic abnormalities and insulin resistance) [32-34] opens a wide spectrum of options for intervention studies focusing on the rate of progression of diabetic nephropathy.

Metabolic control

There are no long-term intervention studies of optimized metabolic control in patients with long-standing NIDDM. The large-scale UK prospective study (presently in progress) will probably enlighten our knowledge on the effects of differentiated levels of glycaemic control on long-term complication risk (retinopathy, nephropathy, neuropathy, cardiovascular diseases, etc). The study does, however, not measure GFR, and levels of albuminuria are based on concentration measurements rather than excretion rates.

Non-pharmacological intervention

Currently, the influence of non-pharmacological intervention (diets, regular exercise or weight loss) on renal function in NIDDM patients have not been reported.

Studies evaluating the renal effects of different pharmacological treatments are sparse, mainly short-term, uncontrolled, and inconsistent in terms of the methods used for estimation of GFR.

Antihypertensive drugs

In an Australian study [35] of a mixed group of diabetic patients (62% NIDDM) with microalbuminuria, treatment with either an ACE-inhibitor or a calcium channel antagonist for 12 months significantly lowered UAE. This effect was predominantly seen in hypertensive patients (who also exhibited the greatest blood pressure reduction). In the same study, patients with GFR above 135 ml • min^{-1} • 1.73 m^{-2} at baseline showed a significant decrease in GFR (from 186 to 161 ml • min^{-1} • 1.73 m^{-2}), while patients with lower baseline levels displayed rather stable GFR values (from 96 to 92 ml • min^{-1} • 1.73 m^{-2}). Similarly, in an uncontrolled, long-term (36 months) study of 10 hypertensive NIDDM patients with microalbuminuria, using the single shot ^{51}Cr-EDTA procedure, treatment with Indapamide significantly reduced blood pressure from 180/100 to 140/85 mmHg and albuminuria from (mean(SEM)) 81.5(1)/24 h to 29.0(4.5)/24 h, whereas GFR was unaffected by treatment $\approx$95 ml • min^{-1} • 1.73 m^{-2} [36]. Essentially, the same results have been described by others [37] and in a number of short-term studies (6-12 months) comparing antihypertensive drugs in hypertensive NIDDM patients with proteinuria [38-40]. Additionally, low dose administration of ß-blockers or ACE-inhibitors to normotensive NIDDM patients with persistent proteinuria for 6-12 months also reduces albuminuria without affecting systemic blood pressure or GFR [31,41]. Reductions in albuminuria, without affection of renal function, following antihypertensive treatment seems a rather early feature, as significant decreases have been demonstrated after no more than 4 weeks of therapy [42].

Very recently, Ravid and colleagues [43] conducted a randomized, double-blind, placebo controlled trial, in which they demonstrated, that treatment of normotensive, microalbuminuric NIDDM patients (mean age 45 years, diabetes duration around 7 years) with an ACE-inhibitor (Enalapril 10 mg per day) for five years exerted a stabilizing effect on albuminuria and kidney function (estimated by reciprocal creatinine level), while a progression was observed in the placebo group. Forty-nine patients received Enalapril and 45 took placebo. A concurrent, significant rise in mean blood pressure was noted only among the placebo treated patients, again stressing the importance of blood pressure in the progression of renal disease in NIDDM.

Lipid lowering agents

In 1982 Moorhead and colleagues hypothesised, that chronic progressive kidney disease may be mediated through abnormalities in lipid metabolism [44], and a number of animal studies supporting this concept have been carried out. NIDDM patients generally present abnormalities of lipoprotein metabolism [45] and these abnormalities seem to progress more readily in patients with abnormal albuminuria

[46]. So far, however, the literature on long-term clinical intervention trials in NIDDM patients is strikingly scarce. In a study by Nielsen et al. [47] 18 patients (mean(SD) age 65(4) years) with long-standing NIDDM (mean(SD) known diabetes duration 10.6(6) years), moderate hypercholesterolaemia and microalbuminuria were enroled in a randomized, double-blind, placebo controlled study assessing the effects of a HMG-CoA-reductase inhibitor (simvastatin 10-20 mg per day for 36 weeks) on kidney function and microalbuminuria. During treatment the mean total cholesterol level was significantly reduced by simvastatin (from 6.7(0.7) to 5.1(0.5) mmol • l^{-1}). Compared to placebo, however, this marked improvement in the hyperlipidaemia did not influence the GFR (single shot ^{51}Cr-EDTA procedure), the degree of microalbuminuria or the systemic blood pressure.

Presently, studies evaluating the renal effects of intervention against haemostatic parameters and insulin resistance are not available.

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12. VON WILLEBRAND FACTOR AND THE DEVELOPMENT OF RENAL AND VASCULAR COMPLICATIONS IN DIABETES

COEN D.A. STEHOUWER

Both in IDDM [1-4] and in NIDDM [5-10], the presence of microalbuminuria or clinical proteinuria identifies a group of patients at very high risk of developing severe vascular complications, ie, proliferative retinopathy, renal insufficiency, and cardiovascular disease. Several hypotheses have been advanced to explain why an increased urinary albumin excretion rate should be associated with an excess of *extrarenal* complications [1,11-13]. This chapter will discuss the role of *von Willebrand factor* (vWF), a haemostatic glycoprotein synthesised by endothelial cells and megakaryocytes.

It has long been known that the plasma vWF level is often elevated in diabetes [reviewed in refs. 13 and 14]. Recent studies have shown such elevated plasma levels to be closely related to an elevated urinary albumin excretion rate [10,15-18] and cardiovascular disease [10], but not to the diabetic state *per se*, nor to early retinopathy [13,15,19].

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This brief review will focus on the significance of the association of elevated vWF levels with microalbuminuria [10,15,16,18], and discuss the implications for clinical research and practice.

1. WHAT IS VON WILLEBRAND FACTOR?

vWF has a key role in platelet adhesion, thrombus formation and coagulation. It facilitates platelet adhesion to the subendothelium by binding to the subendothelial matrix and to platelet glycoprotein Ib; this process exposes glycoprotein IIb-IIIa at the platelet surface, which in turn enhances platelet adhesion and promotes aggregation. In addition, vWF binds and stabilises factor VIII, thus protecting this crucial coagulation cofactor from inactivation. vWF is a polymer of variable molecular weight (MW, 0.5-20 mDa), which consists of a series of dimer subunits (MW $\approx$ 260 kDa). It is secreted by endothelial cells, both constitutively and, under certain circumstances, acutely, the latter by release from a storage compartment, the so-called Weibel-Palade bodies. In addition, it is released from platelet α-granules during platelet aggregation [20,21]. Normal plasma values, measured by electroimmunopheresis or ELISA, are 50-150% (0.5-1.5 U/ml).

2. HIGH PLASMA vWF: MARKER OF ENDOTHELIAL INJURY

Injury to endothelial cells is associated with increased secretion of vWF, both *in vitro* and *in vivo* [reviewed in ref. 13]. Thus plasma levels are elevated in vasculitis [22] and atherosclerosis [23]. By analogy, high vWF levels in diabetic patients with microalbuminuria probably reflect endothelial injury. This contention is supported by the fact that microalbuminuria is also associated with other markers of vascular or endothelial damage. Thus, in IDDM, microalbuminuria is accompanied by increased plasma concentration of angiotensin-converting enzyme, plasminogen activator inhibitor-1 (PAI-1) and fibronectin, a high urinary excretion of type IV collagen fragments, and increased transcapillary escape rate of albumin [1,13]. In NIDDM, microalbuminuria has been shown to be related to elevated levels of plasma fibronectin, thrombomodulin, tissue plasminogen activator, PAI-1 and serum type IV collagen [13,18]. Studied in isolation, these markers are not specific for *endothelial* injury. But their clustering points to the endothelium as the most likely common source. Similarly, it cannot be entirely excluded that platelet activation and/or decreased vWF clearance, rather than increased endothelial secretion, contribute to high vWF levels. But direct evidence to support these possibilities is lacking, whereas the indirect evidence cited above is consistent with the endothelium as the origin of elevated plasma vWF.

3. ENDOTHELIAL INJURY: CAUSE OF DYSFUNCTION

The close linkage between microalbuminuria and endothelial injury in diabetes is an attractive explanation for the fact that microalbuminuria seems to be a risk marker for atherosclerotic cardiovascular disease, because endothelial *injury*, which leads to endothelial *dysfunction*, is a central feature of current models of atherogenesis [24]. Furthermore, endothelial dysfunction may be important in the pathogenesis of albuminuria [25,26]. How does such dysfunction become manifest in diabetes?

The vascular endothelium has extensive regulatory capacities. First, it controls vascular permeability to macromolecules by modulating the biochemical and biophysical properties of the extracellular matrix. Second, it affects vascular smooth muscle and renal mesangial cell function by producing mediators such as nitric oxide and endothelin. Endothelin, a 21-amino acid polypeptide, stimulates contraction and proliferation of smooth muscle and mesangial cells; nitric oxide has opposite effects [27]. Third, endothelial cells normally inhibit platelet adhesion and aggregation by producing prostacyclin and nitric oxide [27], limit activation of the coagulation cascade by the thrombomodulin-protein C and the heparan sulphate-antithrombin III pathways [28], and regulate fibrinolysis by producing tissue plasminogen activator and its inhibitor, PAI-1.

Endothelial injury alters these functions. The extent to which this occurs depends on the nature of the injury and on the intrinsic properties of the endothelium. In diabetes, the proximate causes of endothelial injury are not known but are likely to include hyperglycaemia, advanced glycosylation products, and the components of the insulin resistance syndrome (see 4.). Differences in the intrinsic vulnerability of the endothelium probably contribute to the variation in susceptibility to these factors that is clinically apparent.

Endothelial dysfunction in human diabetes takes various forms. First, it contributes to basement membrane thickening; high levels of plasma fibronectin and serum or urine type IV collagen may be markers of this process. Second, vascular permeability is increased. In IDDM, this may be specifically due to loss of heparan sulphate proteoglycan, which may explain the increased transcapillary escape rate of albumin in microalbuminuric patients [1]. Third, vascular smooth muscle cell contraction is enhanced, predisposing to the development of hypertension [27]. Fourth, platelet adhesion and aggregation are no longer inhibited but may actually be stimulated through increased vWF secretion. Fifth, the endothelium loses its anticoagulant and profibrinolytic nature, and may instead acquire procoagulatory and antifibrinolytic properties [28], a transition marked by high plasma levels of thrombomodulin and PAI-1.

From the foregoing it is clear that endothelial dysfunction is *not* a discrete entity, nor does a gold standard exist. Endothelial dysfunction, in its various

manifestations, is closely linked to an increased urinary albumin excretion rate. Disturbances in endothelial functions are involved in the pathogenesis of both microalbuminuria and cardiovascular disease, and may thus explain their association. High plasma vWF levels represent one particular type of endothelial dysfunction. Importantly, such dysfunction has been shown to precede and predict the development of microalbuminuria in NIDDM [10], a finding supported by cross-sectional studies showing abnormal endothelium-dependent vasodilatation [29] and decreased fibrinolytic potential [30] in patients with *normal* urinary albumin excretion. Whether endothelial dysfunction also precedes microalbuminuria in IDDM is not clear [16,19,31,32]. It is also unclear whether the prognostic value of vWF [10,33] is due to its specific functions, ie, enhancement of platelet adhesion and factor VIII availability [16,34], or to the fact that it tends to parallel other types of endothelial dysfunction [13].

4. WHAT CAUSES ELEVATED vWF LEVELS IN DIABETES?

Insulin-dependent diabetes mellitus

Poor glycaemic control is associated with high vWF levels [13,16], but the relation is relatively weak. This is consistent with current thinking on the pathogenesis of nephropathy, which postulates that hyperglycaemia is necessary but not sufficient to cause severe microangiopathy [1,11]. Elevated levels of vWF have been shown to be related to increases in growth hormone [35], fibrin generation [36], and blood pressure [19]; endothelial dysfunction, in turn, may enhance fibrin formation [28] and increase peripheral vascular resistance [27], thus creating the potential for vicious cycles of increasing vascular damage. Except for hypertension, the importance of these factors in the initiation and progression of diabetic complications has not been definitely established [1,11,13], but these data [35,36] certainly suggest that the effects of growth hormone and fibrin on the endothelium need further study in the context of diabetic micro- and macroangiopathy.

Non-insulin-dependent diabetes mellitus

In NIDDM, the causes of high vWF levels, or of other types of endothelial dysfunction, have not been elucidated. The most likely candidates are hyperglycaemia, hyperinsulinaemia, hypertension and dyslipidaemia, ie, the chief components of the insulin resistance syndrome [12].

Although glucose is clearly toxic to cultured human endothelial cells [37], the relationship between measures of hyperglycaemia and cardiovascular disease incidence in NIDDM is not particularly strong, nor is the relationship with vWF [10]. Possible explanations include unknown protective factors in human endothelium *in vivo* or an overriding influence of other components of the insulin resistance

syndrome. Moreover, it may be the *interplay* among the components of the insulin resistance syndrome which may prove crucial.

The effects of hyperinsulinaemia on endothelial function have not yet been extensively studied. Endothelial cells do have insulin receptors; insulin can increase endothelial production of endothelin [38], a potent vasoconstrictor and mitogen. Endothelin may be involved in atherogenesis [39] and the progression of renal disease [40]. Plasma levels of endothelin have been reported to be elevated in NIDDM [41]. Hyperinsulinaemia may, in addition, increase plasma levels of PAI-1, which inhibits fibrinolysis and facilitates the persistence of fibrin, which can damage the endothelium [30]. Recent data indicate that hyperinsulinaemia is also related to high vWF levels [42].

Similarly, data on the relationship between hypertension or dyslipidaemia and endothelial dysfunction in NIDDM are scarce. In our cohort study, blood pressure and lipid levels were not strongly related to vWF levels [10]. Lipid levels did not predict the development of increases in urinary albumin excretion either [10,43]; rather, serum HDL-cholesterol levels, by unknown mechanisms, seem to decrease *after* microalbuminuria develops [10,43]. Microalbuminuria may be associated with a slightly increased blood pressure [7,10,44], but whether this is the cause of microalbuminuria or the consequence of the processes underlying the development of microalbuminuria (eg, endothelial dysfunction [27]) is not clear.

5. vWF: USE IN CLINICAL RESEARCH AND PRACTICE

The data reviewed strongly suggest that plasma vWF level may be useful as an estimate of endothelial injury in diabetes, similar to its proposed use in vasculitis [22].

The development of microalbuminuria was accompanied by an increase in vWF from (median) 121 to 203% in IDDM [16], and from 116 to 219% in NIDDM [10]. The baseline level of and the change in vWF were strongly related to the development of microalbuminuria in NIDDM and explained 60% of its variance [10]. Note, however, that variable changes in vWF level, of as yet unclear prognostic significance, were also observed in patients with persistently normal urinary albumin excretion [10,16,18,19].

In IDDM and in NIDDM, decreases in urinary albumin excretion achieved by improvement of glycaemic control and/or antihypertensive therapy are often accompanied by decreases in plasma vWF [10,16, and unpublished observations]. Thus, vWF can be used to follow the effects of treatment on vascular (as opposed to renal) function. In addition, vWF may have diagnostic value in NIDDM, because microalbuminuria, in the *absence* of high vWF levels, did not confer an increased risk of cardiovascular disease when compared to patients with normal urinary

albumin excretion [10]. Stated differently, there may be two types of microalbuminuria in NIDDM: one in which vascular damage is *generalised* and the risk of cardiovascular disease is increased, and another in which pathology is limited to the kidney and the risk of cardiovascular disease is similar to that in patients with normal urinary albumin excretion. Plasma vWF level may be used to distinguish between these two types of microalbuminuria. This hypothesis, incidentally, is consistent with the finding that clinical proteinuria in NIDDM is often not due to diabetic glomerulosclerosis [45].

Several problems remain, however. First, the normal range of vWF, from 50-150%, is quite wide, suggesting that changes in vWF may be a more sensitive marker than a single value. Second, the intra-person day-to-day variability of vWF levels may be as high as 20%, although this can be reduced to about 10% by carefully standardising the blood sampling procedure [13].

6. CONCLUSION

Endothelial dysfunction is present from the earliest increase in urinary albumin excretion in diabetes [1,10,16,18] and may in fact precede it [10]. Endothelial dysfunction may explain why microalbuminuria appears to be a marker of a high risk of (extrarenal) cardiovascular disease in diabetes. Elevated and/or increasing plasma vWF levels reflect endothelial injury and dysfunction. The vWF plasma level may serve as a useful marker for the state of the vascular endothelium in trials aiming to prevent or delay progression of cardiovascular and renal disease in diabetes.

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13. SMOKING AND DIABETIC NEPHROPATHY

PETER T. SAWICKI

In 1978, Christiansen reported that cigarette smoking is a risk factor for the development of diabetic nephropathy [1]. He found a significantly higher prevalence of persistent proteinuria among patients who were or had been cigarette smokers. In a later study by Telmer et al. [2], the earlier findings were confirmed in a greater number and better characterised group of Type 1 diabetic patients. In 668 patients, the prevalence of diabetic nephropathy was significantly higher among heavy smokers (more than 10 cigarettes per day for more than 1 year) than among other patients, that is 19% vs. 12%. In addition, a higher frequency of clinical nephropathy was found with increasing cigarette consumption. Among patients who smoked a maximum of 10 cigarettes per day, about 13% had clinical diabetic nephropathy, whereas it was more than 25% among those patients who smoked 30 cigarettes per day. An association between smoking and nephropathy was also observed by Nordén and Nyberg [3]. They compared smoking habits in 47 matched pairs of Type 1 diabetic patients with and without nephropathy. Patients with nephropathy had a significantly higher smoking index than their controls. There were also more current

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smokers, more heavy smokers, and fewer individuals who had never smoked in the nephropathy group than in the control group. With respect to retinopathy, study results had been controversial [4]. It is of note, that in these early studies glycosylated haemoglobin values had not been included into the analyses as a possible confounding factor.

In a later cross-sectional case-control study the association between current cigarette smoking, macroproteinuria, and retinopathy, including glycosylated haemoglobin values has been re-examined [5]. Out of a cohort of 1254 Type 1 diabetic patients, 90 female and 102 male cigarette-smoking patients with a duration of diabetes of at least 6 years were pair-matched with non-smoking patients with respect to sex, duration of diabetes, and age. The percentages of patients with macroproteinuria or proliferative retinopathy were significantly higher in smokers than in non-smokers, although the difference with respect to proliferative retinopathy was significant only for women. On the other hand, glycosylated haemoglobin values and the percentages of patients with hypertension were comparable between smokers and non-smokers. After an average duration of diabetes of 14 years, macroproteinuria was found in 19% of the smoking and 8% of the non-smoking patients, whereas the percentages of patients with normal proteinuria or without retinopathy were comparable between the two groups. Since ex-smokers had been included in the non-smokers patient groups, the associations between smoking and nephropathy might have been underestimated. The main results of this latter study were supported by an observation by Stegmayr and Lithner [6] who found that 21 of 22 uraemic Type 1 diabetic patients were tobacco users, whereas this was the case in only 10 out of 22 well-matched non-uraemic patients selected from their diabetes outpatient clinic. An association between proteinuria and smoking has also been found among Type 1 diabetic patients who survived for 40 years or more [7].

Recent prospective studies support the concept that cigarette smoking is a relevant factor in the clinical course of diabetic nephropathy [8-17]. In a clinic-based study Chase et al. [10] evaluated the association of smoking and progression of albuminuria (borderline and abnormal, over 7.6 μg/min) in young insulin-dependent adults aged about 20 years with a diabetes duration of about 11 years and a rather low prevalence and mild degrees of nephropathy (only 3% were considered to be hypertensive). Over a follow-up period of 2 to 3.5 years the progression of albuminuria and of retinopathy was greater in smokers. Albuminuria decreased significantly when subjects ceased smoking. Smoking remained a significant factor in the logistic regression model for albuminuria when controlled for possible confounding factors, such as glycohaemoglobin levels; the odds ratio of developing a significant increase of albuminuria was 2.2 times higher for smokers.

Other studies have been confirmatory [11,12,15]. In a four-year prospective study the factors predicting albuminuria were evaluated in 172 normotensive, insulin-dependent diabetic patients without overt nephropathy [11]. Initial urinary albumin excretion and glycosylated haemoglobin were the major predictors of the level of albuminuria after four years, whereas weaker associations were found with a history of hospital admission, smoking and treatment of blood pressure. In another observational study including a cohort of 148 non-microalbuminuric, non-hypertensive insulin-dependent diabetic patients followed for four years, poor glucose control, an early rise of arterial pressure and smoking were implicated in the development of persistent microalbuminuria [15]. Ekberg et al. [9,12] reported an association between glomerular hyperfiltration and smoking in insulin-treated patients. The prevalence of hyperfiltration in smokers was 41% compared to 18% in non-smokers.

Although these data strongly suggest an association of smoking with the development and/or progression of diabetic renal damage, other explanations are possible. Thus, it could be, that smoking influences renal tubule and permeability functions independent of any specific effects on clinical propensity to nephropathy and renal insufficiency. Alternatively, smoking may not be directly related to nephropathy at all; the smoking status may merely be an indicator for particular patterns of health behaviour that are due to affect renal function detrimentally.

Some clarification of this question comes from a study by Sawicki et al. [17]. In a prospective investigation possible factors associated with the progression of diabetic nephropathy over a period of one year have been evaluated. The study included 92 Type 1 diabetic patients with long duration of diabetes, hypertension and diabetic nephropathy. All patients were under intensified insulin and antihypertensive therapy. Consequently, these patients had well controlled blood glucose and blood pressure values throughout the observation period. A progression of renal disease was defined according to the stage of nephropathy as an increase in proteinuria or serum creatinine or a decrease in glomerular filtration rate. Progression of nephropathy was found in 53% of smokers as compared to 11% of non-smokers and 33% of ex-smokers. The adjusted odds ratio for progression of nephropathy between smokers (including ex-smokers) and never-smokers was 6.7. It was concluded that smoking represents an important factor associated with progression of diabetic nephropathy in patients who are intensively treated for hypertension. There was a dose dependent increase of risk for progression of nephropathy with the number of smoked cigarettes, figure 13-1.

Further support for a direct role of smoking on the progression of nephropathy comes from observations derived from patients with lupus nephritis [13]. In a retrospective cohort study an inception cohort of 160 adults with lupus nephritis

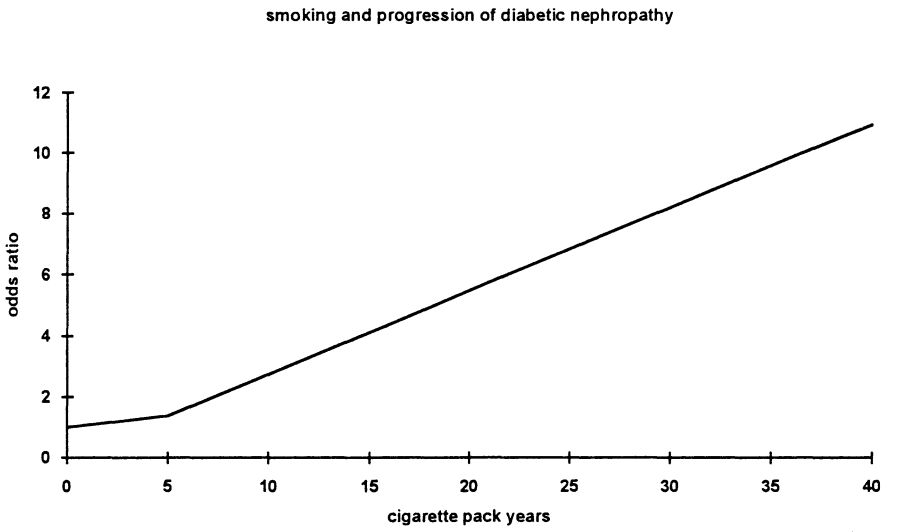

Figure 13-1. Results from logistic regression analysis [17]. Estimated odds ratios for progression of diabetic nephropathy and number of cigarette pack years.

were followed-up for a median of 6.4 years. Hypertension and smoking status at the onset of nephritis were strongly and independently associated with differences in the time to development of end-stage renal disease. The median time to end-stage renal disease was 145 months among smokers and it was longer than 273 months among non-smokers. These effects persisted in multivariable analyses adjusted for differences among patients in age, gender, socio-economic status, renal histology, and immunosuppressive treatment.

Associations between smoking and progression of proteinuria have also been found in Type 2 diabetic patients. In an analysis of the Wisconsin Study [14] including 794 Type 2 diabetic patients with an average age above 60 years, who were free of proteinuria at recruition and still alive at follow-up, the relative risk of developing gross proteinuria during a 4-year interval was 2 to 2.5 for heavy smokers (highest level of total pack-years smoked) compared to those who had never smoked. After controlling for other risk variables, the incidence of gross proteinuria was also associated with higher glycosylated haemoglobin values. It is of note, that in contrast to this prospective study, several cross-sectional analyses of the Wisconsin study had

failed to identify a consistent and strong association between smoking and diabetic late complications, including nephropathy [18,19,20]. A possible reason is selective mortality, that is, persons who developed nephropathy may have died before their examination.

Summing up these studies on smoking and nephropathy, there is increasing evidence that smoking or an unknown factor closely related to smoking has a strong impact on the development and progression of proteinuria and impairment of renal function in diabetes. Therefore, smoking status has to be taken into account in clinical studies on the course of nephropathy.

The mechanisms by which smoking increases albuminuria/proteinuria and promotes nephropathy are unknown. Interestingly, abnormality on urine analysis, including proteinuria, has also been found to be more common in male and female smokers in a population-based study, but the reasons for this finding remained unclear [21].

Smoking a cigarette induces acute haemodynamic and metabolic changes mediated through adrenergic mechanisms. The smoking associated sympathetic discharge is physiologically reflected by a transient rise of pulse rate and blood pressure [22]. In addition to sympathetic stimulation, smoking a cigarette is followed by transient increases of plasma cortisol, ACTH, and aldosterone levels in hypertensive subjects [23]. Despite these complex acute haemodynamic and hormonal effects, in epidemiological studies smoking has not been found to increase the risk of hypertension [24]. However, recent studies have revealed that by continuous monitoring of blood pressure heavy smoking is associated with sustained and substantial increases in blood pressure during the day [25,26]. The blood pressure increasing effect of smoking is short-lived, i.e. it lasts for about half an hour and can therefore be missed during the blood pressure measurement in the clinic. Comparable blood pressure measurements in diabetic patients who smoke have not been published so far. The hypothesis that smoking deters its damaging effects on the kidney via an increase in blood pressure would be in accordance with the fact that the strongest associations are consistently found between cigarette-pack years and parameters of kidney function [1,2,6,8,14,17].

Several recent large prospective cohort studies have shown that diabetic patients who smoke have an approximately two-fold increased mortality risk, and the main cause of death is cardiovascular [27-33]. Patients with overt diabetic nephropathy have an excessively increased risk of dying, the main cause of death being cardiovascular. Patients with end stage renal disease, who smoke, run a particularly high mortality risk [6,8]. In a recent study the prevalence of, and risk factors for, angiographically determined coronary artery disease in Type 1 diabetic patients with nephropathy have been analysed [34]. Coronary artery disease was diagnosed in 52

of 110 patients undergoing routine pre transplant coronary angiography. Smoking of more than 5 pack-years was a significant risk factor for coronary artery disease in this high risk patient group. In addition, higher serum nicotine levels after smoking a cigarette in subjects undergoing haemodialysis [35] may contribute to the particularly high risk of smoking in patients with end stage renal disease.

Programmes to help diabetic patients to stop smoking have been so far unsuccessful [4,36,37]. Even an extensive behaviour therapy anti-smoking intervention programme was as poorly effective as a single unstructured anti-smoking advice given by a physician [38]: Form a total of 794 smoking diabetic patients only 11% agreed to participate in a »stop smoking programme«. These patients who wanted to stop smoking were randomised either to a behaviour therapy group or to a single »physicians anti-smoking advice« group. After 6 months non-smoking was confirmed in 5% of the behaviour therapy group and 16% of the physicians advice group only.

In conclusion, cross sectional and longitudinal studies have identified smoking as an important risk factor for progression of nephropathy cardiovascular diseases and overall mortality in diabetic patients. However, smoking cessation programmes have been unsuccessful in diabetic patients and smoking still represents an important unresolved problem in the treatment of diabetic patients.

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14. LIGHT MICROSCOPY OF DIABETIC GLOMERULOPATHY: THE CLASSIC LESION

STEEN OLSEN

The history of our knowledge of the light microscopy of diabetic glomerulopathy began with the famous paper by Kimmelstiel and Wilson in 1936 [1]. With some justification, it can be said that it has been completed by the careful analysis of large series by Thomsen 1965 [2] and Ditscherlein 1969 [3], the first mentioned taking advantage of the introduction of percutaneous renal biopsies.

Histologic lesions of the renal glomerulus in diabetics were not totally unknown when Kimmelstiel and Wilson reported their findings, but the exact relationship of these alterations to the diabetic state was unclear. Kimmelstiel and Wilson were the first investigators to draw attention to the characteristic »intercapillary«, nodular thickening of mesangial regions and its association with a clinical syndrome consisting of severe proteinuria, edema, hypertension, and eventually a decrease in renal function.

The histology of diabetic glomerulopathy described here rests upon the cornerstones mentioned above as well as on other important contributions published by several authors, among them Allen [4], Bell [5-7], Fahr [8], Spühler and

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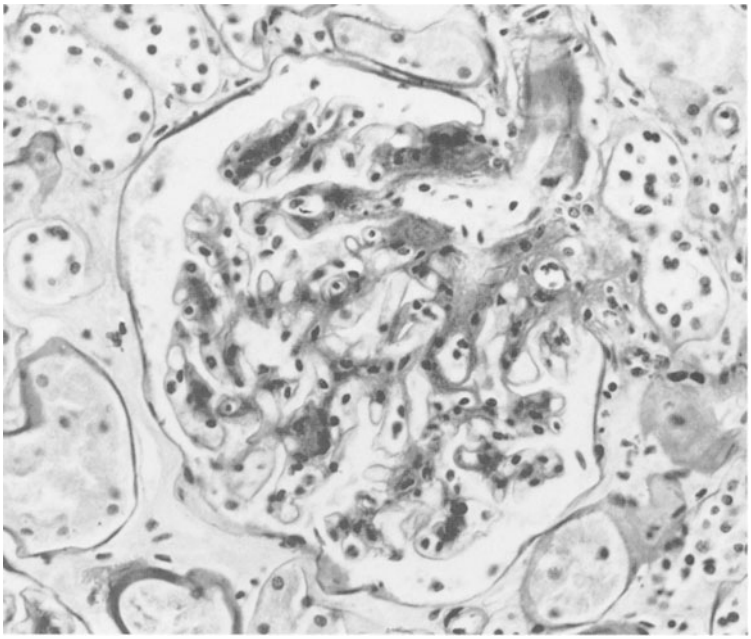

Figure 14-1. Diabetic glomerulosclerosis, diffuse type. There is slight increase of PAS-positive material in all mesangial regions, radiating from the vascular pole (*upper right*). PAS-haematoxylin.

Zollinger [9], Muirhead et al. [10], and Randerath [11]. The juxtaglomerular arterioles will be included in the discussion due to their close functional and anatomic connection with the glomerulus.

1. THE DIFFUSE LESION

This consists of a uniform widening of the mesangial regions (figure 14-1). It is particularly well exhibited in sections stained by periodic acid-Schiff (PAS) or by silver methenamine that display structures often described as finger-like radiations from the glomerular hilum.

2. THE NODULAR LESION

As the volume of the mesangial matrix increases, some mesangial regions become more prominent than others and may take on a globular shape (Figure 14-2). The mesangial nodule is thus created by a gradual increase of the diffuse lesion and the distinction between them is arbitrary. Several nodules may be present in each glomerulus, but usually only a few of the mesangial regions are affected in this way.

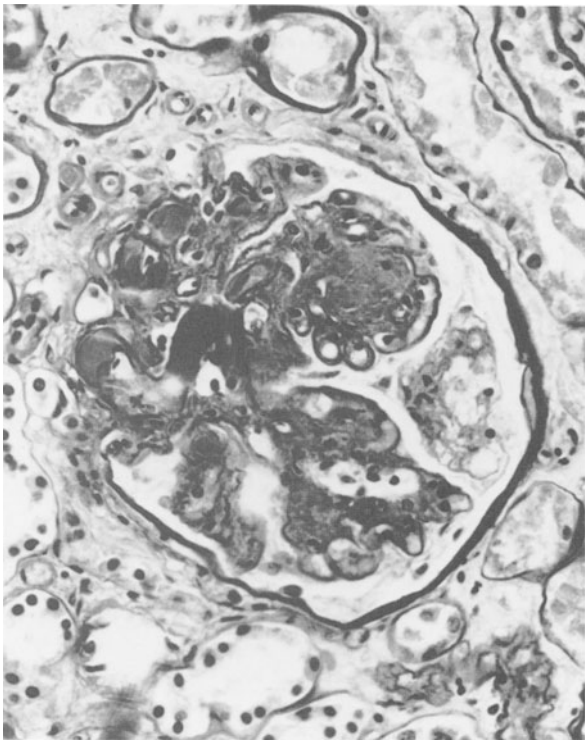

Figure 14-2. Diabetic glomerulosclerosis. The diffuse component is more marked than in figure 14-1 and a nodule has been formed from a particulary voluminous mesangial region. PAS-haematoxylin.

The nodules are distributed in a horseshoe-shaped area corresponding to the peripheral mesangium [12]. The other mesangial regions present the diffuse lesion.

Small nodules contain evenly distributed mesangial cells, but, in medium-sized or large nodules, the central areas are almost always acellular. The periphery of the nodule contains one or a few layers of mesangial cells. Around the nodule, a ring of capillaries is present and they may be dilated. It has been suggested that the formation of the nodule is preceded by focal mesangiolysis [13,14].

3. THE FIBRINOID CAP

This lesion [8,9,15,16], also called fibrin cap, is situated in the peripheral capillary wall and has a crescentic shape (figure 14-3). If the basement membrane is stained by silver methenamine, the cap appears to be situated between this and the

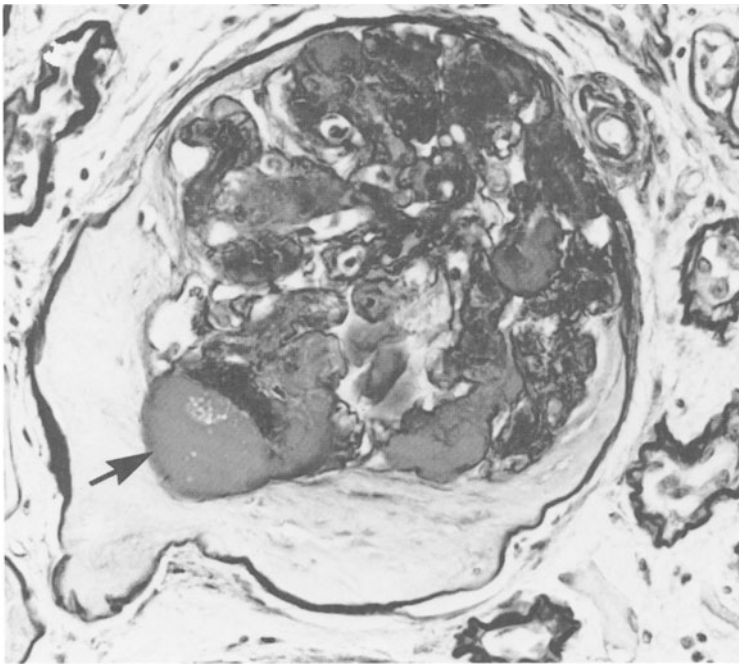

Figure 14-3. Fibrinoid cap in diabetic glomerulosclerosis. Totally obsolescent glomerulus with several fibrinoid caps, one of them indicated by an arrow. The crescent-shaped pale area to the left is subcapsular, fibrotic tissue. The PAS-positive glomerular basement membranes form a solid, retracted tuft. PAS-haematoxylin.

endothelium. Its structure is homogeneous although small vacuoles may be seen in which lipids can be demonstrated in frozen sections stained by oil-red.

4. THE CAPSULAR DROP

This lesion [1,3] is situated on the inner side of the capsule of Bowman. It sometimes looks like a drop (figure 14-4), but it may also be more extended, as a slender, fusiform deposit. Its outer border is formed by the capsule of Bowman; its inner projects toward the urinary space.

5. ARTERIOLAR HYALINOSIS

In the early stage of arteriolar hyalinosis (or hyaline arteriolosclerosis), small drops of strongly eosinophilic material accumulate in the wall of the juxtaglomerular arterioles. They may be situated in the intima or in the media. They gradually

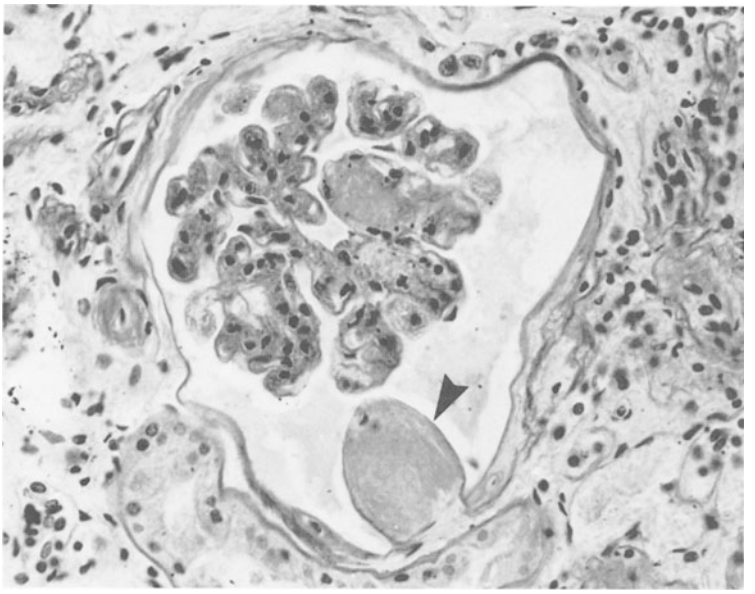

Figure 14-4. Capsular drop in diabetic glomerulosclerosis. A large, drop-shaped deposit (*arrow*). PAS-haematoxylin.

increase in size and eventually involve the whole arteriolar wall, which then appears as a strongly thickened, homogeneous structure. Arteriolar hyalinosis in diabetes involves the afferent arteriole as well as the efferent arteriole (figure 14-5).

6. STAINING CHARACTERISTICS AND HISTOCHEMISTRY

Histochemical studies have been published by several authors [10,16,17]. The most important results are presented in table 14-1. The fibrinoid cap, capsular drop, and arteriolar hyalinosis are identical in staining characteristics, which is why some authors have included them in one group called exudative lesions. Some authors use this term, however, only for fibrinoid caps.

Reports on immunofluorescence data are not unanimous. Some investigators have found immunoglobulin G (IgG), in a finely linear pattern along the capillary walls [18,19]. We found [20] that the reaction was weak and only present in some cases. The nodules were negative. Exudative lesions are positive for fibrinogen, C3, β-lipoprotein, and (weakly) for IgG [20]. Some authors have reported the presence of insulin and/or antiinsulin, detectable by immunfluorescence, but we as well as Westberg and Michael [19] could not demonstrate these proteins. The different

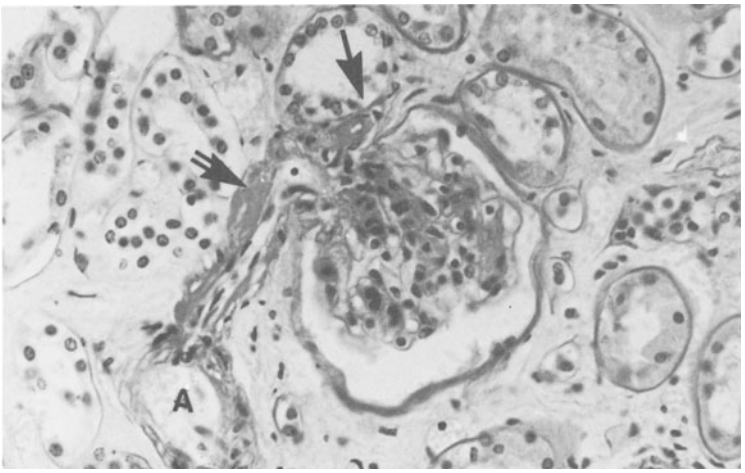

Figure 14-5. Arteriolosclerosis in diabetes. There is moderate hyaline arteriolosclerosis in both the afferent (*double arrow*) and the efferent (*arrow*) arterioles. A, interlobular artery. PAS-haematoxylin.

results may partly be due to technical differences and partly to subjective interpretations.

7. DEVELOPMENT OF THE LESIONS BY TIME

The most powerful determinant for the appearance and development of glomerular and vascular lesions in diabetes is duration of the diabetic state [2]. Diffuse glomerulopathy can be demonstrated by ultrastructural morphometry after a few years of diabetes [21], but is usually not distinct light-microscopically until 5-10 years after the onset of the disease. Nodular glomerulosclerosis demands at least 15 years of diabetes to develop. The nodules tend to disappear with marked glomerular obsolescence.

Whereas the precise onset of the diabetic disease is known in insulin dependent diabetes (IDDM) this is not the case with non-insulin dependent diabetes (NIDDM) in which the disease may have been present several years before diagnosis. This is why glomerular nodules may occasionally be seen in patients with a *known* duration of diabetes of less than 15 years, and they may even occur at the time diagnosis made. The diffuse lesion and arteriolosclerosis occur in 20% of patients before 5 years have elapsed from the apparent onset [2]. These lesions are nonspecific, and thus their presence in a patient suffering from diabetes may be unrelated to the diabetic state.

Table 14-1. Staining characteristics of diabetic glomerular lesions

Stain	Diffuse	Nodular	Exudative[a]
Haematoxylineosin	+ red	+ red	++ red
V.Gieson-Hansen	+ red	+ red	++ yellow
Masson-trichrome	++ blue	++ blue	+++ red
Phosphotungstic acid-haematoxylin	0	0	+++ deep blue
PAS after diastase	++	++	+++
Silver-methenamine	+ +black	+/- black fibrils in pale matrix	0
Alcian-blue	+	0	0
Congo red, other amyloid stains	0	0	0
Neutral fat	0	(+) occasionally	+ fat vacuoles

[a]Exudative lesions are fibrinoid caps, capsular drops, and arteriolar hyalinosis

The fibrinoid cap occurs most frequently in the later stages of glomerulopathy, but, in contradistinction to all other glomerular lesions in this disease, the capsular drop is found almost as often in earlier as in later stages [2].

A peculiar and as yet unexplained fact is that about 60% of patients with long-standing diabetes do *not* develop clinical nephropathy or diabetic glomerular changes.

8. GLOMERULAR STRUCTURE IN THE TERMINAL PHASE

The appearance of glomeruli in advanced diabetic glomerulopathy presents a broad spectrum ranging from totally occluded to almost normal glomeruli. Glomeruli, which are still open, may be hypertrophic and often present global mesangial hypercellularity. Totally occluded glomeruli are not evenly distributed, but tend to be concentrated in radiating stripes parallel to the medullary rays [22]. There is no difference in the severity of glomerular involvement between deep and superficial cortical zones. The total number of glomeruli decreases with progression of the diabetic nephropathy, at least in IDDM [23].

It is important to realize that this terminal pattern is not exclusively due to glomerular alterations specific for diabetes. Ischemic scarring and focal glomerular sclerosis occur and may indicate that causes other than progression of diabetic glomerular lesion may be partially responsible for the development of renal failure, such as vascular constriction with glomerular ischemia and lesions due to hyperfunction of remaining glomeruli. This idea is discussed in Chapter 31.

9. SPECIFICITY OF THE LESIONS

The diffuse lesion is completely nonspecific and may be present in older people without diabetes. The combination of arteriolosclerosis and the diffuse lesion often occurs in hypertension, but involvement of both the afferent arteriole and the efferent arteriole is regarded as a strong indication of diabetes [6,24,25].

The nodular lesion is often regarded as pathognomonic for diabetes. It is true that numerous reports of nodular lesions in non-diabetic patients have been published [for a list, see ref. 3]. Most of these reports can be criticized, however, either because of doubt as to absence of diabetes or to lack of application of precise criteria for the morphologic diagnosis. There are, however, well documented cases on record with typical nodular glomerulopathy without diabetes [26,27].

Although the *typical* nodular lesion is very strongly associated with diabetes, there exist nevertheless other conditions in which glomerular nodules may occur. Since these may present diagnostic difficulties, they will be briefly mentioned here. For a detailed report and illustrations, the reader is referred to an earlier publication [28].

In renal *amyloidosis*, abnormal homogeneous substance is deposited in the peripheral as well as mesangial parts of the glomerular capillary walls. In rare cases, the deposits may take on the shape of typical diabetic nodules with an acellular center. They can be correctly classified by the use of amyloid stains and by demonstration of typical fibrils on electron microscopy.

Some types of advanced *glomerulonephritis* (mesangial proliferative, membranoproliferative) have a histology that resembles nodular glomerulosclerosis. In glomerulonephritis, however, there is a distinct hypercellularity and the central, acellular area that is so characteristic for diabetes is not present. Nodules in glomerulonephritis involve all mesangial areas and are of almost equal size. Immunodeposits are usually present, but are faint or absent in diabetes.

Glomerulonephritis can occur in a patient suffering from diabetic glomerulosclerosis, and this combination has been thought to be more frequent than could be explained by more coincidence [29,30]. A systematic autopsy study of patient with NIDDM did, however, not show increased incidence of glomerulonephritis [31]. The presence of glomerulonephritis in a patient with diabetes mellitus should be

suspected if clinical signs of nephropathy appear prematurely, if persistent haematuria is present, or in the event of sudden increase in proteinuria or deterioration of renal function. In such cases, renal biopsy should be done.

Glomerular nodules may also be present in various *dysproteinemias* (e.g. multiple myeloma and heavy-chain disease [32-35].

The clinical picture may often solve the diagnostic problem, but the occurrence of glomerular nodules in these diseases should be a reminder to the pathologist not to postulate the presence of diabetes on the prima facie detection of nodular structures in the glomeruli.

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15. HAEMATURIA AND DIABETIC NEPHROPATHY

PRISCILLA KINCAID-SMITH and JUDITH A. WHITWORTH

The diagnosis of diabetic nephropathy is often straightforward. The patient has had long-standing juvenile-onset insulin-dependent diabetes mellitus, has developed retinopathy and proteinuria, and then has progressed to chronic renal failure. Haematuria has not been regarded as a prominent feature of the disease, and the urinary sediment has been ignored by the majority of authors.

In this chapter, we consider first the nature and diagnosis of haematuria, secondly the problem of associated glomerulonephritis, and thirdly review the urine findings in our patients with biopsy-proven diabetic nephropathy.

1. HAEMATURIA

In his monograph, The Kidney [1], published in 1973, Professor Jan Brod wrote: »Red cells of glomerular origin generally bear traces of their long journey through the renal tubules, where they are constantly faced by changing surroundings; they are usually shrivelled or deformed and sometimes look as if they had been extracted. Red cells from the pelvis and the urinary passages are normal in appearance«.

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

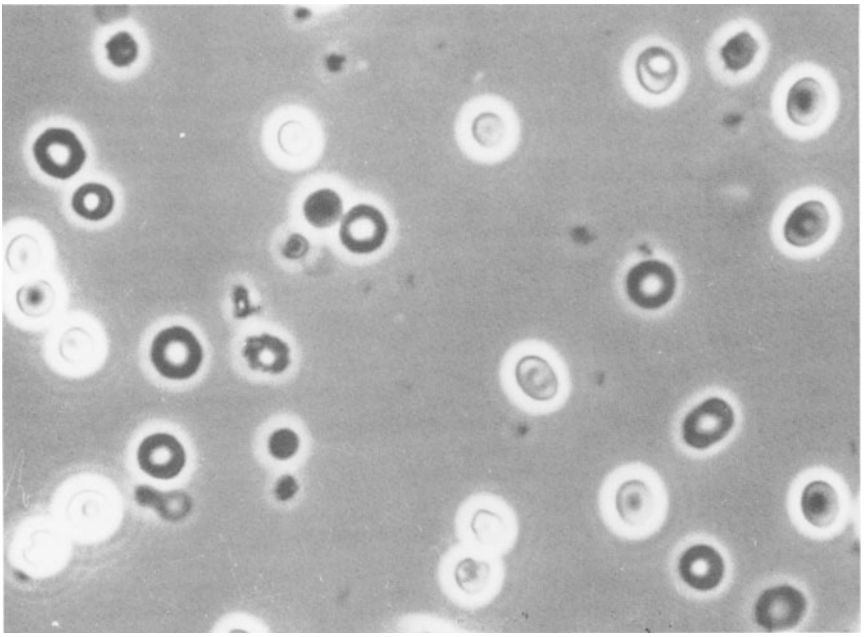

Figure 15-1. Dysmorphic urinary erythrocytes indicative of glomerular bleeding.

The distinction between haematuria of nephrologic significance (i.e., intrinsic renal disease, particularly glomerulonephritis) and hematuria of predominantly urologic interest (e.g., cancer of the urinary tract) has been a vexing clinical problem. An important advance was made when Birch and Fairley in 1979 [2] reported that glomerular bleeding could be distinguished from non-glomerular bleeding by simple examination of the urine sediment using phase-contrast microscopy [3].

The technique for evaluation of the urinary sediment using phase-contrast microscopy [3] is as follows: A 10 ml fresh midstream urine sample is centrifuged for 5 minutes at 750 g in a centrifuge with a swingout head; 9.5 ml of supernatant is removed with a pipette. The deposit is then re-suspended and examined in a Fuchs-Rosenthal chamber using phase-contrast microscopy with an Olympus BH microscope with positive phase-contrast illumination.

Red cells are regarded as dysmorphic, i.e., glomerular in origin, if they are variable in size and shape (figure 15-1). Cells may show extrusion of blebs of phase-dense cytoplasm from the cell membrane, apparent rupture of the limiting membrane

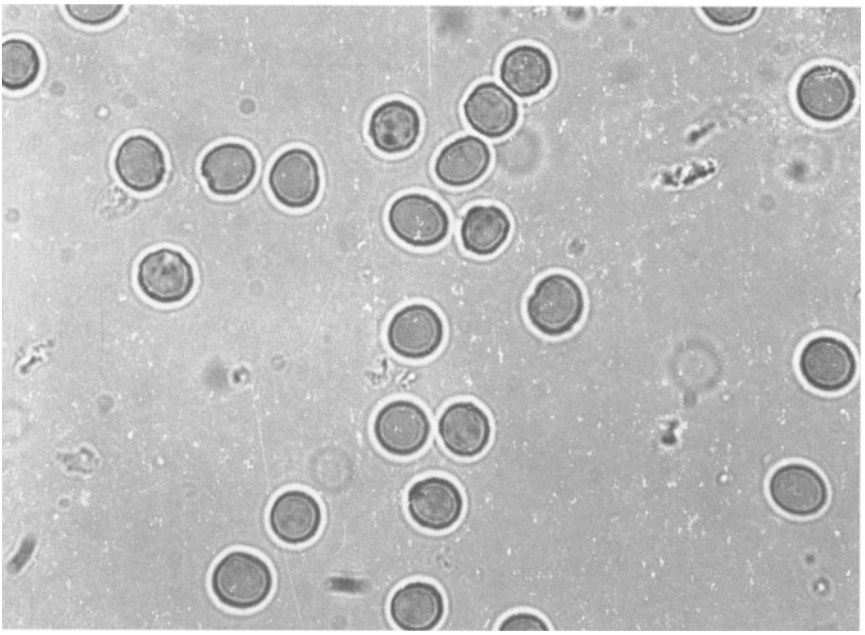

Figure 15-2. Isomorphic urinary erythrocytes indicative of non-glomerular bleeding.

with loss of cytoplasm giving rise to red cell ghosts, granular deposits of phase-dense material around the inner aspect of the cell membrane, peripheral cytoplasmic extrusions resembling »doughnuts«, yeast-like buds, and a variety of cell remnants.

Isomorphic red cells are those that are uniform in shape and size (figure 15-2). The majority resemble conventional red cells with apparently normal haemoglobin content although red cell ghosts may be seen. Such cells are characteristic of lower tract bleeding, e.g., secondary to bladder tumour.

Birch and co-workers [4] established that red blood cells are present in the urine of normal subjects in counts of up to 8,000 mm^3 (0.8×10^7/L). Subsequently they systematically examined urine samples from patients referred for investigation of microscopic haematuria without knowledge of any of the clinical details (table 15-1). Dysmorphic erythrocytes regarded as evidence of glomerular bleeding were found in 86 of 87 patients with glomerulonephritis. Isomorphic cells characteristic of non-glomerular lesions were found in 30 patients with non-glomerular disease, including analgesic and reflux nephropathy, renal calculi, urinary infection, renal carcinoma, hydronephrosis, and warfarin overdose. A mixed morphologic pattern was found in

Table 15-1. Erythrocyte morphology in 117 patients with haematuria (modified from Birch et al. [4])

	Glomerular Disease (n=87)	Non-glomerular Disease (n=30)
Dysmorphic erythrocytes	78 (67%)	0 (0%)
Isomorphic erythrocytes	1 (0.9%)	28 (24%)
Mixed pattern	8 (7%)	2 (1.7%)

ten patients and dual pathology was confirmed in four of these. Electron microscopy of urinary erythrocytes from patients with glomerulonephritis showed a wide range of dysmorphic changes (figure 15-3). A minority of cells showed their normal biconcave disc shape and most were distorted with scattered surface irregularities, some showed plasmalemmal rupture, and prominent projections from the surface were very common in association with an almost spherical cell shape. Scanning electron microscopy also showed a wide range of appearances. Glomerular bleeding was thus detected with a high degree of sensitivity (99%) and specificity (93%). The test was also a sensitive indicator of non-glomerular bleeding with a sensitivity of 100% and a specificity of 90%.

2. GLOMERULONEPHRITIS AND HAEMATURIA IN DIABETES

Carstens and co-workers [5] reported two patients with rapidly progressive glomerulonephritis superimposed on diabetic glomerulosclerosis. They commented in discussion that microscopic haematuria and an occasional RBC cast can be seen in patients with biopsy-proved pure diabetic glomerulosclerosis but no details were provided.

In another study from the United States, O'Neill and co-workers [5] presented clinical and pathologic data from eight patients with established diabetes mellitus, and significant microscopic haematuria and red cell casts. Three of their eight patients had associated glomerular disease (post-infectious glomerulonephritis in two and immunoglobulin-A (IgA) disease in one). In the other five patients, only diabetic nephropathy could be identified. They then examined prospectively the urinary features of a population of patients with diabetic nephropathy: 30 patients had insulin-dependent diabetes mellitus with diabetic retinopathy. Nine (30%) of 30 patients had more than ten red blood cells per high-power field. Quantitative counts were not performed and it should be noted that the upper limit of normal in our hands is very much less than ten cells per high-power field. A total of 13% also had red cell casts. However, none of these patients underwent renal biopsies so a second glomerular disease cannot be excluded. They concluded that microscopic haematuria

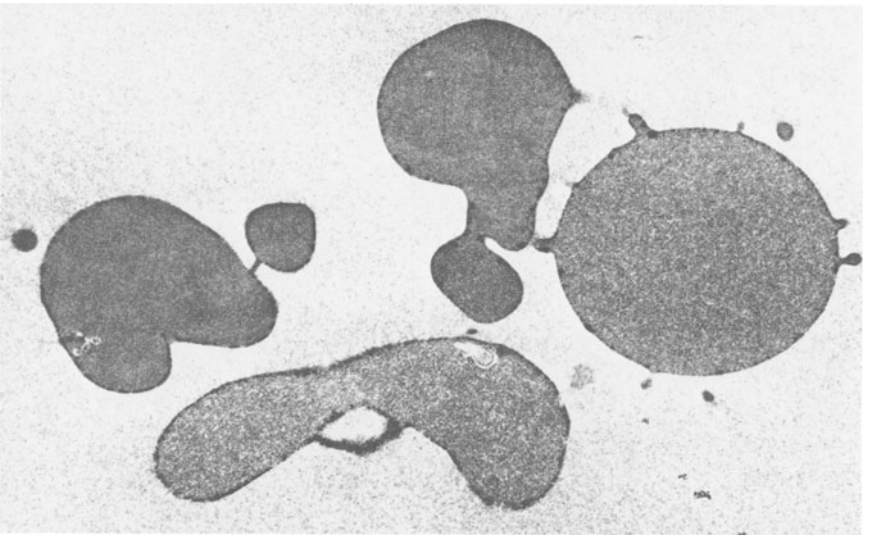

Figure 15-3. Transmission electron micrograph of dysmorphic urinary erythrocytes × 4,200. Courtesy of Professor G.B. Ryan and reproduced with permission [4].

and red cell casts can be found in patients with otherwise typical diabetic nephropathy and in whom no additional glomerular disease can be identified. Kasinath et al. soon after reported non-diabetic renal disease in 10 of 122 diabetic patients undergoing renal biopsy, including lupus, acute post-streptococcal nephritis, membrano-proliferative (type 1) glomerulonephritis, focal glomerulosclerosis, membranous and non-specific immune complex nephritis. Red cell casts were found in 3 cases, 'many' red cells in 3, 10-12 (presumably RBC/hpf although not stated) in 1, 8-10 in 1, 3-5 in 1, 3-4 in 1, and none in 3 patients. These authors regarded haematuria in the absence of urinary infection or RBC casts as clues to the presence of non-diabetic renal disease [7]. Whether haematuria was present in diabetic renal disease was not mentioned.

In a study from Japan in which 164 patients with diabetes mellitus were biopsied [8], haematuria was present in 17 (28%) of diabetic patients with proteinuria but no associated glomerulonephritis, compared with 19 (70%) of 27 diabetic patients with proteinuria and underlying glomerulonephritis ($p < 0.001$). Unfortunately it was not clear how haematuria was defined.

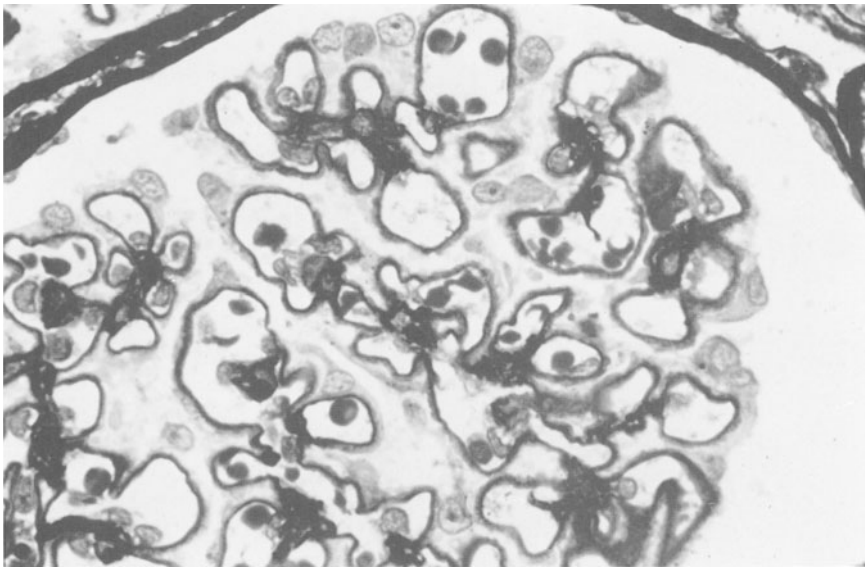

Figure 15-4. Membranous glomerulopathy and mild diabetic glomerulosclerosis.

3. RENAL PAPILLARY NECROSIS AND HAEMATURIA

Renal papillary necrosis in diabetes is considered in detail in Chapter 41. Papillary necrosis may be associated with microscopic or macroscopic haematuria, which is non-glomerular in type, but clinical renal papillary necrosis is rarely seen in our diabetic population.

4. URINE MICROSCOPY AND DIABETIC NEPHROPATHY: THE ROYAL MELBOURNE HOSPITAL EXPERIENCE

Renal disease in diabetics is not always due to diabetic nephropathy, and the association of diabetic nephropathy with other forms of renal disease is not uncommon.

Figure 15-4 shows a renal biopsy with diffuse membranous nephropathy and mild diffuse diabetic glomerulosclerosis from a man with type 2 diabetes and 36×10^7/L glomerular red cells in his urine.

Figure 15-5 shows IgA nephropathy in a biopsy from a man with insulin-dependent diabetes and 160×10^7/L glomerular red cells.

We have reviewed our data on 116 patients seen between 1980 and 1987 with biopsy-proven diabetic nephropathy in whom detailed urine microscopy was

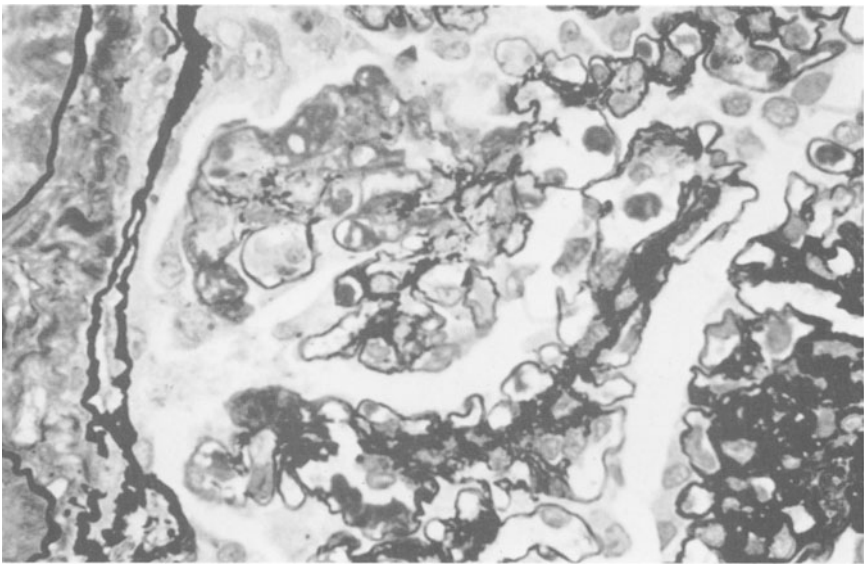

Figure 15-5. IgA nephropathy with diffuse mesangial proliferative glomerulonephritis and superimposed segmental lesions.

available (figure 15-6): 95 patients (82%) had diabetic nephropathy alone and 21 (18%) had both diabetic nephropathy and glomerulonephritis. This figure of 18%, however, is an overestimate of patients with dual pathology, as it is not our practice to biopsy all patients with diabetes and renal disease, particularly where the diagnosis of diabetic nephropathy appears clear-cut on clinical grounds.

Of the 95 patients with diabetic nephropathy alone, 33 (35%) had a normal urinary red cell count ($\leq 10^7$ cells/L) and 51 (54%) had essentially inactive sediments with counts $\leq 2 \times 10^7$/L. A further 21 (22%) had counts of 2-5 $\times$ 10^7/L, and 23 (24%) had counts over 5 $\times$ 10^7/L, including two patients (one of whom was pregnant) who had counts in excess of 20 $\times$ 10^7 cells/L. Thus, although half of the patients with isolated diabetic nephropathy had an inactive urinary sediment, half had elevated counts and in a quarter the counts were in a range seen with active forms of glomerulonephritis ($\geq 5 \times 10^7$ cells/L. Casts were documented in the majority of patients (75 of 95). Ten had red cells in hyaline casts and three had frank red cell casts (4%).

Haematuria was glomerular in origin in almost all the patients with isolated diabetic nephropathy. There was a mixed pattern in two patients, and low counts of non-glomerular cells were reported in two patients with severe renal failure.

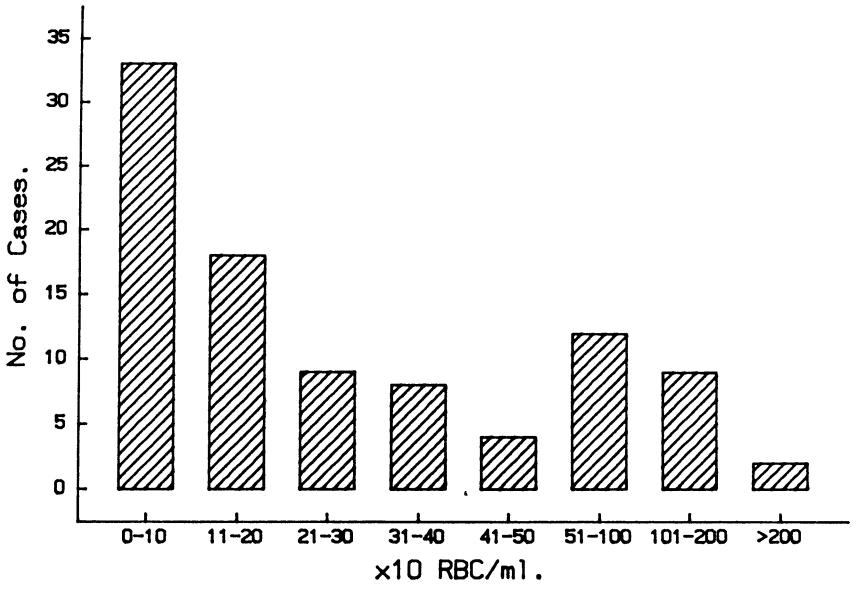

Figure 15-6. Distribution of urinary red cell counts from patients with biopsy-proven diabetic nephropathy alone.

A total of 21 patients had biopsy evidence of diabetic nephropathy in association with glomerulonephritis (IgA, 7; membranous, 6; post-infectious, 4; focal proliferative, 2; mesangiocapillary, 1; and mesangial proliferative, 1). Urine red blood cell (RBC) counts are shown in figure 15-7. Only one patient had a normal red cell count and six (29%) had counts $\leq 5 \times 10^7$ RBC/L. Thus, 71% had counts $> 5 \times 10^7$ RBC/L, compared with 24% of patients with diabetic nephropathy alone.

Seven patients (33%) had counts in excess of 20×10^7 RBC/L, compared with only 2% of patients with isolated diabetic nephropathy. Casts were documented in 19 of these patients and five had red cell casts (26%) and a further three had red cells in hyaline casts.

Thus, the higher the red cell count, the more likely is the patient with diabetes to have glomerulonephritis. Further, although red cell casts may occasionally be seen in isolated diabetic nephropathy, they are much more likely to signify associated glomerulonephritis.

Three patients with associated glomerulonephritis had mixed morphology (glomerular and non-glomerular cells). One had IgA nephropathy, and one focal

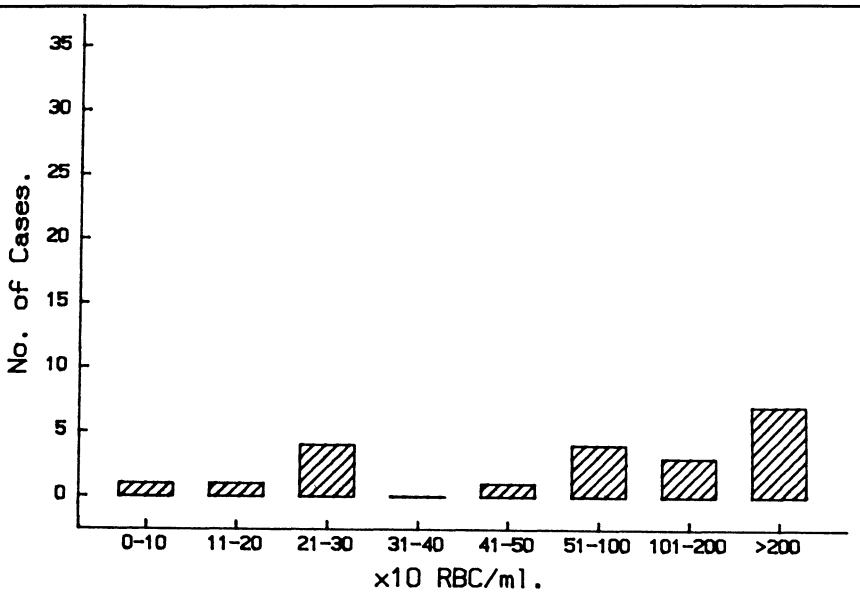

Figure 15-7. Distribution of urinary red cell counts from patients with biopsy-proven diabetic nephropathy and glomerulonephritis.

proliferative and one mesangiocapillary nephritis. All had normal urinary tracts. No patient had non-glomerular bleeding.

In a more recent study from Melbourne [9] co-existent renal pathology with diabetic glomerulosclerosis was found in 38 of 136 (28%) consecutive renal biopsies performed primarily for proteinuria in individuals with diabetes mellitus. The histological lesions found were glomerulonephritis (14), focal tubulointerstitial disease (23), and amyloidosis (1). Significant microscopic haematuria was present in 66% of all patients and did not help to distinguish non-diabetic disease.

5. CONCLUSION

Not all renal disease in diabetics is diabetic nephropathy, and glomerulonephritis and diabetic nephropathy not uncommonly co-exist. Patients with diabetes may have significant haematuria and even red cell casts, although these features raise the possibility of associated or isolated glomerulonephritis.

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16. GLOMERULAR ULTRASTRUCTURAL CHANGES IN MICROALBUMINURIC IDDM-PATIENTS

HANS-JACOB BANGSTAD and RUTH ØSTERBY

Since the term »microalbuminuria« (MA) was coined in 1982 [1] elevated albumin excretion rate has been regarded as the best indicator to signal early diabetic nephropathy [2-5]. Two main aspects of renal function at this stage of diabetic nephropathy, are the relation to glomerular structure and the impact of blood glucose control. Improved blood glucose control has been shown to reduce the risk of developing overt nephropathy in patients with MA [6,7] and retard the progression of AER [8], but the concomitant ultrastructural changes were not investigated.

This chapter concentrates on the glomerular morphological changes in patients with insulin dependent diabetes mellitus (IDDM) and early nephropathy and the influence of blood glucose control on these structural changes.

1. METHODS AND STRUCTURES IN QUESTION

The increased thickness of the glomerular basement membrane (BM) [9] and the mesangial expansion are the most characteristic changes in diabetic glomerulopathy [10]. The methodology involved in the measurement of BM thickness is described

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in detail elsewhere [9]. The relative increase of mesangium and of mesangial matrix is expressed as volume fractions, e.g. mesangium per glomerulus, matrix per mesangium or per glomerulus. The volume fractions are relative measures, estimating the composition of glomeruli and mesangial regions. The matrix star volume [11-13] is an estimate of the confluence and/or convexity of the individual branches of the matrix. Another estimate, the matrix »thickness«, corresponds to the arbitrary thickness of the matrix if transposed to form an even layer on the urinary surface of the mesangial region [12,13]. In order to reduce the imprecision in the estimates of the mesangial volume fraction, a method with complete cross-sections at 3 levels per glomerulus has been advocated [11].

2. PATIENTS WITH MICROALBUMINURIA VS. HEALTHY CONTROLS

In the 60ies several reports indicated that morphological changes were present at the onset of IDDM. Later studies clearly showed that the glomeruli are normal at that time [14] and the impact of that observation was supported by studies of identical twins discordant for IDDM [15]. Since the concept of MA is rather new, only a few studies have dealt with renal structure in this category of patients. We compared 17 normotensive, microalbuminuric subjects with 11 healthy kidney donors [13] Most of the diabetic patients had AER in the low range with median of 32 μg/min (range 15-194). Their mean age was 19 years (18-29) and diabetes duration 12 years (8-15). The microalbuminuric patients showed a clear increment in BM thickness with a mean of 595 nm (95% confidence interval 549-641 nm) versus 305 nm (287-325) in the control group. All of the MA patients had BM thickness above the normal range. The average BM thickening during the years with diabetes was approximately 25 nm per year. This approximation was based on the assumption that the patients had a BM thickness at onset of diabetes corresponding to the mean BMT of the control group, i.e. 305 nm. A significant parallel matrix expansion in the microalbuminuric patients vs. the normal controls was observed. Matrix/glomerular volume fraction was 0.13 (0.12-0.13) vs. 0.09 (0.08-0.10) and matrix star volume 27 μm^3 (21.8-32.2) vs. 13.9 μm^3 (10.7-17.1) in the two groups respectively [13].

Chavers et al. compared three groups of type 1 diabetic patients [16]. One with normoalbuminuria (NA), one with MA (AER >15 μg/min) and normal blood pressure (diastolic <90 mmHg) and normal glomerular filtration rate (creatinine clearance >90 ml/min/1.73 m^2) and the third with MA and elevated BP and/or decreased GFR. They found that the BM thickness in both of the MA-groups ($n=22$) was above the upper normal range (with one exception). The mesangial/glomerular volume fraction was also increased, but to a less degree. Specific matrix parameters were not investigated. It is hardly surprising that it is possible with sensitive methods to show morphological changes in IDDM-patients with clinical

indications of renal impairment (microalbuminuria), when compared to healthy controls, but the extent of the changes should be emphasized.

3. MICROALBUMINURIA VS. NORMOALBUMINURIA

In a clinical setting the transition from normo- to microalbuminuria is of utmost importance. Walker et al. compared two groups of IDDM patients [12]. One with normoalbuminuria (n=9, AER <20 μg/min) and one with microalbuminuria (n=6). Even though the number of patients was low, a significant increment in BM thickness, mesangial/glomerular volume fraction and also the matrix parameters was found in patients with MA compared to those with NA. The patients in the NA group were slightly younger and had a shorter duration of diabetes than the MA-group, although the difference was not statistically significant. The group of patients with microalbuminuria was very heterogeneous with a wide range in diabetes duration. Since the biopsies in the previously mentioned study [13] were investigated at the same laboratory as Walker et al.'s, and the MA-group in this study [13] was rather homogeneous and in fact very similar to Walker et al's normoalbuminuric patients, we compared the groups and confirmed with a greater number of patients (n=17) Walker's principal findings. These results differ from those presented by Chavers et al. [16], who found no difference between patients with normo- and microalbuminuria when patients with elevated blood pressure or decreased GFR, were excluded. MA-patients with low GFR and high blood pressure are atypical, at least in Europe. The failure to find a difference may be related to the composition of the patient groups. All patients studied by Chaver's et al, including those with NA, were candidates for pancreas transplantation. Not all of the MA-patients fulfilled the criteria for persistent MA. Further, the results indicated a very large variation probably reflecting a low precision of the estimates.

4. GLOMERULOPATHY AND BLOOD GLUCOSE CONTROL

The impact of long term hyperglycemia on the development of structural changes has been demonstrated in several studies [17-24], but most of them dealt with animals. One study in man showed that in renal allografts no significant increase in BM thickness and mesangial volume fraction was found 2-10 years after pancreas transplantation in 11 patients [24]. Specific mesangial matrix parameters were not investigated.

The baseline results from a prospective, randomized study showed, as previously mentioned [13], increased BM thickness and matrix expansion in MA- compared to NA-patients. In order to address the question whether structural changes were associated with blood glucose control, we estimated the yearly increment of BMT and matrix volume fraction from the start of diabetes in each patient. We showed

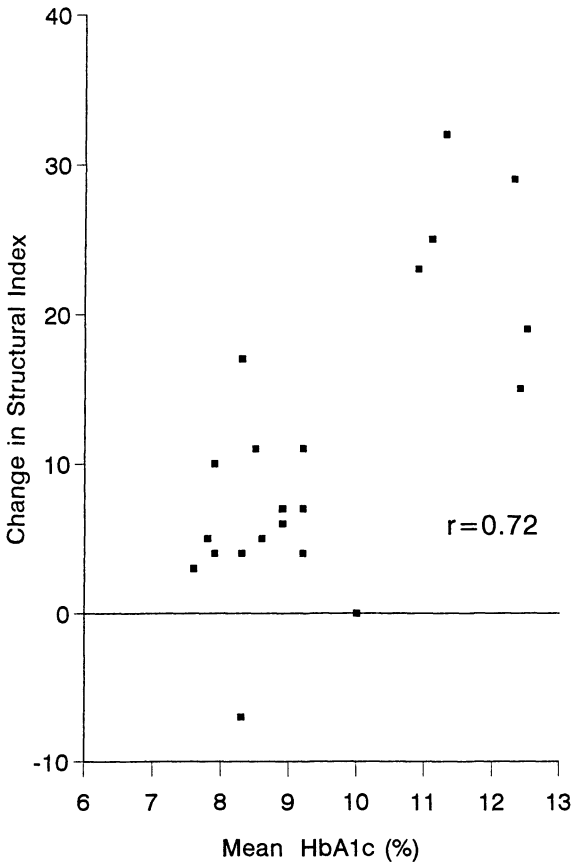

Figure 16-1. Urinary albumin excretion rate vs. structural index (basement membrane thickness/10 + matrix volume fraction of the glomerulus•100) in 21 young, normotensive IDDM patients with microalbuminuria. Reference no. 25.

that the increase in these two structural parameters correlated with mean HbA_{1c} from the year preceding the study, which probably reflects the long term blood glucose control.

The prospective, randomized study went on for 2.5 years [25]. The patients were randomized to either intensive insulin treatment by continuous subcutaneous insulin infusion (CSII) or conventional treatment (CT,- mostly multiple injections). It should be noticed that the mean HbA_{1c}-values in the two groups were rather high, and that the difference between the groups was modest, although significant, 8.7%

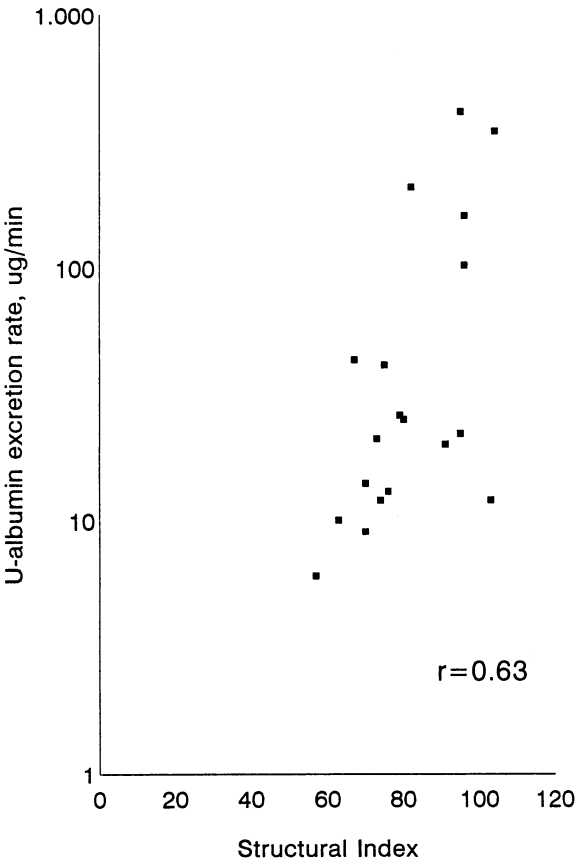

Figure 16-2. Results of a prospective study showing change in structural index (basement membrane thickness/10 + matrix volume fraction of the glomerulus•100) vs. mean HbA_{1c} during 26-34 months in 21 IDDM-patients with microalbuminuria. Reference no. 25.

and 9.9% respectively (normal range 4.3-6.1%),. The AER was for most of the patients in the low microalbuminuric range throughout the study. In fact, 38 % of the patients had AER < 15 μg/min at the end of the study and thus by definition had no longer microalbuminuria. The main finding of the study was that in the CSII-group none of the matrix-parameters increased, whereas they all increased (not significantly for matrix/glomerular volume fraction and matrix-thickness) in the CT-group. The BM thickness increased in both groups,- but the increment during the study period was significantly larger in the CT-group [140 nm (50-230) vs. 56 nm

(27-86)]. The association between blood glucose control and structure was confirmed when all the patients were considered together. A strong correlation was found between mean HbA_{1c} during the study and increase in BM thickness and matrix/glomerular volume fraction (figure 16-1). We thus showed that the progression of morphological changes in the glomerulus can be identified within a short period of only 2-3 years. Furthermore, we observed that reduced mean blood glucose levels clearly retarded the progression of morphological changes in the glomeruli. However, the glycated hemoglobin level achieved in the CSII-treated group (8.7%) was not sufficient to stop the progression of morphological changes.

In a prospective long term (12 years) study of renal allografts, the increment of the mesangial volume fraction, but not the BM thickening, was prevented when blood glucose control was improved [26].

5. GLOMERULAR STRUCTURE VERSUS ALBUMIN EXCRETION AND SYSTEMIC BLOOD PRESSURE

AER is an important parameter of kidney function in the early stages of nephropathy. In the combined group of NA and MA-patients Walker et al. [12] found a significant correlation between AER and the severity of glomerular lesions. Our study [25] is the first to demonstrate a clear relationship within the MA-group between most of the structural parameters and AER (figure 16-2).

It is still unclear whether the elevation of blood pressure observed in diabetic nephropathy precedes, develops in parallel with or follows the initial increment of AER [27]. In our prospective study none of the patients had arterial hypertension ($>$ 150/90 mmHg)[25]. No associations between blood pressure (BP) and glomerular parameters were found, neither at baseline nor at follow-up, but all patients had BP within a fairly narrow range. This might indicate that BP has little impact on the initiation of structural lesions at this early stage of diabetic nephropathy. However, Chavers et al. reported on a group of MA-patients with AER in the medium range ($\approx$65 μg/min) with elevated BP (and/or reduced GFR) and found that they had more advanced structural changes than MA-patients with normal BP and GFR [16].

6. MECHANISMS OF ALBUMINURIA

The urinary excretion of negatively charged proteins, e.g. albumin, is restricted by the negatively charged basement membrane. In the aforementioned prospective study [25] the charge selectivity index (clearances of IgG/IgG_4) was not associated with BM thickness at the beginning of the study. However, a striking correlation was found between the increase of BM thickness and the loss of charge selectivity during the study [28]. This may imply that the increase in BM thickness takes place concomitant with qualitative changes (e.g. loss of negative charge).

It is not known which substances that are responsible for the early thickening of BM and matrix expansion in diabetes. In the BM collagen IV predominates quantitatively, while laminin and heparan-sulphate proteoglycan probably play an important role as well. The mesangial matrix contains in addition collagen V, fibronectin, and chondroitin/dermatan sulfate proteoglycans [29]. Short-term experimental studies show that hyperglycemia induces increased production of most of the aforementioned proteins [30-32], increased levels of the proteins respective mRNA [33,34], increased matrix synthesis [35], and reduced amount of heparan-sulphate proteoglycan [36,37]. Furthermore, hyperglycemia leads to accumulation of advanced glycated end products of proteins (AGE). These glycated proteins do contribute to the formation of pathological tissue deposits [38].

Even if we have demonstrated a close linkage between long term hyperglycemia and change in structural parameters on one hand, and also an association between renal function and glomerulopathy in the early stages of nephropathy, we still lack the deeper insight into the mechanisms behind the increment in albumin leakage.

The increase in BM thickness in itself is unlikely to be responsible for the increased albumin excretion rate, but qualitative changes, e.g. reduced negative charge and/or presence of large pores, which develop concomitantly with the increase in thickness, may be decisive. An interesting observation in advanced glomerulopathy [39] and occasionally also in the early stage in microalbuminuric patients [40] is capillary loops with extremely thin and fluffy BM, contrasting markedly the other capillaries in the biopsies. They may be an expression of a compensatory glomerular growth, setting in at this early stage, and could represent the »large pores«. The BM-thickening develops in parallel with matrix expansion. Matrix changes, quantitative and qualitative, may interfere with the function of the mesangial cells [41]. One immediate consequence of the matrix expansion is that the distance between mesangial cells increases. This may impair the cell to cell interaction. Mesangial cell function plays a role in many aspects of glomerular physiology [42].

Altogether, the present data indicate that the increased loss of albumin across the glomerular filtration barrier is a sign associated with early structural lesions of diabetic glomerulopathy.

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17. UNDERSTANDING OF DIABETIC NEPHROPATHY FROM KIDNEY AND PANCREAS TRANSPLANTATION

PAOLA FIORETTO and MICHAEL MAUER

Kidney and pancreas transplantation in IDDM patients have helped in the understanding of some important aspects of the pathogenesis of diabetic nephropathy (DN). Studies on renal structure in IDDM kidney transplant (KT) recipients have clarified that: (1) the diabetic milieu is necessary for diabetic glomerular lesions to develop; (2) the natural history of diabetic nephropathy in the renal allograft (RA) parallels that occurring in the native kidney; (3) DN lesions develop linearly over time; and (4) glycaemic control only partially explains the rate of development of glomerular lesions in the RA. Improved glycaemic control or pancreas transplantation (PT): (1) is able to prevent or halt the development of early diabetic glomerular lesions in RA, but (2) normoglycaemia is unable to reverse established diabetic glomerulopathy in long-term IDDM patients with their own kidneys. This chapter reviews these lessons learned from studies on renal structure in IDDM patients undergoing KT and/or PT.

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1. THE DIABETIC MILIEU IS NECESSARY FOR DIABETIC GLOMERULAR LESIONS TO DEVELOP

The demonstration that DN occurs in normal kidneys transplanted into streptozotocin diabetic rats [1] led to series of studies on glomerular structure in IDDM patients undergoing KT for end-stage renal disease (ESRD) due to DN. The first study demonstrated arteriolar hyalinosis lesions, most often in the glomerular arterioles of IDDM RA recipients [2]; in half of them both the afferent and efferent limb of arteries were involved, a finding virtually diagnostic of diabetes [3-5]. Also, mesangial expansion was detectable by light microscopy in several diabetic patients, and in one Kimmelstiel-Wilson nodular lesions were evident [2]. Immunohistochemical studies demonstrated increased amounts of albumin and IgG localization in tubular basement membrane, glomerular basement membrane (GBM) and Bowman's capsule in RA in IDDM recipients [6], changes known to be characteristic and, in fact, diagnostic of the diabetic state [7-9]. Thus, these studies demonstrated that the diabetic environment is necessary for diabetic glomerulopathy to occur. Prior to this time controversy raged as to whether these lesions were secondary to carbohydrate intolerance or whether the microangiopathy of diabetes was determined by a separate genetic disorder. Thus, Siperstein and co-workers, finding thickening of muscle capillary basement membranes in non diabetic relatives of diabetic patients, argued that the tendency to develop microvascular complications of diabetes was inherited separately and was unrelated to hyperglycaemia [10]. The first electron microscopic studies of diabetic lesions in the RA were reported in 1983 [11]. Baseline and 2 year post-KT biopsies were obtained in 6 non diabetic and 5 diabetic patients. None of the non-diabetic but all of the diabetic patients developed increased GBM width within 2 years following KT. None of the non-diabetic and 2 of the diabetic patients had an increase in the percent of the glomerular tuft occupied by mesangium (mesangial volume fraction or VvMes). This mesangial expansion, consistent with observations in the native kidney of IDDM patients [12], was due to an expansion of mesangial matrix rather than of mesangial cells. Østerby et al. confirmed these findings in a more extensive study [13]. GBM expansion and mesangial matrix accumulation was confirmed in the IDDM but not in the control patients. In summary, all the important lesions of DN [3] including GBM widening, mesangial expansion with predominant increase in mesangial matrix, Kimmelstiel-Wilson nodule formation, arteriolar hyalinosis and increased binding of IgG and albumin to renal extracellular basement membranes occur in the RA in diabetic patients.

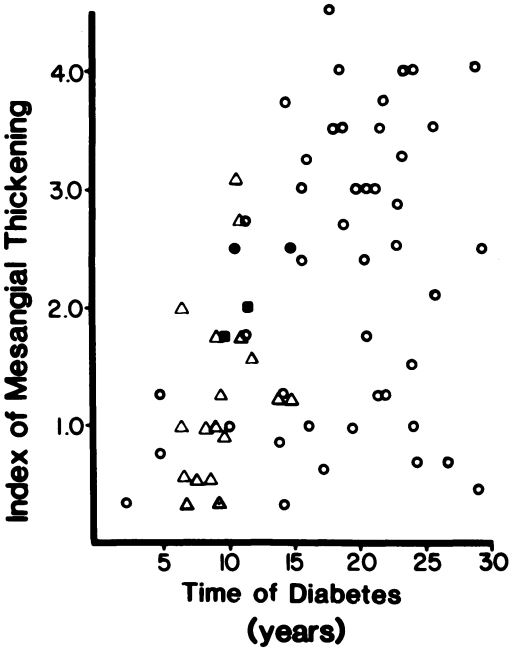

Figure 17-1. Index of mesangial expansion (IME) in last biopsy and time since kidney transplantation (△) plotted along with IME in native kidneys in type I diabetic patients (○ or ●) in relationship to time since onset of diabetes. From Mauer et al. Diabetes 1989; 38: 516-523 (with permission).

2. THE NATURAL HISTORY OF DIABETIC NEPHROPATHY IN THE RENAL ALLOGRAFT PARALLELS THAT IN THE NATIVE KIDNEY

GBM widening is documentable and mesangial expansion just detectable by two years after KT, and both are often easily discernible at 5 years after KT in IDDM patients [11,13]. This mirrors the changes seen in native diabetic kidneys in which an increase in GBM width is detectable within 18 months of the diagnosis of diabetes and mesangial expansion by 3.5 years or later [14]. The light microscopic index of mesangial expansion (IME) at 6 to 13 years after KT is similar to the IME in native kidneys of patients with similar IDDM duration. This indicates that the rate of development of mesangial expansion in the RA largely parallels that in the native kidney (figure 17-1) [15]. These studies suggest that the renal haemodynamic consequences of »uninephrectomy« are not associated with a measurable increase in the rate of development of diabetic mesangial expansion. As is true in the native

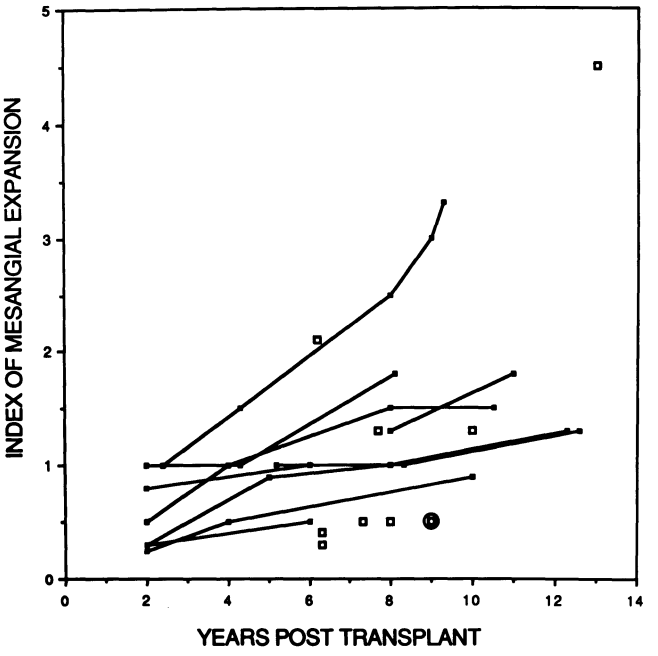

Figure 17-2. Light microscopic analysis of development of mesangial expansion with time in long-term kidney allografts transplanted into diabetic recipients. Results of sequential biopsies in same patient (■), results from patients with only 1 biopsy (□), patient with renal artery stenosis in transplanted kidney (◎). From Mauer et al. Diabetes 1989; 38: 516-523 (with permission).

kidney in patients with IDDM, renal failure due to DN is, in our experience, unusual in the first decade following KT.

3. DIABETIC NEPHROPATHY LESIONS DEVELOP LINEARLY OVER TIME

GBM thickening and increases in VvMes develop linearly over time in IDDM patients biopsied at baseline, 2 and 5 years after KT (unpublished data). However, the rate of change varies markedly between one patient and another. A longer-term study provided similar results [15]. Again, although each recipient had end-stage DN with his/her own kidneys, there was marked variability in the rate of development of mesangial and GBM expansion in the RA. However the rate of progression of mesangial expansion tended to be linear over time (figure 17-2). This is similar to the natural history of nephropathy lesions in native kidneys where some patients

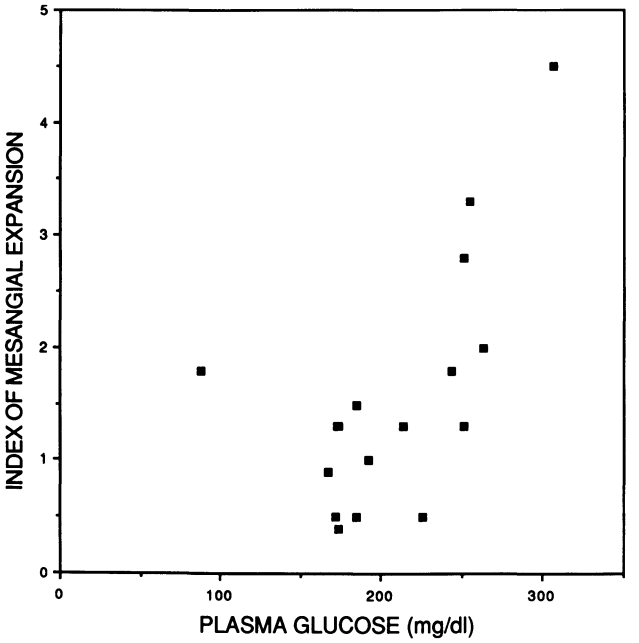

Figure 17-3. Index of mesangial expansion in last biopsy compared with mean plasma glucose levels from transplantation to time of biopsy. From Mauer et al. Diabetes 1989; 38: 516-523 (with permission).

develop serious lesions in the first 10-20 years of IDDM whereas others have little or no changes despite decades of diabetes.

4. GLYCAEMIC CONTROL ONLY PARTIALLY EXPLAINS THE RATE OF DEVELOPMENT OF GLOMERULAR LESIONS IN RENAL ALLOGRAFTS

The rate of development of mesangial expansion in the KT does not correlate with several potential risk factors such as donor source, histocompatibility match, recipient or donor age, age at onset of diabetes, immunosuppressive drug dose, blood pressure, and the presence or absence of chronic rejection [15]. Further, there is no correlation between the duration of diabetes prior to ESRD and the rate of recurrence of lesions in the RA. There was a direct correlation between the rate of mesangial expansion and glycaemic control ($r = +0.61$, $p < 0.01$) but this was rather imprecise (figure 17-3) [15]. This led to the hypothesis that some IDDM kidney recipients receive kidneys that are »resistant« and others that are »susceptible« to the development of DN lesions. Accordingly the factor(s) that confer susceptibility are,

at least in part, different from the risk factors for the development of diabetes. Since these susceptibility factors could be genetically regulated, this hypothesis could be compatible with Siperstein's suggestion of an inherited susceptibility to microvascular complications. In fact, there is mounting evidence that in the presence of the diabetic milieu familial, probably genetic, factors operate in the pathogenesis of DN [16,17].

5. IMPROVED GLYCAEMIC CONTROL PREVENTS THE DEVELOPMENT OF EARLY GLOMERULAR LESIONS IN RENAL ALLOGRAFTS

Studies of long-term RA mentioned above suggested that glycaemic control is a significant determinant of the risk of developing lesions of DN. PT offers a unique opportunity to evaluate the effects of prolonged normoglycaemia, without exposing the patients to the risks of severe hypoglycaemia on this process. Bohman et al. demonstrated that PT performed simultaneously with KT was able to prevent the development of diabetic glomerular lesions [18]. In these studies, renal structural values were still within the normal range after 2 to 8 years. However, baseline biopsies were not performed and, since values for structural components of the glomerulus vary widely among normal persons [19], it cannot be securely concluded that subtle changes had not occurred despite euglycaemia. In another study, PT was performed shortly after KT [20]. In this study, baseline renal biopsy specimens were obtained from RA of IDDM patients before successful PT, performed 1 to 7 years after KT [20]. Renal biopsies were then repeated 4 years later and compared to those of IDDM patients on insulin therapy who were biopsied at similar times after KT. VvMes was lower in the IDDM recipients of PT than in those receiving KT alone [20]. GBM width was not different between groups. PT patients had smaller mean glomerular volumes compared to the recipients of KT alone, suggesting that the glomerular enlargement associated with diabetes is reversible [20]. Improved glycaemic control can also be obtained by intensified insulin-therapy. A prospective, randomized controlled trial tested the impact of optimized glycaemic control on the development of diabetic lesions in the RA [21]. 48 patients were randomized to strict or to standard glycaemic control and had renal biopsies at baseline and 5 years after KT. Mean HbA1 during the 5 years of the trial was $9.6 \pm 1.6\%$ in the strict control compared to $11.7 \pm 1.3\%$ in the standard control patients ($p < 0.001$). There was no effect of strict control on GBM width. However, volume fraction of mesangial matrix increased less in the strict control (0.019 ± 0.038) compared to the standard control group (0.043 ± 0.034, $p < 0.03$) over the 5 years of the study. Also, arteriolar hyalinosis was less in the strict vs. standard control patients ($p < 0.02$). Thus, improved glycaemic control, achieved by PT or by aggressive use of

conventional technologies, slows or halts the development of early lesions of DN in the RA.

6. NORMOGLYCAEMIA IS UNABLE TO REVERSE ESTABLISHED GLOMERULOPATHY IN PATIENTS WITH THEIR OWN KIDNEYS

Islet transplantation [22] or whole PT [23] is able to rapidly reverse mesangial expansion and glomerular enlargement, but not increased GBM width, in long-term diabetic rats. A single study has examined the effects of PT on DN in patients with native kidneys [24]. Thirteen IDDM patients had a baseline kidney biopsy performed at the time of successful PT and 5 years later. Ten IDDM controls (C) had two kidney biopsies performed 5 years apart. Baseline studies indicated that both the PT and the C were heterogeneous groups with a wide range of renal function and structure, form normal to far advanced. All PT patients were treated with triple immunosuppressive therapy including cyclosporin. HbA1 was normal following PT but remained elevated in C. GBM did not changes in 5 years in either group. VvMes increased similarly in PT (from 0.33 ± 0.08 to 0.38 ± 0.11, $p < 0.01$) and C (from 0.29 ± 0.05 to 0.35 ± 0.07, $p < 0.01$), despite the different metabolic environment. Glomerular volume, enlarged at baseline in both groups, decreased after PT (from 2.13 ± 0.63 to 1.74 ± 0.32, $p < 0.05$) but increased in C (from 1.52 ± 0.4 to 2.06 ± 0.57, $p < 0.005$). Thus the increase in VvMes was a consequence of the reduction in glomerular volume in PT but was due to an expansion of the mesangium out of proportion to glomerular enlargement in C. PT corrected glomerular hypertrophy; however, since both groups had an increase in VvMes (the morphologic parameter that better correlates with renal function), it is premature to conclude that PT was beneficial. Further, we observed a significant increase in interstitial fibrosis and in the number of globally sclerosed glomeruli in PT recipients. These changes were not detectable in C and are likely to be the consequence of the nephrotoxic effects of cyclosporin. From this experience, and at variance with the reversal of mesangial expansion observed in the diabetic rat, mesangial expansion is not quickly reversible and has not yet been proven to be arrestable in man. Moreover the possible benefits of PT on diabetic nephropathology in IDDM patients have to be counterbalanced by the detrimental renal effects of cyclosporin. Larger and longer term studies, hopefully using newer non-nephrotoxic immunosuppressive drugs, may change these conclusions. However, at the present time, PT cannot be recommended as a cure for DN.

CONCLUSIONS

DN recurs in RA with pathological features and a natural history that mirrors that seen in native kidneys. The factors influencing the rate and extent of recurrence are

not fully elucidated. However, it appears that variables residing within the KT influence this process and this suggests a need for novel ideas regarding the pathogenesis of DN. Improved glycaemic control and PT can prevent or slow the earliest lesions of DN. However, later lesions persist and may even progress despite PT [25]. Diabetic patients undergoing KT and/or PT represent valuable resources for important inquiries into the nature of DN.

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18. SODIUM-HYDROGEN ANTIPORT, CELL FUNCTION AND SUSCEPTIBILITY TO DIABETIC NEPHROPATHY

ROBERTO TREVISAN and GIANCARLO VIBERTI

The annual incidence of diabetic nephropathy rises rapidly over the first 15-20 years of diabetes, but declines sharply afterward for longer disease duration [1]. This pattern of risk indicates that only a subset of diabetic patients are susceptible to renal damage and, indeed, clinical renal disease cumulatively develops in approximately 30% of Type 1 (insulin-dependent) diabetic patients [2] and between 25 and 60% of Type 2 (non-insulin-dependent) diabetic patients, depending on their ethnic origin [3]. Familial clustering of diabetic nephropathy has been shown both in insulin-dependent [4] and non-insulin-dependent diabetic patients [5]. These findings are consistent with the possibility that genetic factors may explain the liability to or protection from renal disease of diabetic patients.

Recent reports suggest that raised blood pressure levels play an important role not only in the progression of renal complications, but also in the initiation of a multistage process leading to end-stage renal failure. Two prospective studies have shown that the patients who progress to microalbuminuria have either raised or rising blood pressure before microalbuminuria becomes persistent [6,7]. Raised

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blood pressure [8] and an increased frequence of cardiovascular disease [9] are also more prevalent in parents of diabetic patients with nephropathy. Taken together, these findings indicate that a familial predisposition to hypertension and cardiovascular disease may be an important determinant of susceptibility to renal disease and its cardiovascular complications in diabetes.

In accord with these observations, studies of sodium-lithium countertransport activity, an intermediate phenotype of essential hypertension and its vascular complications [10,11], have shown significant elevation in the rate of this cation transport system in insulin-dependent [12,13] and non-insulin-dependent diabetic patients [14] with proteinuria or microalbuminuria and hypertension. Diabetic patients with high sodium-lithium countertransport activity display a clustering of metabolic and haemodynamic risk factors for renal and cardiovascular complications well before the development of overt renal disease [15]. The activity of sodium-lithium countertransport also shows significant familial aggregation [16].

These results have raised growing interest in the search for cell markers that would prove suitable for early diagnosis and would help clarify the molecular mechanisms leading to diabetic nephropathy.

BASIC PROPERTIES OF THE Na^+/H^+ ANTIPORT

Sodium/lithium countertransport is not operating in vivo and, therefore, the pathophysiological implication of this abnormality remains uncertain. Sodium-lithium countertransport has similarities of operation with the ubiquitous physiological Na^+/H^+ antiport [17].

Na^+/H^+ antiport is a membrane transport system found in all eukaryotic cells. Under normal physiological conditions, Na^+/H^+ antiport employs the sodium concentration gradient from extracellular to intracellular fluid to drive protons out of the cells in exchange for an influx of sodium ions. This transport is activated cooperatively by an increase in the cytosolic proton concentration through a proton regulatory site [18]. Molecular biology studies have revealed the presence of at least five different isoforms of Na^+/H^+ antiport. The first isoform, referred to as NHE1, ubiquitously expressed in most cell types, is sensitive to amiloride and activated by growth factors. The human cDNA coding for this protein has been cloned and the gene is located on the short arm of chromosome 1. It encodes a protein of 815 amino acids with two distinct domains [19]. The N-terminal domain contains 10-12 transmembrane segments, while the C-terminus is largely cytoplasmic. The second isoforms (NHE2) is expressed on the apical membrane of polarized epithelia and it is involved in the transcellular transport of Na, Cl and bicarbonate. The structure and the functional implications of the other isoforms require further investigations.

Na^+/H^+ antiport is involved in three major cellular events: 1) intracellular pH regulation, 2) cell volume control and 3) stimulus-response coupling and cell proliferation. At kidney level, this transport system plays an important role in Na reabsorption [18].

Many studies have shown that the Na^+/H^+ antiporter is activated in response to growth factors and various cell activating agents such as hormones, chemotactic peptides and phorbol esters. The sequence of intracellular events triggered by growth factors binding to their membrane receptors is as yet not fully understood. The trophic action of these compounds appears in part to be dependent on the elevation of intracellular free calcium and the activation of phospholipase C that mediates the formation of inositol triphosphate and diacylglycerol which, in turn, activates protein kinase C. The effect on the Na^+/H^+ antiport is triggered by an increase of the affinity of the antiporter protein for H^+ at the internal H^+ regulatory site [18]. A phosphorylation step is required for this activation of Na^+/H^+ antiport.

Na^+/H^+ ANTIPORT ACTIVITY IN DIABETIC NEPHROPATHY

An increased leucocyte Na^+/H^+ antiport activity has been reported in Type 1 diabetic patients with nephropathy [20] as well as in patients with essential hypertension [21]. Insulin-dependent diabetic patients with microalbuminuria and raised blood pressure have also higher red blood cell Na^+/H^+ antiport activity [22]. In all these cases the increased activity was due to a raised maximal velocity of the antiport. These observations are consistent with the view that arterial hypertension or the predisposition to it are important components in the pathogenesis of diabetic nephropathy.

In all these studies, however, measurements, were performed soon after blood sampling and a potential effect of the disturbed metabolic milieu of the diabetes state on the transporter activity, therefore, could not be excluded. These studies could not establish whether the higher activity of this cell-membrane transport system was an intrinsic abnormality of these cells.

Cultured fibroblasts are a useful tool for investigations of various genetic errors of metabolism and we chose skin fibroblasts as a model for evaluating Na^+/H^+ antiport activity in diabetic patients [23]. A skin biopsy was taken from nine insulin-dependent diabetic patients with overt nephropathy and from eighth normoalbuminuric patients matched for diabetes duration, sex and body mass index. Fifteen normal subjects served as controls. All experiments were performed after fibroblasts reached at least the sixth passage. Na^+/H^+ exchange was assayed by measuring amiloride-sensitive net sodium uptake. The transport was activated by acid loading the cells with the ammonium chloride prepulse method. The kinetic parameter of Na^+/H^+ exchange were determined by measuring the initial velocity of amiloride-

sensitive Na-uptake at different external sodium concentration under pH gradient conditions. Na^+/H^+ antiport activity was significantly elevated in insulin-dependent diabetic patients with nephropathy compared with diabetic patients without nephropathy and normal control subjects. A kinetic analysis of Na^+/H^+ exchange revealed that the raised activity was caused by an increased maximal velocity (Vmax) for extracellular Na^+ (table 18-1). The external Na^+ concentration that yields 50% of the Vmax (Km) was similar in the three groups (table 18-1). In this study intracellular pH was also measured using the distribution of [7-^{14}C]benzoic acid. In quiescent, non proliferating cells, intracellular pH was similar in diabetic patients with and without nephropathy and control subjects. When cells were exposed to serum for 10 min, a greater intracellular alkalinization was found in fibroblasts of diabetic patients with nephropathy than in patients without nephropathy and normal subjects. Intracellular pH was also higher in exponentially growing cultures of fibroblasts of patients with nephropathy (table 18-1).

All these findings in long-term cultured cells from insulin-dependent diabetic patients with nephropathy are consistent with an intrinsic overactivity of the Na^+/H^+ antiport and with an increased responsiveness to the action of growth factors.

Similar studies of Na^+/H^+ antiport activity and intracellular pH were also performed in skin fibroblasts using the pH-sensitive dye. BCECF [24]. Cells on cover slips were loaded with BCECF and inserted in cuvettes warmed to 37°C in a thermostatted holder. Fluorescent measurements of intracellular pH were performed in HEPES buffered saline using a single photon counting dual excitation fluorometer. The two excitation wavelengths were set at 500 and 439 nm with emission at 530 nm. The 500/439 emission ratios were converted to pH values by construction of a calibration curve for every coverslip using a double ionophore intracellular pH clamping technique (nigericin plus monesin in a potassium rich medium). By this technique intracellular pH was clamped to pH 6.5 or 6.2. After removing the ionophores, addition of ammonium enabled the determination of intrinsic buffering capacity of the cells. After a period of reclamping to intracellular pH 6.5 or 6.2, active H^+ efflux was determined in HEPES buffered saline. Na^+/H^+ antiport activity was obtained after multiplying the rate of change in intracellular pH (after addition of Hepes buffered saline to acid loaded cells) by the intrinsic buffering capacity. Growing fibroblasts from diabetic patients with nephropathy were significantly more alkaline compared to both normoalbuminuric diabetic patients or normal controls. This was associated with a raised Na^+/H^+ antiport activity when intracellular pH was clamped to pH 6.5, without any difference in the Vmax at intracellular pH 6.2. These data suggest an increased apparent affinity of the antiporter for H^+ at the internal H^+ regulatory site. Using both intracellular pH and

Table 18-1. Intracellular pH (pHi) and kinetic parameters of Na^+/H^+ antiport in long-term cultured skin fibroblasts form insulin-dependent diabetic patients with (DN) and without D) nephropathy and normal controls (C). Values are mean ± SD

	DN	N	C
pHi in quiescent cells	6.98±0.05	6.95±0.16	6.92±0.05
pHi 10 min after serum stimulation	7.18±0.04*	7.07±0.07	7.08±0.08
pHi in exponentially growing cells	7.23±0.05*	7.12±0.07	7.09±0.1
Na^+/H^+ antiport Vmax nmol/mg protein/min	226±37*	132±48	124±51
Na^+/H^+ antiport Km mM	26.9±3	27.9±2	27.0±2

*$p < 0.01$ vs N and C

Na^+/H^+ antiport activity at pH 6.5, a discriminant function was described that separates the majority of the patients with nephropathy from both controls and patients without nephropathy. It remains to be established if this function will be useful in identifying those patients at risk of nephropathy.

Taken together, the findings of these two complementary studies have shown that Na^+/H^+ antiport form cells of patients with diabetic nephropathy is characterized by a raised maximal velocity for extracellular Na^+ and a raised apparent affinity for internal H^+ ions.

CELL FUNCTION IN DIABETIC NEPHROPATHY

Increased Na^+/H^+ antiport activity has been found to be associated with enhanced smooth muscle cells [25] and skin fibroblast [26] proliferation in response to growth factors in the spontaneously hypertensive rat. In hypertensive patients a significant correlation between Na^+/H^+ antiport activity in lymphocytes and left ventricular hypertrophy has also been described [27].

In fibroblasts of insulin-dependent diabetic patients with nephropathy, we demonstrated an enhanced DNA synthesis after stimulation of quiescent cells with serum [23] (figure 18-1). This abnormality suggests a difference in the ability of these cells to enter the synthetic S phase after mitogen stimulation. A positive

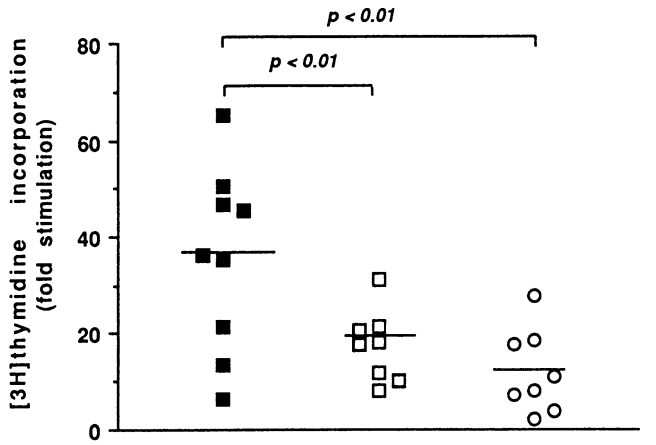

Figure 18-1. [^{3}H]thymidine incorporation into newly synthesized DNA in fibroblasts from diabetic patients with (filled squares) and without (open squares) nephropathy, and normal subjects (open circles), in response to 10% fetal calf serum. Values are the mean of 8 wells and are expressed as fold stimulation (ration of cpm per well under stimulated conditions to cpm per well at baseline in quiescent cells.

correlation was found between Na^+/H^+ antiport activity and DNA synthesis indicating that the antiport may be involved in this altered cell function.

Abnormalities in DNA cell cycle and in the cell life cycle of these fibroblasts have recently been reported by our group [28]. Na^+/H^+ antiport can be activated by extracellular matrix molecules, such as fibronectin [29], and any interaction between extracellular matrix production and Na^+/H^+ antiport is of particular importance in view of the relevance of excessive matrix deposition to the sclerotic process of diabetic nephropathy [3]. In preliminary studies we have found that long-term cultured fibroblasts derived from Type 1 diabetic patients with nephropathy exhibit an increased total collagen synthesis compared with that of patients without nephropathy and normal controls [30].

The persistence of all these abnormalities in ion transport and cell function despite serial passaging of cells in identical media in vitro indicates a likely intrinsic component in their pathogenesis. If an enhanced activity of Na^+/H^+ antiport constitutes a primary permissive factor leading to cell function disturbances or is simply secondary to other more basic defects remains to be clarified.

In diabetic patients, phenomena such as mesangial and vascular smooth muscle cell hypertrophy and/or hyperplasia, enhanced extracellular matrix production and fibrotic processes represent important steps in the pathogenesis and progression of their renal and arterial disease [3]. If the abnormalities in cell function described in

fibroblast and in leucocytes apply to other cell types, as it seems likely, they could explain why only a subset of insulin-dependent diabetic patients are susceptible to renal and cardiovascular complications.

The recent advances in molecular biology should better clarify the relation between Na^+/H^+ antiport activity, cell growth and extracellular matrix production and, in particular, elucidate the interaction between diabetes and those cells functions regulated by Na^+/H^+ antiport activity. The knowledge of the cellular and molecular mechanisms responsible for those abnormalities may lead to effective primary prevention strategies.

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19. BIOCHEMICAL ASPECTS OF DIABETIC NEPHROPATHY

ERWIN D. SCHLEICHER

The dominant histological feature of diabetic nephropathy is the thickening of the glomerular basement membrane and expansion of the mesangial matrix [1-3]. The changes correlate strongly with the clinical onset of proteinuria, hypertension and kidney failure. Although more than 50 years have elapsed since Kimmelstiel and Wilson [4] described in diabetic glomeruli the distinctive periodic acid-schiff (PAS)-reactive nodular deposits, progress in elucidating the pathobiochemistry has been slow. Recent investigations with electron microscopic, immunochemical and biochemical methods have led to an improved understanding of the structure-function relationship of the glomerular filtration unit in normal and pathological conditions [5].

MOLECULAR STRUCTURE AND FUNCTION OF GLOMERULAR EXTRACELLULAR MATRIX

The extracellular matrix of the glomerulus consists of the basement membrane interposed between endothelial and epithelial cells and the closely adjoining

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Table 19-1. Structure and function of the major components of the glomerular basement membrane and mesangial matrix

Component	Structure	Function
Collagen type IV	Triplehelix with non-helical segments; 5 different chains with approximately 1700 amino acids are known [6,9]	Mechanical scaffold; Size selective filter; Binding to cell adhesion molecules
	Chains are unequally distributed in the glomerular matrix [6]	
Collagen type VI	3 different chains [8]	Formation of microfibrils
Laminin	3 different poly-peptide chains MW 800 KD [9]	Cell adhesion Integrin binding
Heparan sulfate proteoglycan (HSGP)	Coreprotein MW 470 KD [7,10] 3 heparan sulfate side chains	Integrin binding Charge selective filter Antiproliferative Binding of humoral factors

extracellular matrix surrounding the mesangial cells. The structural and functional properties of the matrix components are summarized in table 19-1. The basement membrane representing the size and charge selective area of the filtration unit is composed of a filamentous network of collagen type IV fibrils. Immunohistochemical studies revealed that the collagen IV chains are inhomogenously distributed within the glomerulus. The $\alpha 1,\alpha 2$-chains are primarily detected in the mesangial matrix whereas the $\alpha 3,\alpha 4$-chains are exclusively found in the glomerular basement membrane [6]. The basement membranes also contain a proteoglycan which consists of three heparan sulfate side chains covalently attached to the protein core [10,11]. It has been convincingly shown that the negatively charged heparan sulfate chains form the anionic barrier of the glomerular filtration unit [5,12,13]. A detailed review of this heparan sulfate proteoglycan (HSPG) and its changes in diabetes is given in the following chapter. The traces of fibronectin found in normal glomerular matrices are probably derived from plasma since the tissue specific fibronectin A+ which contains the extra domain A is not detected in normal glomeruli [14]. The mesangial matrix, although developmentally and morphologically distinct from the glomerular basement membrane, contains essentially the same components but in different distributions.

Several functions of the matrix components can now be explained by features of these components on the molecular level. Specific cell-matrix adhesion molecules which are intercalated in the cellular plasma membrane recognize well-defined amino acid sequences found in collagen, laminin and fibronectin [9,15]. Furthermore, these adhesion molecules (integrins) which are in contact with the cytoskeleton influence cell migration and cell proliferation. Changes in matrix composition may therefore alter cellular adhesion, migration and proliferation and thus influencing repair processes [15]. The finding that HSPG by virtue of its side chains specifically binds polypeptide growth factors like basic fibroblast growth factor (bFGF) or transforming growth factor ß (TGF-ß) is important in this context. It has been suggested that the matrix-bound growth factors may act as a reservoir for vascular repair mechanisms [16]. The anti-proliferative role of heparan sulfate on mesangial cells underlines the possible importance of this the proteoglycan in glomerular matrix [17].

STRUCTURAL AND FUNCTIONAL GLOMERULAR ALTERATIONS IN DIABETES

The first major change after the onset of diabetes is the increased volume of the whole kidney [18] and the glomeruli [19]. These hypertrophical glomeruli have normal structural composition. After a few years the amount of glomerular matrix material is increased [1,3]. Biochemical determinations indicate an increased amount of collagen in the glomerular extracellular matrices [20]. More recently, an increase in collagen type VI in the glomerular matrix of diabetic patients has been documented [21]. On the basis of immunochemical measurement, it has become evident that the HSPG content of glomerular matrix is lower in diabetic patients [22] consistent with previous chemical analyses of the heparan sulfate chains [23,24]. These immunochemical measurements, although yielding reliable quantitative values, were performed with preparations of glomerular matrices which contain firstly, both the basement membrane and the mesangial matrix and secondly a mixture of glomeruli which may be affected to a variable degree. Therefore, immunohistochemical studies have been performed to distinguish the changes within the different compartments of the glomerulus and between the individual glomeruli.

These immunohistochemical studies, summarized in table 19-2, indicate that in diabetic kidneys with slight lesions only a minor increase in all basement membrane components was found except for HSPG. More pronounced diffuse glomerulosclerosis showed a further increase in basement membrane components, especially collagen IV α1,α2-chains in the expanded mesangial matrix. However, HSPG which was entirely absent from the enlarged matrix could only be observed in the periphery of the glomeruli. The staining of collagen IV α3,α4-chain showed a similar

Table 19-2. Changes of glomerular matrix composition in different stages of diabetic glomerulosclerosis (GS)*

	diffuse GS		nodular GS	
	GBM	mesangium	GBM	mesangium
laminin	↑	↑	↑	↓
collagen IV				
α1,α2-chain	↑	↑	↑	↓
α3,α4-chain	↑	-	↑	↑
HSPG	↓→	↓	↓	-
fibronectin A^+	-	n.d.	-	↑
collagen III	-	-[1]	-	↑[2]
collagen VI	↓	↑[3]	↓	↑↑

↑ = increased; ↓ = decreased; → = unchanged; - = not detectable; *see also [6-8]; n.d. = not determined; [1]traces in late diffuse GS; [2]only peripheral; [3]focally

distribution as found for HSPG however, with intense staining of the thickened glomerular basement membrane [6]. To this stage of nephropathy the accumulation of excess matrix material can be attributed to quantitative changes of the components present in normal glomeruli. In contrast, pronounced nodular lesions exhibited a strong decrease of collagen IV α1,α2-chains, laminin, and HSPG which were only detectable in the periphery of the noduli. Staining sequential sections with collagen VI antiserum or PAS revealed coincidence of both stainings indicating that the noduli consist mostly of collagen type VI [8]. Peripheral areas of these noduli were also positive for collagen III which was not detected in earlier lesions. It appears that in diffuse glomerulosclerosis an increase in normal matrix components occurs while the nodular glomerulosclerosis is characterized by qualitative changes (table 19-2).

Morphological and structural changes occurring in the interstitium, tubuli or glomerular arterioles are a concomitant of diabetic nephropathy [1].

The likelihood that increased matrix content occurring in diffuse glomerulosclerosis is the consequence of increased synthesis coupled with decreased degradation is supported by in vivo and in vitro studies of collagen metabolism in glomeruli obtained from diabetic animals [20,25,26]. An increased synthesis was unequivocally demonstrated by extracellular matrix gene expression. Fukui et al.

[27] showed increased steady state mRNA levels of the collagen IV α1-chain, laminin B1 and B2 and fibronectin while the collagen I α1-chain was unchanged in the kidneys of diabetic rats after one month of diabetes. The message for HSPG was decreased after induction of diabetes and increased steadily afterwards. The changes in mRNA levels which preceded the glomerular matrix expansion could be prevented by normalisation of blood glucose by insulin treatment. Obviously, the increased synthesis of collagen IV, laminin and fibronectin is the biochemical correlate of the expansion of the mesangial matrix and the thickening of glomerular basement membrane observed histologically. The occurrence of decreased degradation of matrix components has also been documented [26].

Extensive studies have shown that the changes in glomerular ultrastructure are closely associated with renal function [2,3]. Comparing the immunohistochemical findings with clinical data Nerlich et al. [7] found that the increase in the glomerular matrix components was consistently associated with impaired renal filter function. Late stage nodular glomerulosclerosis associated with decrease of all basement membrane components and increase in collagen III and VI coincided with severe renal insufficiency. In all cases, even in early diffuse glomerulosclerosis, HSPG was decreased.

INVOLVEMENT OF GROWTH FACTORS IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

The morphological changes occurring in diabetic micro- and macroangiopathy have led to the idea that growth hormone or other growth factors may play an active role in mediating these alterations [28]. In a recent study with experimental animals Nakamura et al. [29] demonstrated the gene expression of different growth factors including TGF-ß, bFGF and platelet derived growth factor in glomeruli of diabetic rats within 4 weeks after induction of diabetes. The gene expression was relatively specific since other growth factors like IGF-I were unchanged. Insulin treatment partially ameliorated the induction of growth factors. In a related study Yamamoto et al. [14] report that in glomeruli of diabetic rats there is a slow, progressive increase in the expression of TGF-ß mRNA and TGF-ß protein. A key action of TGF-ß is the induction of extracellular matrix production and specific matrix proteins, known to be induced by TGF-ß, were increased in diabetic rat glomeruli. Corresponding changes were found in patients with diabetic nephropathy , whereas glomeruli from normal subjects or individuals with other glomerular diseases were essentially negative. These findings suggest that TGF-ß plays a pivotal role in the glomerular matrix expansion that occurs in diabetic nephropathy. A causal relationship between TGF-ß expression and matrix accumulation in the acute model

of glomerular nephritis was proven by preventing matrix accumulation with TGF-ß antiserum [30].

BIOCHEMICAL PATHWAYS INVOLVED IN THE PATHOGENESIS OF DIABETIC GLOMERULOPATHY

The biochemical mechanisms leading to the quantitative and finally qualitative alterations of the glomerular matrix and to the induction of growth factors are not well understood. Epidemiological studies indicate that the development of diabetic nephropathy is linked to hyperglycaemia [31, 32]. Three pathobiochemical pathways are favoured in the current discussion:

The first possibility involves the direct action of elevated glucose on the cells. Ayo and coworkers reported that prolonged exposure to high glucose concentration leads to an increase in collagen IV, laminin and fibronectin synthesis on the protein and mRNA level in mesangial cells [33]. Furthermore, mesangial cells exposed to elevated glucose synthesize less HSPG [34]. Studies with epithelial, endothelial and mesangial cells revealed that all three cell types of the glomerulus produce more collagen type IV when exposed to elevated glucose levels [35]. The in vitro experiments suggest that hyperglycaemia rather than hyperinsulinaemia or hyperosmolarity is the cause of enhanced matrix synthesis [33-35]. Recent in vitro studies suggest how elevated glucose concentrations may exert their effects on cellular metabolism. High glucose levels induce the transcription and secretion of TGF-ß in mesangial cells [36] and elevate cellular transcripts of TGF-α and bFGF in vascular muscle cells [37]. Several reports provide evidence for the involvement of glucose-induced activation of protein kinase C in the elevated synthesis of matrix components [38-40]. PKC activation may be also involved in the elevation of lipooxygenase products [32] which may lead to increased matrix production [41].

The second pathomechanism linking elevated glucose levels with diabetic nephropathy may be the non-enzymatic glycosylation (glycation) of matrix proteins which are freely accessible to glucose. The extent of glycation is dependent on proteins' half lives and the mean glucose level of the patient during the life time of the respective protein [42,43]. The amount of glycation in these tissues seemed to be related to the extent and severity of the patients' late complications [43]. More recent approaches suggest that the development of diabetic late complications may be linked to the formation of advanced glucosylation end-products (AGE-products) [44]. The AGE-products result from the slow decomposition of glycated proteins. With time highly reactive products are formed which may yield new modifications on the same or the neighbouring protein. These AGE-products lead to synthesis and secretion of cytokines like tumour necrosis factor, interleukin-1 and IGF-1 when bound to a specific AGE-receptor identified on macrophages [45]. AGE-products

also act on mesangial cells via platelet derived growth factor causing the cells to synthesize increased amounts of collagen IV, laminin and HSPG [46] while prolonged exposure to glycated matrices reduced collagen synthesis and proteoglycan charge [47]. Recently, pentosidine a well defined AGE-product has been implicated in the pathogenesis of diabetic nephropathy [48].

The third pathochemical mechanism involves intracellular formation of sorbitol from glucose catalysed by aldose reductase [49]. Chronic hyperglycaemia leads to sorbitol accumulation in a variety of tissues like peripheral neurons, lense and renal tubuli [50]. The initial hypothesis that sorbitol accumulation causes tissue damage is unlikely to operate in kidney [32]. The inositol depletion theory suggested by Greene and coworkers explains tissue damages as impairment of myo-inositol uptake leading to a decrease of phospatidyl-inositides in the cell membrane [49]. Although the cellular inositol uptakes is competitively inhibited by D-glucose [51] and non-competitively inhibited by hyperosmolar intracellular sorbitol [52], recent studies show that cells may counterregulate inositol depletion [39,53]. Thus, it is not generally agreed that the increase in intracellular sorbitol is the cause of the impaired function of the affected tissues in diabetes. Furthermore, after treatment of diabetic rats for six months with the aldose reductase inhibitor tolrestat only a slight reduction in the urinary albumin excretion rate was observed indicating that other mechanisms are operating in diabetic nephropathy [54].

CONCLUSIONS

The morphological observations of an expanded matrix in diabetic glomeruli are now supported by the immunohistochemical findings showing an increased deposition of normally occurring matrix components. The biochemical findings suggest that increased glucose concentrations stimulate the synthesis of the matrix components like fibronectin, laminin and collagen IV either by direct action or via formation of AGE products (figure 19-1). The increased matrix synthesis is probably mediated by cytokines. In particular, glucose-induced TGF-ß expression would explain the progressive accumulation of matrix material in diabetic patients with chronic hyperglycaemia since TGF-ß is unique among the cytokines in (i) stimulating the synthesis of matrix, (ii) inhibiting matrix degradation and (iii) inhibiting mesangial proliferation. The latter property of TGF-ß is consistent with the absence of mesangial cell proliferation in diabetic glomerulopathy. The in vitro and in vivo results indicate that diabetes induces a wound repair-like mechanism in glomeruli. A failure to turn off TGF-ß production due to a defect in TFG-ß regulation or repeated induction by glucose elevations may lead to a vicious cycle resulting in glomerulosclerosis and finally end-stage diabetic kidney. However, several characteristics of diabetic nephropathy like the paradoxical elevation and/or decrease

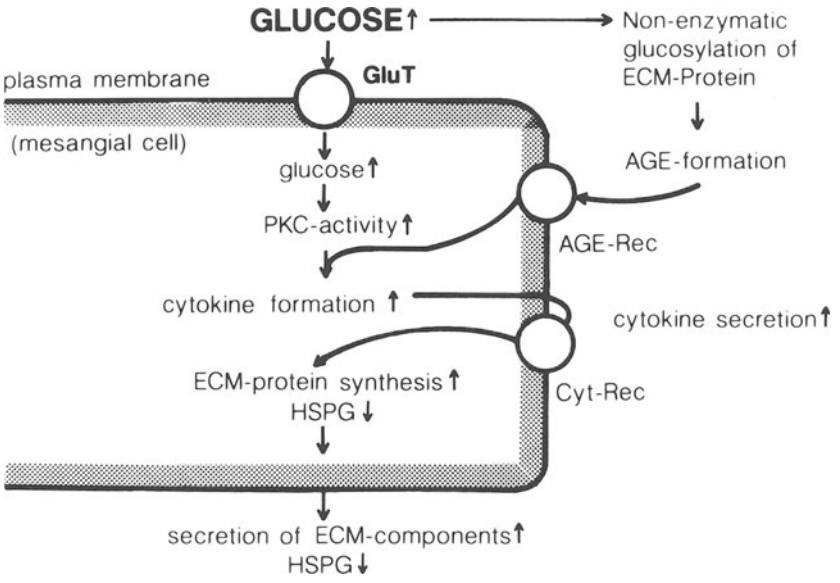

Figure 19-1. Sequence of molecular mechanisms possibly involved in the alterations of glomerular matrix proteins in diabetes. Two possibilities are shown by which elevated glucose may alter cellular metabolism and the metabolism of glomerular extracellular matrix components. AGE-Rec and Cyt-Rec indicate the receptors for AGE-products and cytokines, respectively. ECM = extracellular matrix; AGE = advanced glucosylation end products; PKC = protein kinase C; GluT = glucose transporter.

in HSPG, and the qualitative changes in matrix composition are not explained by the action of TGF-ß. Further studies which should include the use of inhibitors of the proposed pathobiochemical pathways will improve our understanding of the pathobiochemistry leading to diabetic nephropathy.

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20. THE STENO HYPOTHESIS AND GLOMERULAR BASEMENT MEMBRANE BIOCHEMISTRY IN DIABETIC NEPHROPATHY

ALLAN KOFOED-ENEVOLDSEN

INTRODUCTION

So far, at the biochemical level, the pathogenesis of diabetic nephropathy is unresolved. Not surprisingly perhaps since even a our understanding of the biochemical fundaments of normal glomerular function remains incomplete. In addition, when exploring the pathogenesis of diabetic nephropathy, we are likely to witness the composite course of succeeding stages, each of which may have its own pathogenetic trait.

The Steno hypothesis [1] suggests that impairment of heparan sulphate metabolism is a key-event in the development of diabetic nephropathy, and identifies impaired heparin sulphate metabolism as the link between diabetic nephropathy and the associated generalized cardiovascular disease. It may seem risky to postulate a single mechanism as a key feature in the pathogenesis of diabetic nephropathy, having recognised the possible complexity of the disease process. On the other hand however, the need to forward specific hypotheses is augmented by our current stage

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of incomplete knowledge, the alternative being to go on »fishing trips« with the risk of getting the net plugged with trivial catch.

LOSS OF CHARGE SELECTIVITY AND THE DEVELOPMENT OF ALBUMINURIA

Urinary protein excretion is normal from the onset of diabetes, except during episodes of poor metabolic control. After some years, the urinary excretion of albumin and other large plasma proteins eventually start to increase. With reservations to the effect of current and future more aggressive metabolic and blood pressure control, ultimately 30 to 40% of all IDDM patients will progress to clinical diabetic nephropathy. The cumulative incidence of microalbuminuria (30-300 mg/24 h) is not known, but the overall prevalence seems to be around 20% [2].

Reduced glomerular charge selectivity may serve as the pathophysiological fundament of the initial rise in urinary albumin excretion. Charge selectivity is effective for proteins of a wide size range, e.g. from 61 Å ferritin molecules to 30 Å horse radish peroxidases [3]. It has been calculated a 30% decrease in the glomerular filtration barrier charge (from 150 to 100 meq/l) may cause a 25-fold increase in the fractional clearance of albumin [4]. In comparison, a doubling of the effective pore radius may not cause more than a 5-fold increase in the fractional albumin clearance [4]. Glomerular charge-selectivity can not be quantitated directly in man, but may be estimated from measurements of the relative clearance of differently charged, similarly sized endogenous proteins.

The first indication of reduced glomerular charge-selectivity in microalbuminuric IDDM patients was published by Viberti et al. [5]. Succeeding studies have confirmed this finding, the most recent one being from Deckert et al. [6]. In the later study, patients with urinary albumin excretion in the range 30-100 mg/24 h had a 50% reduction in the total-IgG:IgG_4 selectivity index compared both to normoalbuminuric patients and to healthy control subjects. Strict metabolic control may retard the progression of microalbuminuria, and Bangstad et al. recently studied the effect of intensified insulin treatment on the total-IgG:IgG_4 selectivity index in microalbuminuric IDDM patients, demonstrating a significant normalization of total-IgG:IgG_4 selectivity index within a few months [7]. Although in our study [6] no accompanying impairment of glomerular size selectivity using dextran clearance during the early stages of diabetic nephropathy could be demonstrated, formation of a subtle non-size-selective glomerular shunt - as suggested in advanced diabetic nephropathy [8] [9] - may however still explain the observed changes in the proposed charge sensitive indices [Kofoed-Enevoldsen 1993, unpublished].

In conclusion, current data are in accordance with an initial impairment of glomerular charge selectivity as responsible for the development of microalbuminuria, although definite proof has not yet been presented.

THE GLOMERULAR BASEMENT MEMBRANE

The structural domain responsible for glomerular charge selectivity includes the glomerular basement membrane [3]. Anionic sites present in the glomerular basement membrane may be of crucial importance for maintenance of charge selectivity. Heparitinase treatment removes 80-100% of the anionic sites from the lamina rara externa, indicating that within the lamina rara externa these sites are predominantly composed of heparan sulphate glycosaminoglycan [10]. Removal of glomerular basement membrane heparan sulphate glycosaminoglycan by heparinase treatment induces increased permeability for albumin [11]. Recently Van Den Born et al. [12] demonstrated that a rapid loss of charge-selectivity and onset of proteinuria can be induced in rats by injecting a monoclonal antibody directed towards the heparan sulphate glycosaminoglycan chain whereas antibodies directed towards the heparan sulphate core protein or other glomerular basement membrane components had no effect.

Information regarding biochemical changes in the glomerular basement membrane in diabetes in general or in diabetic nephropathy specifically is scarce. A likely biochemical abnormality is the formation of advanced glycosylation end-products, which in turn may interfere with basement membrane assembly [13]. Whether this phenomenon is specifically associated to the development of diabetic nephropathy is however unknown. A 10% reduction in sialic acid content has been found in patients with diabetic nephropathy, but in general no major specific alterations in the basement amino acid or carbohydrate content have been demonstrated [14].

Quantitative measurement of glomerular basement membrane heparan sulphate in IDDM patients with microalbuminuria was recently published [10] reporting a 30-40% reduction in number of heparinase digestible anionic sites in the glomerular basement membrane lamina rare externa in IDDM patients with urinary albumin excretion above 200 mg/24 h. No reduction in the number of sites was however found in 3 patients with urinary albumin excretion in the range from 30 to 100 mg/24 h compared to 5 patients with normal urinary albumin excretion. Shimomura & Spiro [15] and Parthasarathy & Spiro [16] found a 70% decrease in glomerular basement membrane heparan sulphate core protein and a 40% decrease in glomerular basement membrane heparan sulphate glycosaminoglycan content in patients with »histological evidence of varying degrees of diabetic glomerulopathy«. Semiquantitative immunohistochemical measurements have indicated a reduction in

HS core protein in the glomerular basement membrane of patients with advanced diabetic nephropathy [17]. In contrast, Van Den Born et al. [18] using a different panel of antibodies found normal immunohistochemical staining of HS core protein while segmental or absent staining was observed with an antibody directed against the heparan sulphate glycosaminoglycan chain in 8 out of 10 biopsy samples from IDDM patients with diabetic nephropathy. Thus in man, demonstration of significant changes in basement membrane HS content is restricted to advanced diabetic nephropathy.

Animal experiments provide diverging results regarding the impact of poorly controlled diabetes on glomerular basement membrane heparan sulphate. A 50% decreased de novo synthesis of overall glomerular heparan sulphate in isolated glomeruli from diabetic rats was found by Reddi et al. [19] whereas Klein et al. [20] found no significant change. Incorporation of newly synthesized heparan sulphate into the glomerular basement membrane was reduced 30-60% in two studies [20] [21]. In vivo labelling of newly synthesized glomerular basement membrane heparan sulphate has suggested either a decrease [22] or no change [20,23]. Steady-state glomerular basement membrane heparan sulphate content per glomeruli has been measured in three studies, showing either a 60% decrease [24] or no significant change [25,26]. Sulphation of heparan sulphate was 50% decreased in one study [26] and not significantly changed in two [25,23]. Heparan sulphate GAG chain size has not been significantly altered in any of the above mentioned studies. Abnormalities in heparan sulphate-matrix interactions causing increased constitutive release of heparan sulphate from isolated glomerular basement membranes have been suggested [23]. Finally, Fukui et al. [27] reported a specific 50% decrease in glomerular heparan sulphate core protein (HSPG2) mRNA expression after 4 weeks of diabetes duration, while the mRNA's of other glomerular basement membrane components were increased. Subsequently a specific 2-fold increase in HSPG mRNA from week 4 to week 24 of diabetes was found. In our STZ- and spontaneously diabetic rats, no significant reduction in kidney cortex HSPG2 mRNA was seen after 4 weeks of diabetes when comparing animals in poor and good metabolic control [28]. Thus, although animal studies offer a variety of results, the all round trend for heparan sulphate is either »unchanged« or »reduced«. It is not possible to pin-point one single pathobiochemical mechanism.

Diabetes may be associated with a decrease in the ratio between the biosynthesis heparan sulphate and the rate of biosynthesis of several other extracellular matrix components. In the isolated perfused rat kidney, reactive oxygen species produced a 10 to 20-fold decrease in heparan sulphate core protein synthesis and glomerular basement membrane ^{35}S incorporation, whereas collagen IV and laminin were only slightly affected [29]. In cultured porcine mesangial cells high glucose induced a 10

to 50% decrease in basement membrane heparan sulphate core protein, whereas the content of fibronectin remained unchanged [30]. In contrast, Doi et al. [31] found a general increment in mRNA for both collagen IV, laminin *and* heparan sulphate core protein in mouse mesangial cells exposed to advanced glycosylation end-product-modified albumin. Several studies have found a stimulatory effect of high glucose on collagen IV synthesis rate and mRNA expression in vitro in rat mesangial cells, human umbilical vein endothelial cells, and mouse proximal tubular cells [32,33,51], a tendency markedly contrasting to the findings of impaired rather than stimulated heparan sulphate synthesis as discussed above. Thus a reduction in basement membrane heparan sulphate may result from a *dys*coordinated regulation of the synthesis of basement membrane components.

The summary above is primarily related to diabetes-induced changes in glomerular basement membrane heparan sulphate obtained in IDDM patients and models of type 1 diabetes mellitus. In defiance of a vast amount of studies reported, a definite description of the pathobiochemistry of diabetic nephropathy may not be for long time yet.

THE STENO HYPOTHESIS

The Steno hypothesis states that »*Decreased concentration of heparan sulphate in the extracellular matrix explains the simultaneous occurrence of albuminuria and premature atherosclerosis in IDDM. The decrease in heparan sulphate is caused by the combined effect of poor metabolic control and genetic factors, possibly mediated through inhibition of the glucosaminyl N-deacetylase*« [1]. Thus besides establishing a connection with albuminuria, decreased heparan sulphate concentration is suggested to be involved in the development of premature atherosclerosis among patients with diabetic nephropathy.

Endothelial cell surface and vascular smooth muscle cell basement membrane heparan sulphate express a variety of anti-atherogenic properties. These include increasing antithrombin III activity, interaction with lipoprotein lipase, maintenance of cellular adhesion, and regulation of cellular proliferation [34,35] [36]. Extensive reviews of the background for hypothesising a role for heparan sulphate in the development of premature atherosclerosis can be found in [37] and [38].

The methodological difficulties in measuring the concentration of vascular heparan sulphate are not less than those of quantitating glomerular basement membrane heparan sulphate. A recently applied alternative is measurement of the plasma concentration of prothrombin fragment 1+2 which may provide a close-up indirect estimate of the effective concentration of vascular heparan sulphate. The rationale is that a reduction in endothelial heparan sulphate content will reduce the antithrombin III mediated inhibition of coagulation factor-Xa in turn leading to the

production of increased amounts of prothrombin fragment 1+2 by factor-Xa induced convertion of prothrombin to thrombin. The Steno hypothesis has postulated this mechanism to cause increased fibrin deposition and increasing the plasma concentration of von Willebrand factor. Indeed increased plasma concentration of prothrombin fragment 1+2 was recently reported in IDDM patients with microalbuminuria [39]. In contrast however, another recent study could not confirm this finding [40] although a positive correlation between prothrombin fragment 1+2 and transcapillary escape rate of albumin (known to be elevated in diabetic nephropathy) was found.

The mechanism behind the increased transcapillary escape rate of albumin in patients with microalbuminuria or clinical diabetic nephropathy, according to the Steno hypothesis, may be loss of subcutaneous capillary charge-selectivity much parallel to the hypothesized mechanism behind the development of increased urinary albumin excretion. Again recent studies specifically addressing this hypothesis provides diverging results. Estimating capillary charge selectivity from interstitial fluid concentrations of differently charged endogenous proteins we found no evidence of reduced charge selectivity in patients with nephropathy [41]. In contrast, Bent-Hansen et al. [42] - using exogenous tracers and possibly a more sensitive study design - have presented data to support the hypothesized reduction in general capillary charge selectivity.

The Steno hypothesis finally proposes that diabetes-induced impairment of heparan sulphate metabolism may be mediated by inhibition of the key enzyme glucosaminyl N-deacetylase. This enzyme plays a key role in the biosynthesis of heparan sulphate, since N-deacetylation is prerequisite to N-sulphation and further modifications of the newly synthesized glucosaminoglycan polymer. Prompted by the original demonstration by Kjellén et al. [43] of diabetes-induced reduction in hepatic heparan sulphate sulphation, several studies within the recent few years have demonstrated that experimental diabetes per se leads to inhibition of N-deacetylase activity [28,44-46]. The degree of inhibition correlates to blood glucose control reducing activity by 40-50% when blood glucose exceeds 15 mmol/l, and may be completely prevented by near-normalisation of blood glucose by intensified insulin treatment. An intriguing finding relating the role of inhibition of N-deacetylase to the development of diabetic nephropathy is the apparent correlation between glomerular N-deacetylase activity and urinary albumin excretion [28,46]. Finally our animal experiments have indicated that genetic factors seem to influence the vulnerability of the N-deacetylase towards diabetes-induced inhibition, as evident from studies including different rat strains [28,45,46]. Measurements of N-deacetylase activity in patients with diabetic nephropathy have till now been restricted to in vitro studies of fibroblast cell cultures. No major constitutive reduction in

N-deacetylase activity was found in cultured skin fibroblasts from IDDM patients with diabetic nephropathy [47]. However the possibility that activation of protein kinase A might be involved in the diabetes-induced N-deacetylase inhibition was suggested in this experiment. Insulin inhibits protein kinase A activity by decreasing its binding of cAMP [48] and insulin resistance is associated with a decrease in insulin-induced protein kinase A down-regulation [49]. Our study may, therefore, have identified a general pathway, i.e. protein kinase A activation, for down-regulation of N-deacetylase activity in diabetes. This mechanism could provide an explanation for the postulated association between development of diabetic nephropathy and the presence of insulin resistance [50], involving decreased N-deacetylase activity.

CONCLUSION

Since the publication of the first studies relating heparan sulphate to diabetic nephropathy a decade has passed during which the Steno hypothesis has found both support and neglect. As a working hypothesis, it remains a valuable guiding tool when exploring the pathogenesis of diabetic nephropathy.

Improvement of methodological means for quantitative and qualitative measurements of cell surface and basement membrane heparan sulphate may be essential to allow for further significant progress.

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21. VOLUME HOMEOSTASIS AND BLOOD PRESSURE IN DIABETIC STATES

JAMES A. O'HARE and J. BARRY FERRISS

1. BLOOD PRESSURE AND BODY FLUIDS

The final determinants of arterial blood pressure are cardiac output and systemic vascular resistance [1]. Cardiac output is determined by extracellular fluid (and blood volume) and filling pressure. Peripheral resistance is influenced by a host of factors, with the renin-angiotensin-aldosterone axis, atrial natriuretic factor and the sympathetic nervous system playing the leading neuro-endocrine roles in volume/resistance homeostasis.

In this chapter we will review studies of extracellular fluid, sodium and the status of their homeostatic neuroendocrine systems in a variety of diabetic states.

2. METABOLIC CONTROL INFLUENCES VOLUME HOMEOSTASIS

It is a fundamental clinical observation that states such as ketoacidosis and hyperosmolar non-ketotic coma are characterised by profound dehydration and electrolytes deficits. In less severe states of poor metabolic control there appears to be mild stimulation of the renin angiotensin-aldosterone system in human studies and

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with improvements in metabolic control there is an increase in total exchangeable sodium and plasma volume and down regulation of the renin-angiotensin system [2]. By contrast studies in streptozotocin induced diabetes in rats are associated with a paradoxical increase in fluid volumes, suppression of renin and stimulation of atrial natriuretic factor [3]. While these unexpected trends have not been seen in most human studies, higher plasma atrial natriuretic peptide (ANP) and lower plasma renin activity (PRA) were found in poorly controlled diabetics in one report [4].

3. SODIUM RETENTION OCCURS IN NORMOTENSIVE DIABETICS

Exchangeable sodium is frequently elevated in both IDDM and NIDDM normotensive diabetic patients without overt nephropathy [5,6,7]. Total body sodium measured by neutron activation analysis is also increased [8]. Extracellular volume is expanded [7-9] to a similar degree in IDDM patients with both elevated and normal glomerular filtration rates [9].

Sodium retention in the absence of elevated blood pressure might be explained by cardiac impairment, by altered vascular reactivity, or by a change in Starling's forces in the microcirculation. Significant myocardial dysfunction is unusual in insulin-dependant diabetics in good metabolic control [10]. Vascular reactivity to infused norepinephrine [5] and angiotensin II [11] is enhanced in diabetics without complications, findings which do not favour decreased vascular reactivity as a cause of sodium retention. Increased microvascular permeability to albumin [12,13] and fluid [14] have been demonstrated especially in patients with microvascular complications. The transcapillary escape rate of albumin is positively related to 24-h urinary albumin excretion and to exchangeable sodium in normotensive diabetics [15].

Sodium retention may result from a primary renal defect. Normotensive IDDM patients without clinically overt renal disease have an impaired ability to excrete a water load [9] and have a diminished natriuresis in response to underwater immersion [16]. This impaired natriuresis occurs despite an increase in creatinine clearance and in filtered sodium, indicating enhanced tubular sodium reabsorption [9].

Physiological or elevated levels of insulin may stimulate sodium retention in the renal tubule [17,18] although infusions of insulin at physiological concentrations do not impair the natriuretic response to immersion in normal subjects [19]. Marked hyperinsulinaemia reduces urinary sodium excretion even in subjects and animals who are insulin resistant in respect of glucose metabolism [18,20]. However despite sodium retention insulin does not raise blood pressure acutely in diabetics [21]. Thus it is possible that the hyperinsulinaemia that occurs episodically in IDDM and that is seen in some patients with NIDDM contributes to sodium retention. Proximal

tubular absorption of sodium may be amplified in the presence of hyperglycaemia [22].

Plasma aldosterone concentrations are generally normal in metabolically well controlled patients [5,23]. By contrast basal ANP concentrations are slightly elevated in IDDM [9] and NIDDM [24]. In IDDM patients the ANP response both to saline loading [9] and to water immersion [16] are normal. However the natriuretic response to a saline load remained impaired during ANP infusion [25] demonstrating the presence of impaired renal responsiveness to ANP. Nevertheless renal blood flow responsiveness to short term infusions of ANP was preserved in diabetics with established chronic renal failure (26).

It is possible that blood pressure is sodium dependent in such patients, albeit in the normal range. In contrast to normal subjects, normotensive diabetics without overt nephropathy show a weak positive association between systolic blood pressure and exchangeable sodium [27]. Exchangeable sodium in these patients also correlates with 24-h urinary albumin excretion [15] and sodium retention is a possible explanation for the small blood pressure rise often seen in patients with incipient nephropathy [7].

Blood volume appears to be normal in normotensive diabetics without long-term complications [5,6]. A small increase in blood volume may result in a substantial increase in blood pressure [28] however, and current techniques may not detect subtle changes.

Despite the presence of sodium retention, PRA is generally normal in IDDM patients without complications [27,29-31]. In contrast PRA is suppressed in normotensive non-insulin dependent diabetics compared with similar-aged control subjects [32], findings consistent with functional suppression by increased body sodium.

4. HYPERTENSION IN NON-INSULIN DEPENDENT DIABETICS

Up to 50% of patients with NIDDM may have hypertension [33]. It is often present at the time diabetes is detected [34]. There are likely to be a variety of causes, including factors co-associating through insulin resistance [35], nephropathy from diabetes and other causes of hypertension.

We measured exchangeable sodium and PRA in hypertensive non-insulin dependent diabetic patients without overt nephropathy [32]. The findings were compared with those in control subjects, normotensive diabetics and patients with essential hypertension of similar age. Urinary albumin excretion was similar in normotensive and hypertensive diabetics and in patients with essential hypertension. It is unlikely that hypertension could be attributed to nephropathy in diabetic patients and was present at diagnosis of diabetes in most. Exchangeable sodium was similar

in control subjects and in essential hypertension, as previously described [36]. Exchangeable sodium was elevated in normotensive non-insulin dependent patients, but was not clearly elevated in hypertensive diabetic subjects. A similar pattern has been described in non-nephropathic hypertensive diabetics when total body sodium was measured by neutron activation analysis [8]. Exchangeable sodium and blood pressure were not related in either hypertensive group [32]. On the other hand PRA was suppressed in both normotensive and hypertensive diabetic patients. Intravascular volume tended to be lower in both non-diabetic and diabetic hypertensives, compared with their control groups.

Thus, as in essential hypertension, the hypertensive NIDDM patient without nephropathy is not characterised by volume expansion, and PRA is appropriately suppressed. The findings contrast with those in nephropathic hypertension discussed below.

5. DIABETIC NEPHROPATHY

Overt diabetic nephropathy is associated with marked fluid retention and a disturbance of a variety of endocrine regulators of volume homeostasis.

Exchangeable sodium is further increased in nephropathic patients compared with patients with uncomplicated diabetes [6], and is positively related to blood pressure in incipient [7] and overt nephropathy [6]. Again, the causes of sodium retention are multiple. The transcapillary escape rate of albumin is usually elevated [12] and in more advanced cases hypoalbuminemia may be present. Some patients develop neuropathic oedema secondary to loss of autonomic nervous regulation of microvascular blood flow in the lower extremities [37], and myocardial failure may also contribute to fluid retention [38]. Intravascular volume is not increased [6]. This is not surprising however, in the light of other forms of renal disease with hypertension [39].

Early reports of PRA and plasma aldosterone in patients with advanced diabetic nephropathy described diminished responses to volume depletion [40,41]. In patients with less severe disease and receiving an unrestricted sodium intake, plasma levels of renin, angiotensin II and aldosterone may not be suppressed [6,23], although low plasma angiotensin 11 concentrations have been reported in IDDM patients with and without nephropathy despite normal renin values [7]. Higher renin levels have also been described in diabetic nephropathy [42]. The sodium-renin product which reflects the combined influence of exchangeable sodium and plasma renin activity, is increased in patients with diabetic nephropathy, compared with diabetic patients without complications and non-diabetic controls [6]. While overt hyporeninemic hypoaldosteronism is relatively rare [23], an elevation of circulating inactive renin

is common and appears to be a marker for microvascular complications [43]. It's functional significance if any, is unknown.

Plasma ANP concentrations are elevated in diabetic nephropathy showing a marked increase during water immersion but renal cyclic GMP responses are blunted suggesting renal resistance to ANP [44]. In NIDDM patients urinary dopamine excretion is significantly lower in patients with overt nephropathy compared to those with normal albumin excretion [45]. PRA has been reported to suppress during water immersion in normal subjects and in diabetic patients with normal albumin excretion or microalbuminuria [46] but not in diabetic nephropathy [44].

In other forms of chronic renal failure, raised blood pressure appears to be related to sodium retention and inappropriate activity of the renin-angiotensin system. Exchangeable sodium is elevated, PRA is inappropriately high and blood pressure is positively related to both exchangeable sodium and the sodium-renin product [47,48]. Similar mechanisms seem to operate in patients with diabetic nephropathy; exchangeable sodium is increased, PRA is not suppressed despite marked sodium retention and blood pressure is positively related to both exchangeable sodium and the sodium-renin product [6,49].

Orthostatic hypotension due to sympathetic autonomic neuropathy can accompany diabetic nephropathy. Despite this orthostatic hypotension, blood pressure may be quite elevated in the supine position constituting a difficult clinical problem. Exchangeable sodium tends to be highest in subjects with nephropathy and supine hypertension, while values are relatively low in non-nephropathic patients [50].

6. IMPLICATIONS FOR MANAGEMENT OF HYPERTENSION

As is discussed elsewhere in this volume effective treatment of hypertension delays the decline of renal function in IDDM patients with diabetic nephropathy. How are volume and its homeostasis effected by therapy of hypertension in diabetics? In view of the evidence that hypertension in nephropathy be may be at least partly maintained by sodium retention and inappropriate activity of the renin-angiotensin system, initial treatment with a diuretic seems logical. Thus, Weidmann et al. [51] studied a mixed group of mildly hypertensive diabetic patients, with and without long-term complications including nephropathy. Chlorthalidone produced a fall in blood pressure and in exchangeable sodium, while exaggerated pressor responses to norepinephrine, and angiotensin II were restored to normal. Plasma renin and aldosterone rose briskly, perhaps blunting the antihypertensive effect. A recent worrisome observation is that diuretic therapy was associated with higher cardiovascular mortality compared to similar hypertensive diabetics who were not treated [52].

ACE inhibition produces a substantial natriuresis in diabetics [26] supporting the role of abnormal sodium-renin relationships in some patients with diabetic nephropathy. Furthermore renal responsiveness to plasma ANP was restored. Finally, moderate sodium restriction [53] in hypertensive type 2 diabetics seems to have a clinically significant effect in lowering BP to a degree comparable to antihypertensive therapy.

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22. PATHOGENESIS OF DIABETIC GLOMERULOPATHY: THE ROLE OF GLOMERULAR HEMODYNAMIC FACTORS

JITEN P. VORA, SHARON ANDERSON and BARRY M. BRENNER

INTRODUCTION

Glomerular hyperfiltration in insulin-dependent (type 1) diabetes mellitus (IDDM) has been recognized for many years [1-3], with increments in renal plasma flow (RPF) and nephromegaly [3]. With the finding of hyperfiltration, Stalder and Schmid proposed that these early functional changes may predispose the subsequent development of diabetic glomerulopathy [1]. Early support for the hypothesis that renal hyperperfusion and hyperfiltration contribute to diabetic glomerulopathy emanated from the finding of diabetic glomerulopathy only in the non-stenosed kidney in the setting of unilateral renal artery stenosis [4].

Although glomerular hyperperfusion and hyperfiltration have been well documented in IDDMs [1-3], similar studies have only recently been performed in the much larger patient population with non-insulin-dependent (Type 2) diabetes mellitus (NIDDM). Studies reveal a wide range of renal hemodynamics in NIDDMs, but provide clear evidence for elevations of GFR and RPF in significant proportions of patients of Caucasian, Native- and Afro-American origin [5-8]. Hyperfiltration

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(defined as GFR values above the mean + two standard deviations for age-matched normal subjects [120 ml/min/1.73 m^2]) was detected in 45% of newly presenting normotensive non-proteinuric NIDDMs [5]. Filtration fraction was also elevated, suggesting an increase in glomerular capillary pressure. Preliminary longitudinal data in Pima Indians also reveals significant increases in GFR and RPF at the time of development of NIDDM [8].

It has been proposed that the glomerular hyperfunction of early Type 1 diabetes predicts the later development of overt nephropathy and diabetic glomerulopathy [9,10], while others have failed to document such a relationship [11,12]. The reasons for these disparate results are as yet unclear. Likewise, the role of the glomerular hyperfiltration observed in NIDDMs in the subsequent development of nephropathy remains to be established in longitudinal studies. However, preliminary results indicate a reduction in GFR in NIDDMs over the first 2 years after diagnosis, with the greatest changes in the younger patients with initial GFR values greater than 120 ml/min [13]. Despite the controversy in human diabetes concerning the significance of hyperfiltration in the subsequent development of overt nephropathy, extensive experimental data provides considerable insight into the importance of hemodynamic factors in the initiation and progression of diabetic glomerulopathy [14,15].

Renal Hemodynamics in Experimental Diabetes Mellitus

Several animal models with spontaneous or induced diabetes have been used to study the role of altered hemodynamics in the development of diabetic glomerulopathy [14,15]. As in Type I diabetic patients [16], diabetic rats tend to exhibit reduced values for whole kidney GFR during periods of severe uncontrolled hyperglycemia; single nephron (SN) GFR and plasma flow rates are also normal or reduced in animals in such catabolic states [17]. In the more clinically applicable model with moderate hyperglycemia, whole kidney GFR and SNGFR increase by about 40% as compared to normal rats [17-19]. Reductions in intrarenal vascular resistances result in elevation of the glomerular capillary plasma flow rate, Q_A. Despite normal blood pressure levels, transmission of systemic pressures to the glomerular capillaries is facilitated by proportionally greater reduction in afferent compared to efferent arteriolar resistances [17-19]. Consequently, the glomerular capillary hydraulic pressure (P_{GC}) rises. Thus, the observed single nephron hyperfiltration results from both glomerular capillary hyperperfusion and hypertension [17-19]. In longterm studies, diabetic rats develop morphologic changes reminiscent of those in the diabetic human, including glomerular basement membrane thickening, renal and glomerular hypertrophy, mesangial matrix thickening and hyaline deposition, and ultimately glomerular sclerosis [18-23].

Evidence that these glomerular hemodynamic maladaptations contribute to the development and progression of diabetic glomerulopathy has been shown by studies involving maneuvers which aggravate or ameliorate glomerular hyperperfusion and hyperfiltration, without affecting metabolic control. Uninephrectomy, which increases SNGFR, Q_A and P_{GC} in normal rats, accelerates the development of albuminuria and glomerular sclerosis in diabetic rats [24]. Intensification of glomerular lesions is observed in the unclipped kidney of diabetic rats with two-kidney Goldblatt hypertension, while the clipped kidney is substantially protected from glomerular injury [25]. Diabetic renal injury is similarly amplified by augmentation of dietary protein content, which increases glomerular perfusion and filtration [18].

By contrast, dietary protein restriction, which reduces SNGFR, Q_A and P_{GC} in other models, has clarified the role of hemodynamic factors in diabetic glomerulopathy. In long-term diabetes, low protein diets limited SNGFR by reducing the elevated P_{GC} and Q_A, and virtually prevented albuminuria and glomerular injury. In contrast, diabetic rats fed a high protein diet exhibited glomerular capillary hyperfiltration, hyperperfusion and hypertension, and marked increases in albuminuria and glomerular morphologic injury [18]. As there were no differences in metabolic control between the various groups, this study provided clear evidence that amelioration of the maladaptive glomerular hemodynamic pattern could dramatically lower the risk of diabetic glomerulopathy.

Mechanisms of Hyperfiltration in Diabetes

The pathogenesis of diabetic hyperfiltration is multifactorial. Numerous mediators for this effect have been proposed (table 22-1), and are briefly reviewed here. The metabolic milieu may contribute: hyperglycemia and/or insulinopenia *per se* [26], together with augmented growth hormone and glucagon levels [27,28]. Reduction of plasma glucose with initial institution of insulin therapy reduces GFR in both Type 1 and 2 diabetes [26,29]. In moderately hyperglycemic diabetic rats, normalization of blood glucose levels reverses hyperfiltration [30], and insulin infusion reduces P_{GC} [31]. By contrast, insulin infusion sufficient to produce hyperinsulinemia, with euglycemia, increases P_{GC} and hyperfiltration in normal rats [32]. Further, infusion of blood containing early glycosylation products reproduces glomerular hyperfiltration in normal rats [33].

Diabetes is also characterized by other physiologic changes with hemodynamic consequences, including elevation of plasma atrial natriuretic peptide levels [34]; possible augmentation of endothelium-derived relaxing factor activity [35]; reduced glomerular receptor sites for the vasoconstrictive Ang II and thromboxane [36,37]; vascular hyporesponsiveness to catecholamines and Ang II [38], and blunting of the

Table 22-1. Potential mediators of diabetic hyperfiltration

Hyperglycemia/insulinopenia
Extracellular fluid volume expansion
Blunted tubulo-glomerular feedback
Advanced glycosylation end-products
Atrial natriuretic peptide
Endothelial-derived relaxing factor
Vasodilator prostaglandins
Increased plasma ketone bodies, organic acids
Increased plasma glucagon levels
Increased plasma growth hormone levels
Increased insulin-like growth factor-1
Relative renin-angiotensin deficiency
Hyporesponsiveness to catecholamines/angiotensin II
Abnormalities in calcium metabolism
Abnormal myo-inositol metabolism
Tissue hypoxia/abnormalities in local vasoregulatory factors

tubulo-glomerular feedback mechanism [39]. Each of these may contribute; for example, blockade of atrial natriuretic peptide action with an antibody [34] or a specific receptor antagonist [40] blunts hyperfiltration in diabetic rats. Enhanced activity of vasodilator prostaglandins is another mechanism proposed as a mediator of diabetic hyperfiltration, as prostaglandin synthetase inhibition results in significant reductions in SNGFR, Q_A and P_{GC} [41]. Diabetes related abnormalities of other vasodilator mechanisms have also been suggested, with findings of elevated urinary metabolites of the kallikrein-kinin system [42]. Indeed, infusion of a specific bradykinin BK_2 receptor antagonist reduces GFR and RPF in diabetic rats [43].

Increased activity of the polyol pathway and related disturbances in cellular myo-inositol metabolism have been implicated in the pathogenesis of several diabetic microangiopathic complications. Dietary myo-inositol supplementation and pharmacologic inhibition of aldose reductase sometimes [44] though not always [45] prevent renal hypertrophy, hyperfiltration and proteinuria in diabetic rats.

Role of glomerular capillary hypertension

Of the glomerular hemodynamic determinants of hyperfiltration, the available evidence suggests that glomerular capillary hypertension plays the key role in progression of renal injury. Long-term protection against albuminuria and glomerular sclerosis was obtained in normotensive diabetic rats by angiotensin I converting enzyme inhibitor (CEI) therapy in doses which modestly lowered systemic blood pressure, but selectively normalized P_{GC}, without affecting the

supranormal SNGFR and Q_A [19]. Studies in a variety of experimental models, including diabetes, have consistent shown that interventions which control glomerular capillary hypertension are associated with marked slowing of the development of structural injury [46].

Little is yet known of the exact mechanism(s) by which glomerular capillary hypertension eventuates in structural injury. Recently, innovative new techniques using a variety of *in vitro* systems have been developed to address this question. These studies postulate that glomerular hemodynamic factors modify the growth and activity of glomerular component cells, inducing the elaboration or expression of cytokines and other mediators which then stimulate mesangial matrix production and promote structural injury. For instance, increased shear stress on endothelial cells enhances activity of such mediators as endothelin [47], nitric oxide [48], and platelet-derived growth factor [49]. Altered hemodynamics also influence mesangial cells: it has been postulated that expansion of the glomerular capillaries, and stretching of the mesangium in response to hypertension, might translate high P_{GC} into increased mesangial matrix formation [50]. Evidence for this mechanism comes from observations in microperfused rat glomeruli, in which increased hydraulic pressure was associated with increased glomerular volume; and in cultured mesangial cells, where cyclic stretching resulted in enhanced synthesis of protein, total collagen, collagen IV, collagen I, laminin, fibronectin, and transforming growth factor-ß (TGF-ß)[50,51]. Additionally, growing mesangial cells under pulsatile conditions has been reported to stimulate protein kinase C, calcium influx, and proto-oncogene expression [52], while shear stress activates latent forms of TGF-ß in mesangial cells [53].

Antihypertensive therapy in experimental diabetes

Further support for the notion that glomerular capillary hypertension constitutes a central mechanism of glomerular injury in experimental diabetes comes from studies comparing differing antihypertensive agents [14]. Of the agents studied, CEIs have consistently limited injury parameters (albuminuria and glomerular sclerosis) in normotensive diabetic rats, uninephrectomized diabetic rats, and diabetes superimposed on genetic hypertension [19,54-59], as well as in diabetic dogs [60]. In studies where glomerular hemodynamics were measured, the protection afforded by CEIs was associated with reduction of P_{GC}, due to preferential reduction of efferent arteriolar tone.

By contrast, conflicting results have been reported for antihypertensive regimens which fail to control glomerular hypertension. Agents such as calcium channel blockers, β-blockers and combinations of vasodilators and diuretics (»triple therapy«) have not resulted in structural and functional protection in experimental diabetes with

any consistency [19,54-60]. Failure to exert longterm control of glomerular hypertension has frequently been found to explain lack of protection with these alternate agents.

That the beneficial effects of angiotensin converting enzyme inhibition are due in large part to limitation of Ang II formation has been confirmed in studies showing that the beneficial hemodynamic [61] and structural [62] effects can be reproduced with specific Ang II receptor antagonists. Ang II possesses a number of physiological actions. Limitation of several of these have been postulated to contribute to the protective effect of CEIs, including control of systemic and glomerular hypertension; decreased mesangial and tubular macromolecular and solute transfer; decreased proteinuria with improved glomerular permselectivity; and limitation of glomerular hypertrophy and microvascular growth. Although experimental diabetes is characterized by glomerular enlargement, longterm protection with CEIs has been observed without consistent limitation of glomerular size [54,55,57]. The proposed beneficial mechanisms of CEIs are, however, not mutually exclusive.

Although the role of aggressive control of hypertension in the preservation of renal function in diabetic nephropathy has been indisputably proven, clinical studies directly comparing different antihypertensive agents have remained somewhat controversial. Of note, however, are recent meta-analyses [63,64] as well as clinical trials [65] which are highly suggestive of a superior ability of CEIs to slow the pace of diabetic nephropathy, as compared to other antihypertensive agents.

Elucidation of the complex mechanisms that contribute to diabetic hyperfiltration remains a challenge. It is also clear that many genetic, metabolic and hemodynamic factors act in concert with the end result of glomerular obsolescence. The enormity of the clinical problem of end-stage renal disease in this highly susceptible patient population behooves continued intense research into pathogenetic mechanisms, and approaches to specific therapy of patients at risk for renal disease.

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23. ROLES OF GROWTH FACTORS IN DIABETIC KIDNEY DISEASE

ALLAN FLYVBJERG, BIRGITTE NIELSEN, CHRISTIAN SKJÆRBÆK, JAN FRYSTYK, HENNING GRØNBÆK and HANS ØRSKOV

Diabetic kidney disease is characterized by an early increase in kidney size, glomerular volume and kidney function and later by the development of mesangial proliferation, accumulation of glomerular extracellular matrix (ECM), increased urinary albumin excretion (UAE) and glomerular sclerosis. The search for significant *pathogenic mechanisms* in diabetic kidney disease has focused on the *early* events, at the point in time when the above mentioned pathophysiological changes take place. Several metabolic, functional and structural renal changes in streptozotocin (STZ)-diabetic rats have fundamental similarities to those occurring in diabetic patients and this model has accordingly been used extensively in diabetes research aiming to elucidate the pathogenesis of diabetic kidney disease.

The term 'growth factor' is used as a generic designation for any substance capable of inducing cellular differentiation and/or proliferation and embraces an ever increasing number of peptides found in the circulation and in different tissues. Growth factors have therefore attracted attention in several areas of diabetes research

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including conceivable effects on the renal changes seen in experimental and human diabetes.

The present review will describe the most recent evidence for a causal role of growth factors in diabetic kidney disease, with emphasis on studies performed in experimental diabetes as only a few clinical studies has been published on this topic.

1. GROWTH HORMONE (GH) AND INSULIN-LIKE GROWTH FACTORs (IGFs)

Virtually all members of the GH-IGF axis are present in the kidney, ranging from GH-receptors [1], through messenger RNA (mRNA) expression for IGF-I and IGF-II [2] and their respective receptors: the IGF-I receptor and the IGF-II/Mannose-6-phosphate receptor [3], to the presence of six different classes of specific binding proteins (IGFBPs) for IGF-I and -II [4,5].

IGF-I exerts a number of actions on renal tissues at a cellular level, having both proliferative and differentiative effects. In glomerular mesangial cells in mice [6] and rats [7], and in rabbit renal cortical tubular cells [8], IGF-I has mitogenic actions. In human fetal mesangial cells, IGF-I stimulates protein and proteoglycan synthesis [9].

There is today substantial evidence that GH is capable of increasing kidney function and size indirectly through IGF-I [10], but also that IGF-I, independently of GH, acutely stimulates kidney function [11] and after some days also renal growth [12]. In addition, GH and IGFs are implicated as mediators of renal hyperfunction and hypertrophy in diabetes. When GH was given subcutaneously twice daily to well-controlled Type 1 diabetic patients for one week to raise plasma levels to approximately those found in diabetic patients in average to poor metabolic control, significant increases in GFR and RPF were found [13]. Whether this effect is mediated through IGF-I is, however, unknown. In STZ-diabetes increase in renal growth and function is preceded by a rise in renal tissue concentration of IGF-I reaching a peak 24-48 h after the induction of diabetes and returning to basal levels after about 4 days [14,15]. In addition, IGF-I infusion into diabetic rats commencing after the initial rapid growth rate has abated, with restoration of the initial high kidney IGF-I levels, re-accelerates diabetic renal hypertrophy [16]. Concomitantly with the rise in endogenous kidney IGF-I, a transient increase in kidney IGFBP species is seen, supporting the notion that IGFBPs may modulate the renotropic action of IGF-I in diabetic renal enlargement [17]. Diabetic dwarf rats with isolated GH and IGF-I deficiency exhibit slower and lesser initial renal and glomerular hypertrophy as well as a smaller rise in kidney IGF-I than diabetic controls with intact pituitary, indicating that GH per se may be involved in the modulation of renal enlargement [18]. Strict insulin treatment abolishes both the increase in kidney IGF-I

and renal hypertrophy [14] and a long-acting somatostatin analogue (octreotide) equally inhibits kidney IGF-I accumulation and growth without affecting the blood glucose levels [15]. These results indicate that IGF-I acts as an *initiating* growth factor for diabetic renal enlargement in experimental diabetes.

At present there is no direct evidence that IGF-I is involved also in *maintaining* diabetic kidney hypertrophy and function. However, in view of the evidence that octreotide may directly inhibit IGF-I synthesis independently of GH inhibition [19], it is intriguing that six months administration of octreotide to diabetic rats reduces diabetic UAE, renal hypertrophy and serum and kidney IGF-I without affecting metabolic control [20]. Furthermore, reduction in renal size and hyperfunction is seen in Type 1 diabetic patients treated with octreotide for a period of three months without discernible reductions in serum GH, glucagon or HbA_{1c}, but with pronounced reductions in circulating IGF-I levels [21]. Finally, long-term diabetic dwarf rats, with a diabetes duration of six months, display a smaller degree of renal and glomerular hypertrophy and rise in UAE, when compared to the changes observed in pituitary intact diabetic rats [22].

2. EPIDERMAL GROWTH FACTOR (EGF)

The kidney is one of the main sites of EGF synthesis and the urinary excretion is halved after removal of one kidney [23]. EGF is also synthesized in submandibular glands and in the gastrointestinal tract, but removal of these organs does not alter the urinary excretion of EGF [23]. Recent studies have suggested that the kidney is also a target organ of EGF. The presence of EGF receptors has been demonstrated in several segments of the nephron [24], and EGF administered *in vivo* systemically or directly into the renal artery increases urine flow and urinary sodium and potassium excretion [25]. The demonstration of acute effects of EGF on renal function [26,27] opens some intriguing possibilities for a physiological role of EGF in the kidney. Although one study [23] reported reduced urinary EGF excretion after reduction of renal mass, increased renal EGF synthesis and a transiently increased amount of immunoreactive EGF in distal kidney tubules have been demonstrated after unilateral nephrectomy [28]. In addition, a recent study focusing on a possible role for EGF in the early renal enlargement in experimental diabetes demonstrated a pronounced elevation in diurnal urine EGF excretion, while no significant changes were obtained in renal and plasma EGF within the first 7 days after induction of diabetes [29].

No measurements of the renal EGF content and EGF excretion have yet been published in long-term experimental diabetes, however, three recent cross-sectional clinical studies looked at the possible participation of EGF in diabetic nephropathy by measuring the urinary excretion of EGF [30-32]. Both Mathiesen et al. [30] and

Dagogo-Jack et al. [31] examined urinary excretion of EGF in Type 1 diabetic patients with and without incipient or overt nephropathy. Both studies demonstrated reduced urinary excretion of EGF in patients with elevated UAE compared with controls. A significant inverse correlation between urinary excretion of EGF and UAE was also reported and furthermore urinary excretion of EGF correlated positively to GFR [30] and creatinine clearance [32]. These studies demonstrate that the urinary excretion of EGF diminished with increasing nephron impairment, and that renal tubular function as judged by urinary EGF excretion is reduced early in the development of diabetic kidney disease. These findings in diabetic patients are in accordance with the findings of reduced urinary EGF excretion in patients with various non-diabetic glomerulopathies [33], and seem to preclude a possible pathogenic role in the development of the long-term diabetic glomerulopathy.

3. TRANSFORMING GROWTH FACTOR β (TGF-β)

TGF-β is a 25 kDa polypeptide, synthesized as an inactive precursor protein which may bind to a 125 kDa TGF-β binding protein, and is proteolytically changed into its active form. TGF-β is a prominent member of a family of cell regulatory proteins and is unique among growth factors in its broad effects on extracellular matrix. The kidney is both producing TGF-β and a target of TGF-β action, as both mRNA TGF-β, the active protein and TGF-β receptors have been demonstrated in all cell types of the glomerulus and in tubules.

There is strong evidence for TGF-β playing a role in different forms of kidney diseases characterized by ECM accumulation. In cultured glomerular cells obtained from immunologically induced glomerulonephritis, increased amounts of active TGF-β can be measured [34]. Furthermore, both the administration of an antibody raised against TGF-β [35] or decorin [36], a natural inhibitor of TGF-β, to glomerulonephritic rats suppresses glomerular matrix production and prevents matrix accumulation in injured glomeruli. In the diabetic kidney, the pathological changes in glomeruli and tubules may be due to an altered synthesis/degradation of ECM. Interestingly, Ziyadeh et al. [37] have shown that elevated glucose levels *in vitro* stimulate TGF-β gene expression and bioactivity, cellular hypertrophy and collagen transcription in proximal tubules. Furthermore, Nakamura et al. [38] have shown sustained glomerular mRNA TGF-β levels in long-term STZ-diabetic rats. It would be interesting, in the near future, to study the possible beneficial effects of antiserum against TGF-β or administration of the natural TGF-β inhibitor, decorin, in experimental diabetes.

4. PLATELET DERIVED GROWTH FACTOR (PDGF)

PDGF, stored in platelet α-granules, is synthesized and released by many other cells, such as macrophages, smooth muscle and endothelial cells. PDGF exists in three forms as heterodimer of A and B chains or homerdimers of either chain. Platelets interact with the vascular wall in several ways and can affect vascular contractility, prostanoid metabolism, and cell proliferation [39]. Major interest in the involvement of platelets in the pathogenesis of vascular disease was aroused following the hypothesis of Ross and Glomset [40]. According to this model a sequence of events leads to endothelial damage which allows platelets to adhere to the vascular endothelium and release their contents; increased permeability of vascular endothelium to plasma factors; and the migration and proliferation of vascular smooth muscle cells.

Vascular smooth muscle is one target of PDGF [41] and cultured microvessel endothelial cells has been shown to have high affinity binding sites for PDGF [42]. In the kidney, both glomerular mesangial and renal epithelial cells [43] synthesize PDGF, and in human mesangial cells PDGF itself and EGF induce the production of mRNA PDGF [43].

Gesualdo et al. [44] and Iida et al. [45] have reported that the glomerular mRNA expression for both the PDGF-A and PDGF-B chain are increased in two models of mesangial proliferative glomerulonephritis. Nakamura et al. [38] very recently reported that in long-term STZ-diabetes in rats, a specific increase in glomerular mRNA PDGF-B was found without any measurable changes in the glomerular PDGF-A expression.

5. TUMOR NECROSIS FACTOR α (TNF-α)

TNF-α is a potent cytokine originally defined on the basis of its ability to induce hemorrhagic necrosis of solid tumors and has later been shown to be identical to cachectin, a mediator of wasting diathesis in infected animals. TNF-α is now recognized to exert a number of proinflammatory actions, including neutrophil activation, induction of coagulation on vascular endothelium and stimulation of collagenase secretion. Originally, mononuclear phagocytes were considered to be the sole source of this growth factor. TNF-α has, however, been shown to be produced by a variety of different cell types, including glomeruli and glomerular mesangial cells [46], opening the possibility for actions on the kidney through both endocrine and paracrine/autocrine mechanisms.

Recent studies have shown that TNF-α may be involved in various forms of renal injury, including experimental diabetes. In lupus nephritis, mRNA TNF-α is expressed in the renal cortex [47] and in antiglomerular, basement membrane glomerulonephritis an association between glomerular TNF-α production and

glomerular macrophage infiltration has been shown [48]. In STZ-diabetic rats, with a diabetes duration of 3 months, Hasegawa et al. [49] showed increased release of TNF-α from glomerular basement membranes when compared with non-diabetic controls. In addition, Nakamura et al. [38] recently showed that the glomerular mRNA TNF-α expression in STZ-diabetic rats with a diabetes duration of 4, 12, and 24 weeks revealed a pronounced and sustained increase. Until now no published studies have looked at the possible role for TNF-α in the early diabetes-induced renal hypertrophy.

6. FIBROBLASTIC GROWTH FACTORs (FGFs)

In 1948 Michaelson postulated that ischaemic retina produced a vasculogenic factor [50]. Since that time several angiogenic factors produced by the retina have been isolated, including retina derived growth factor and retina derived angiogenic factor [51]. These have been shown to be identical to acidic and basic fibroblastic growth factor (a and b FGF) [52]. These growth factors stimulate growth of cells *in vitro*, bFGF, being the more potent [53], stimulates the proliferation of myoblasts, vascular endothelial cells, fibroblasts, and smooth muscle cells [54]. Although bFGF has been demonstrated in a wide variety of tissues, including the kidney [54], very little information is available about the *in vivo* regulation of bFGF in pathophysiological states. Using a sensitive radioimmunoassay bFGF has been shown to be released from cultured bovine retinal endothelial cells, but it appears from the gene expression of bFGF in cultured cells that there is normally very little bFGF secretion [55]. However, bFGF could be a cell associated angiogenic factor which is released only under special circumstances such as ischaemia or cell death. Interestingly, Baird and Ling showed that bFGF interacts with the heparin sulphate proteoglycan component of the extracellular matrix [56].

Karpen et al. [57] reported that mRNA bFGF expression in whole kidney in STZ-diabetic rats with a diabetes duration of four days was unchanged, whereas a recent study also using STZ-diabetic rats with a diabetes duration of 4, 12, and 24 weeks revealed a pronounced and sustained increase in mRNA bFGF in glomeruli [38] suggesting a role in the development of diabetic kidney disease. It may be suggested that an increase in tissue protein kinase C activity may be responsible for the rise in glomerular mRNA bFGF levels, as *in vitro* experiments have shown that activation of protein kinase C by phorbor esters or other ligands increases mRNA FGFb tissue levels [58].

7. SUMMARY AND CONCLUSIONS

This review has brought together the most recent facets of evidence for the significance of growth factors in relation to an involvement in the development of

diabetic kidney disease. It seems evident, however, from the present review that there is still an extensive number of questions that needs to be elucidated before the exact role of growth factors in the development of diabetic kidney disease is fully understood.

In summary, GH, IGFs and EGF seem of importance as stimulators of *early* renal and glomerular growth in experimental diabetes, whilst the possible role of TGF-β, PDGF and TNF-α in the initial kidney growth phase has not yet been established. Furthermore, GH and IGFs may be of importance for the *long-term* diabetic renal changes, along with TGF-β, PDGF, TNF-α and bFGF; however a substantial amount of information is still needed to substantiate or refute this.

During the last five years progress and new information have been generated and one important result of this research seems to be the increasing favour among scientists, that actions of a single growth factor cannot be considered in isolation. It appears of importance to study under one umbrella, the complicated framework of growth factors with enhancing and/or inhibitory interactions in the diabetic kidney, rather than just focus on the isolated action of a single growth factor.

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24. BLOOD PRESSURE ELEVATION IN DIABETES: RESULTS FROM 24-H AMBULATORY BLOOD PRESSURE RECORDINGS IN DIABETES

KLAVS WÜRGLER HANSEN and PER LØGSTRUP POULSEN

Ambulatory blood pressure measurement is a new technique which permits assessment of blood pressure in the patients own surroundings, during normal daily activities on the job and in the night. The first true ambulatory 24h report of indirectly measured blood pressure obtained with a portable and fully automatic monitor was published in 1975 [1]. Previously semiautomatic monitors which required manually inflation of the cuff [2] or direct (intraarterial) blood pressure measurement were used [3].

The application of the technique to diabetic patients was first reported by Rubler et al. in 1982 using an equipment weighing 3.07 kg [4]. The number of studies using ambulatory blood pressure monitoring in diabetic patient in the eighties were moderate and with a few exceptions [4-7] focusing on autonomic neuropathy [8-13].

The knowledge from ambulatory blood pressure measurement in general has recently been reviewed [14-16]. Four reviews of ambulatory blood pressure measurement in diabetes have appeared [17-20], one of these also attempting to give

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recommendations for the clinical use [19]. The following summarize present results and also serves as an update of the rapidly increasing literature on the subject.

1. METHODOLOGICAL ASPECTS: A GUIDE TO THE CRITICAL READER

The two most popular ways of obtaining automatic indirect blood pressure recordings is either by use of a microphone in the cuff or by oscillometric technique [21]. Some monitors offers both options. While the manufacturer of the monitor is always stated the technique is not necessarily described.

No monitor is perfect and even in monitors which has fulfilled national standards, major discrepancies between the monitors and values obtained by sphygmomanometry is observed in about 10 % of the patients. Some papers state that individually »calibration« of the monitors to each of the studied patients has been performed (by 3 to 5 simultaneous or sequential measurements). However, it is not possibly to calibrate a fully automatic monitor in strict terms (without returning to the manufacturer) and the word calibration is a misnomer in this context. The difference between each patient and the monitor can be evaluated (rather unprecisely) and this difference can either be accepted or not.

If the results of clinic measurements of blood pressure is provided it should be observed whether this is obtained by sphygmomanometry or by use of the same monitor as used for ambulatory measurements [22]. Only in the latter case are clinic and ambulatory values directly comparable.

Although more sophisticated methods exist [23,24], the diurnal variation of blood pressure is usually reported as the night/day ratio of blood pressure. Obviously this must be based on individual information of the night period, otherwise the night/day ratio is overestimated [25].

2. AUTONOMIC NEUROPATHY AND AMBULATORY BLOOD PRESSURE

Numerous studies in mixed type 1 and type 2 populations or unclassified diabetic patients have demonstrated a reduction or (in a few patients) even a reversal of the normal nocturnal decline of blood pressure [11-13,26-30]. Also studies in homogenous type 1 [10,31-33] or type 2 diabetic patients [34,35] demonstrates the association between signs of autonomic neuropathy and a blunted diurnal variation of blood pressure. Postprandial hypotension is also a phenomenon observed in patients with autonomic neuropathy [36].

3. TYPE 2 DIABETES AND AMBULATORY BLOOD PRESSURE

3.1 Comparison with healthy individuals

Some discrepancies exist with respect to the comparison of 24h average blood pressure in the two groups. One study has reported an increase in 24h systolic (but

not diastolic) blood pressure in normoalbuminuric type 2 diabetic patients [37], while two other groups did not find any statistical significant difference when patients and controls were divided into groups with and without hypertension [6,7,38].

3.2 The relation to abnormal albuminuria

In a group of type 2 diabetic patients including patients with antihypertensive medication no difference in 24h ambulatory blood pressure were noticed between normo- and microalbuminuric patients. This was also true if analysis was restricted to patients without antihypertensive treatment [37]. Abnormal diurnal blood pressure pattern are seen in type 2 patients with microalbuminuria [39,40] and overt diabetic nephropathy [35]. As in type 1 diabetes this abnormality seems closely linked to the presence of autonomic neuropathy [34,35].

4. TYPE 1 DIABETES AND AMBULATORY BLOOD PRESSURE

4.1 Comparison with healthy individuals

Most studies [41-43] (but not all [44]) agree that day time blood pressure is indistinguishable between normoalbuminuric diabetic patients and healthy subjects, while a slightly elevated systolic night blood pressure has been reported [43]. No statistical significant difference between night/day ratio have been published so far. The slight diversities may be explained by varying diabetes duration, proportion of males/females or smokers/non-smokers. Thus, as a rule normoalbuminuric patients have a 24h blood pressure very similar to healthy control subjects (figure 24-1).

4.2 The relation to abnormal albuminuria

Ambulatory blood pressure is significantly higher and the diurnal blood pressure pattern is abnormal in consecutively studied patients [45]. This largely depends on abnormal albuminuria present in some of the patients [45]. Four studies comparing normo- and microalbuminuric patients as well as healthy controls are summarized in table 24-1. Both day and night blood pressure are significantly increased in microalbuminuric as compared with normoalbuminuric patients despite comparable auscultatory clinic blood pressure [41]. In some studies day time blood pressure were only numerically but not statistically significantly higher in microalbuminuric patients [44,46,47]. This is probably due to lower number of microalbuminuric patients in these studies. The night/day ratio of diastolic blood pressure is significantly higher in microalbuminuric patients than in healthy individuals [48] and night/day ratio for normoalbuminuric patients is in between (table 24-1).

Ambulatory blood pressure correlates more closely with urinary albumin excretion than clinic blood pressure (table 24-2). This is probably due to the

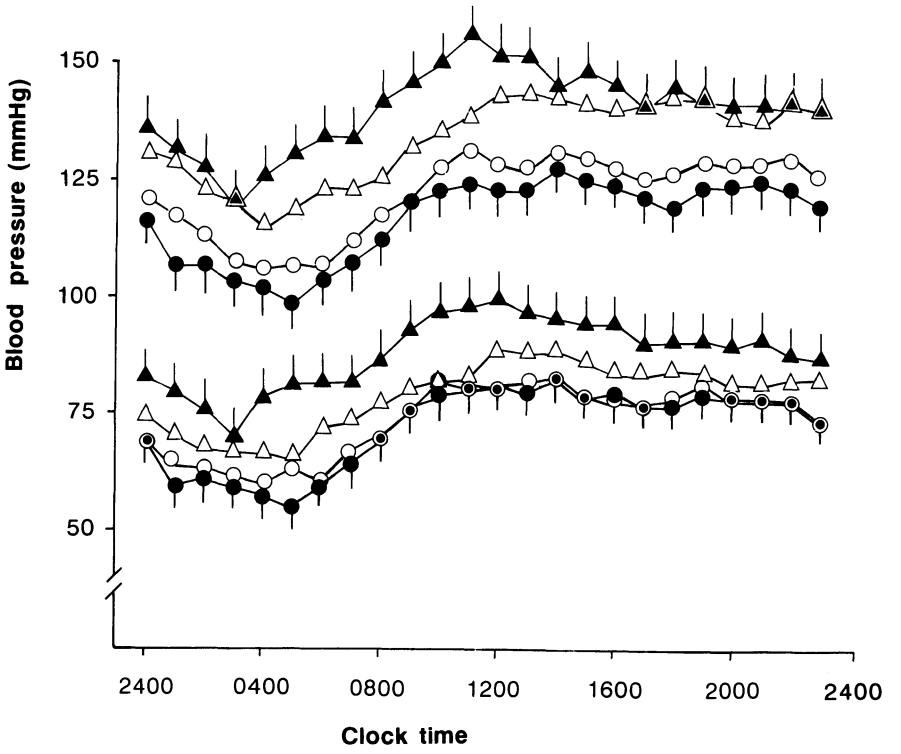

Figure 24-1. Twenty-four hour profile of mean systolic and diastolic blood pressure for type 1 diabetic patients and healthy controls. Diabetic patients with nephropathy and without antihypertensive treatment (n=13, filled triangles), microalbuminuric patients (n=26, open triangles), normoalbuminuric patients (n=26, open circles) and healthy individuals (n=26, filled circles). From [48] with permission.

multiplicity of measurements rather than their quality as true ambulatory values (figure 24-2).

Ambulatory blood pressure is further increased in patients with overt diabetic nephropathy [48] (figure 24-1) and the circadian variation of blood pressure is severely disturbed in patients with advanced diabetic nephropathy and antihypertensive medication [48,49] (figure 24-3).

4.3 The transition from normo- to microalbuminuria

In a recent study 40 initially normoalbuminuric patients were reinvestigated with ambulatory blood pressure monitoring and measurement of UAE after a mean period

Table 24-1. Four studies comparing ambulatory blood pressure in micro- and normoalbuminuric type 1 diabetic patients and healthy control subjects.

	A Hansen et al. [7]			B Moore et al. [12]		
	Controls	Normo	Micro	Controls	Normo	Micro
N	34	34	34	36	27	11
Sex (male/female)	24/10	24/10	24/10	19/17	14/13	5/6
Age (years)	31	31	30	17	18	19
Diabetes duration (years)	-	18	18	-	9	14*
HbA_{1c} (%)	5.1	8.3	9.1*	-	12.5	12.7
Body Mass Index ($kg \cdot m^{-2}$)	23.1	23.7	23.9	-	-	-
UAE ($\mu g \cdot min^{-1}$)	Three overnight collections			One 24h collection		
	5.2	5.1	51.7	-	5.3	45.2
Monitor and frequency of measurements	Spacelabs 90202 06.00h-23.00h every 20 min 23.00h-06.00h every 60 min			Spacelabs 90202 06.00h-22.00h every 20 min 22.00h-06.00h every 60 min		
Definition of day and night periods	Individually recorded periods			Day (06.00h-22.00h) Night (22.00h-06.00h)		
BP criteria for inclusion of patients	All patients included (no antihypertensive treatment)			< 130/85		
Clinic BP (auscultatory)	119/75	121/77	124/81	-	-	-
Clinic BP (monitor)	125/74	128/74	132/79*	102/54	106/64*	118*/70*
Day time BP	125/77	127/77	136*/82*	117/67	123*/71*	130/76
Night time BP	109/61	112/63	122*/69*	110/59	116*/63*	126*/71*
Night/day ratio (systolic/diastolic)	0.87/0.80	0.88/0.82	0.90/0.85	0.94/0.88[a]	0.94/0.89[a]	0.97/0.93[a]
day-night BP difference	16/16	15/14	14/13	7/8[a]	7/8[a]	4/5[a]
24h BP	119/71	122/73	131*/78*	116/66	122*/70*	129/75
Comments	Normoalbuminuric patients individually matched to microalbuminuric patients for sex, age and diabetes duration			Glycosulated hemoglobin HbA is presented. Clinic BP is not measured with the same monitor as ambulatory blood pressure		

Values are numbers or mean except for UAE in study A (geometric mean) and in study C (median). For clarity the level of statistical significance is not indicated more specific and the results of comparison between microalbuminuric patients and healthy controls is not given. *; $p < 0.05$ versus controls (for normoalbuminuric patients) or versus normoalbuminuric patients (for microalbuminuric patients). [a]; the values are derived from original data without access to statistical analysis.

Table 24-1. Four studies comparing ambulatory blood pressure in micro- and normoalbuminuric type 1 diabetic patients and healthy control subjects.

	C Benhamou et al. [13]			D Lurbe et al. [14]		
	Controls	Normo	Micro	Controls	Normo	Micro
N	12	12	12	45	34	11
Sex (male/female)	7/5	7/5	7/5	20/25	-	-
Age (years)	≈31	≈31	31	23	18	24
Diabetes duration (years)	-	7	15*	-	5	13*
HbA_{1c} (%)	-	7.3	8.8*	-	-	-
Body Mass Index ($kg \cdot m^{-2}$)	≈21.5	≈21.5	21.5	22.2	20.1	24.8
UAE ($\mu g \cdot min^{-1}$)	Three overnight collections			Three 24h collections		
	-	<15	56	-	4.5	111
Monitor and frequency of measurements	Spacelabs 90207 07.00h-17.00h every 15 min 17.00h-07.00h every 30 min			Spacelabs 90207 06.00h-24.00h every 20 min 24.00h-06.00h every 30 min		
Definition of day and night periods	Day (09.00h-19.00h) Night (23.00h-07.00h)			Day (08.00h-22.00h) Night (24.00h-06.00h)		
BP criteria for inclusion of patients	<140/90			<140/90 or <95 percentile level		
Clinic BP (auscultatory)	118/79	119/78	116/73	121/70	120/69	125/74
Clinic BP (monitor)	-	-	-	-	-	-
Day time BP	116/76	118/78	124/81	117/71	117/71	122/72
Night time BP	100/61	103/65	113/68	113/60	114/60	121*/69*
Night/day ratio (systolic/diastolic)	0.86/0.80[a]	0.88/0.83[a]	0.91/0.84[a]	0.94/0.83	0.93/0.84	0.97/0.94*
day-night BP difference	16/15	15/13	11/13	4/11[a]	3/11[a]	1/3[a]
24h BP	110/71	112/71	119*/75	114/67	116/66	121/71
Comments	Patients were admitted to hospital during the night			No statistical analysis between controls and normoalbuminuric patients have been performed		

Values are numbers or mean except for UAE in study A (geometric mean) and in study C (median). For clarity the level of statistical significance is not indicated more specific and the results of comparison between microalbuminuric patients and healthy controls is not given. *; $p < 0.05$ versus controls (for normoalbuminuric patients) or versus normoalbuminuric patients (for microalbuminuric patients). [a]; the values are derived from original data without access to statistical analysis.

Table 24-2. Correlations between blood pressure and urinary albumin excretion in combined normo- and microalbuminuric type 1 diabetic patients.

	A Hansen et al. [7]	B Moore et al. [12]
UAE	Three overnight collections	One 24h collection
Correlations:	Normo (n=34) and Micro (n=34)	Normo (n=27) and Micro (n=11)
UAE vs. clinic BP (auscultatory)	r=0.21, NS (systolic)	-
UAE vs. day time BP	r=0.45, $p<0.05$ (systolic)	-
UAE vs. night time BP	r=0.53, $p<0.00001$ (systolic)	-
UAE vs. 24h BP	r=0.49, $p<0.0001$ (systolic)	r=0.40, $p<0.01$ (systolic) r=0.60, $p<0.01$ (diastolic)

Table 24-2. Correlations between blood pressure and urinary albumin excretion in combined normo- and microalbuminuric type 1 diabetic patients.

	C Benhamou et al. [13]	D Lurbe et al. [14]
UAE	Three overnight collections	Three 24h collections
Correlations:	Normo (n=23) and Micro (n=12)	Normo (n=34) and Micro (n=11)
UAE vs. clinic BP (auscultatory)	r=-0.01, NS (systolic)	r=0.19, NS (MAP)
UAE vs. day time BP	r=0.17, NS (systolic)	r=0.35, $p<0.05$ (MAP)
UAE vs. night time BP	r=0.38, $p<0.05$ (systolic)	r=0.60, $p<0.01$ (MAP)
UAE vs. 24h BP	r=0.29, NS (systolic)	-

of 3 years [50]. Six patients progressed to microalbuminuria and their baseline UAE (9.7 $\mu g\ min^{-1}$) was statistically significantly higher than baseline UAE in non-progressors (5.5 $\mu g\ min^{-1}$). Importantly, no difference was noticed between 24h ambulatory blood pressure at baseline in progressors (124/74 mmHg) and non-progressors (124/75 mmHg). However, the rise in UAE even to low microalbuminuria (31.7 $\mu g\ min^{-1}$) was accompanied with an increase in 24h ambulatory blood pressure (12/5 mmHg) which was statistically higher than the increase in non-progressors (4/2 mmHg). No statistically significant changes were seen if these

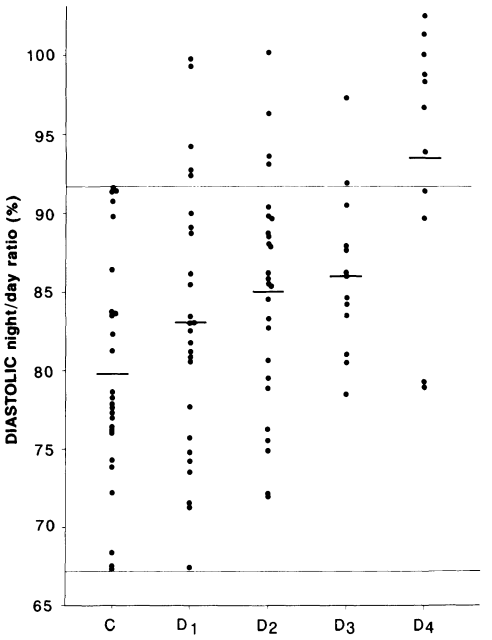

Figure 24-2. Individual night/day ratio for diastolic blood pressure in healthy individuals and type 1 diabetic patients. C= control subjects (n=26), D_1= normoalbuminuric patients (n=26), D_2= microalbuminuric patients (n=26), D_3= patients with diabetic nephropathy without antihypertensive treatment (n=13), D_4= patients with diabetic nephropathy with antihypertensive treatment. From [48] with permission.

changes were evaluated from the average of three clinic blood pressure measurements at baseline and at follow up.

In a cross sectional study of normoalbuminuric patients the 24h average blood pressure was statistically significantly higher in patients with »high« normal UAE than in patients with »low« normal UAE [25].

These results support the idea that rise in UAE and ambulatory blood pressure can not be separated even in the very early phase of incipient diabetic nephropathy.

4.4 The relation to clinic blood pressure

When studying young professionally active normotensive subjects the diastolic clinic blood pressure is in mean 3-4 mmHg higher than day time averages [41]. This is the opposite of what is normally seen in about 20-25% of mildly hypertensive non-diabetic subjects (white-coat hypertension). The important clinical implication is that

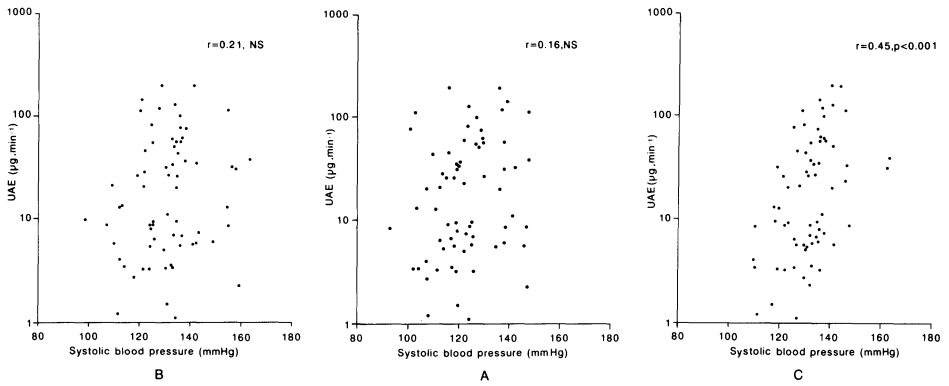

Figure 24-3. The correlation between overnight urinary albumin excretion (UAE, three collections) and blood pressure in normo- and microalbuminuric type 1 diabetic patients. A) systolic clinic blood pressure measured by sphygmomanometry (average of three values) B) systolic ambulatory blood pressure (average of three values about 11.00 h) C) day time average of systolic ambulatory blood pressure (average of approximately 48 values). The correlation coefficient (Pearson) and significance level are indicated. Partly from [41] with permission.

blood pressure is underestimated in some microalbuminuric patients with normal clinic blood pressure.

4.5 Non-dipper: Nephropathy or autonomic neuropathy ?

The term non-dipper has become a popular short term for a person who do not describe a normal reduction of blood pressure at night. A commonly used definition of a non-dipper requires a relative reduction of night blood pressure less than 10% of the day value for both systolic and diastolic blood pressure [51]. Unfortunately no consensus on this subject exist.

Autonomic neuropathy and diabetic nephropathy are closely associated [52-55]. Their relative role for the abnormal diurnal variation blood pressure is therefore difficult to ascertain. However, the literature gives no examples of a group of type 1 diabetic patients with blunted diurnal variation of blood pressure without concomitant signs of autonomic neuropathy either by formal test [31-33] or by increased heart rate [41]. In contrast a reduced night blood pressure and increased heart rate is seen in long term diabetic patients who are strictly normoalbuminuric [56].

4.6 The influence of diabetes duration

One cross sectional study reports a reduction of the nocturnal blood pressure fall in long term diabetic patients [56].

4.7 The influence of gender

The well known blood pressure difference between healthy males and females seems attenuated in young diabetic patients [57].

4.8 The influence of short term changes in metabolic control

This important question has never been studied by intervention studies. Only reports using clinic blood pressure are available.

5. AMBULATORY BLOOD PRESSURE AND INTERVENTION STUDIES

Due to the high reproducibility of ambulatory blood pressure compared with clinic measurements it is an ideal tool for intervention studies [22,58]. The 24h effectiveness of the intervention can be evaluated, the number of patients needed can be reduced without loosing power and small changes in blood pressure which would be overlooked by traditional measurements can be recognised. Ambulatory blood pressure has been used both in pharmacological [59-61] and non-pharmacological [62] intervention trials in diabetes.

6. AMBULATORY BLOOD PRESSURE AND CARDIAC MASS

An early study did not find any significant differences in either 24h blood pressure or left ventricular dimensions between type 2 diabetic patients and healthy subjects [6]. Later, increased cardiac mass has been reported in diabetic patients (mixed type 1 and 2) with autonomic neuropathy and associated reduced nocturnal decline of blood pressure [63]. It is unknown if this is an effect of autonomic dysfunction per se or of the higher nocturnal blood pressure.

7. CONCLUSION

Ambulatory blood pressure is increased in type 1 diabetic patients with abnormal albuminuria even in the absence of a detectable difference in clinic blood pressure. This also counts for the very early phases of diabetic nephropathy. An association exist in both type 1 and type 2 diabetic patients between impaired reduction of night blood pressure and the two complications, autonomic neuropathy and diabetic nephropathy. It remains to be elucidated if the abnormal blood pressure variation independently contributes to the progression of diabetic nephropathy or is merely a cophenomenon found in patients with advanced diabetic complications including autonomic neuropathy.

The high reproducibility of ambulatory blood pressure permits registration of small changes in blood pressure which are overlooked by conventional blood pressure measurement. The St. Vincent declaration prompts the clinicians to act if blood pressure in microalbuminuric patients rises by more than 5 mmHg per year [64]. Such precision of intraindividual registration of blood pressure can only be achieved by implementation of ambulatory blood pressure measurements. Large scale longitudinal studies of ambulatory blood pressure and UAE are necessary to characterize the important transition phase from normo- to microalbuminuria.

Simultaneous continuous indirect registration of both the sympathovagal balance [55] and blood pressure [65] are perspectives for the future, which probably will add to the understanding of blood pressure variation in diabetes.

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25. INSULIN AND BLOOD PRESSURE

RIJK O.B. GANS and AB J.M. DONKER

Insulin resistance and compensatory hyperinsulinaemia are common features of obesity and non-insulin-dependent diabetes mellitus, conditions that are frequently complicated by hypertension [1,2]. The documentation of insulin resistance, i.e. a defective non-oxidative glucose disposal, and hyperinsulinaemia in untreated patients with essential hypertension and a normal glucose tolerance [3] has been the incentive for a vast number of studies assessing hyperinsulinaemia as the potential link between hypertension, obesity and diabetes mellitus. Apart from its role in glucose metabolism, insulin has several effects that might interfere with blood pressure homeostasis (table 25-1). In this chapter we will focus on the effect of insulin on the kidney and its (acute) cardiovascular effects, and conclude with alternative hypotheses to explain the association between hyperinsulinaemia, insulin resistance and hypertension.

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

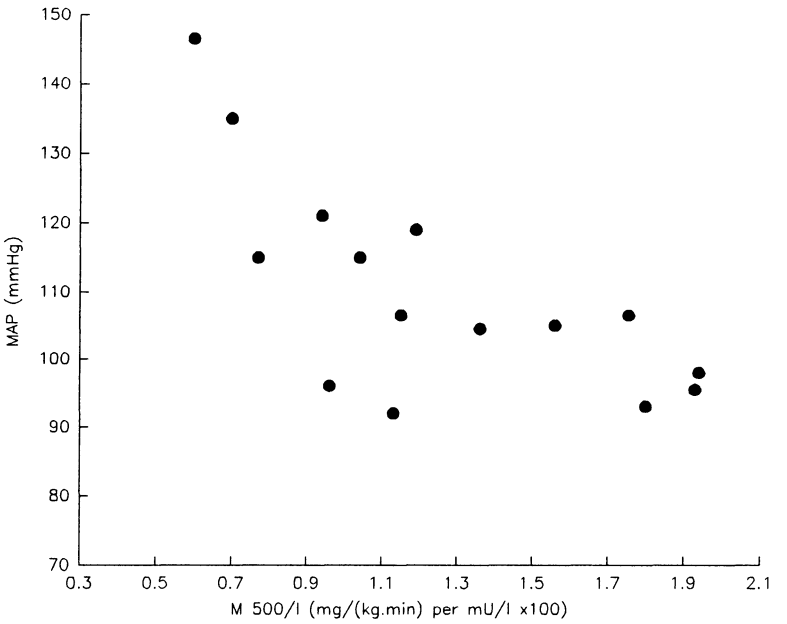

Figure 25-1. Relation between mean arterial pressure (MAP) and the amount of glucose (M) metabolized per unit of plasma insulin (I; 500 mU/kg/h) in 16 patients with NIDDM (adapted with permission from ref 5).

1. EPIDEMIOLOGY

Clear correlations between plasma insulin levels, insulin resistance and blood pressure height have been reported in relatively small, disease-defined groups i.e. essential hypertension, obesity and non-insulin dependent diabetes mellitus (NIDDM) (figure 25-1) [3-5]. Less consistent and weaker associations have been reported in population-based studies [6,7]. The latter may be partly explained by the considerable heterogeneity that exists between different racial and ethnic groups [8]. Also, only about 40% of patients with essential hypertension turn out to be insulin resistant [9,10]. The persistence of insulin resistance during antihypertensive treatment and the fact that hyperinsulinaemia is not a feature of secondary forms of hypertension exclude the possibility that elevated insulin levels are due to hypertension per se [11]. The suggestion that disproportionally elevated proinsulin levels that masquerade as insulin when measured by RIA, instead of insulin itself may be the culprit [12], has yet to be confirmed.

Table 25-1

Insulin	Insulin resistance
Blood pressure elevation	Blood pressure elevation
Renal sodium retention	Increased vascular reactivity
Activiaton SNS	Arteriolar rarefaction
Activation RAAS	Impaired endothelium-(in)dependent relaxation
Positive chrono- and inotropic effects	
Endothelin release	
Increased cardiovascular reactivity	
Impairment of ANP	
Arteriolar hypertrophy	
Blood pressure decline	
Attenuation of vascular reactivity	
Vasodilatation	

Abbreviations: SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ANP, atrial natriuretic peptide

2. RENAL EFFECTS

Short-term administration of physiological amounts of insulin induces sodium retention in healthy individuals [13-16]. Most authors agree that its site of action is located beyond the proximal tubule, possibly in the loop of Henle or at a more distal tubular site [14,16]. Preservation of the antinatriuretic action of insulin in NIDDM and obesity has been shown (figure 25-2) [5,17]. These observations, however, do not prove that insulin's antinatriuretic action would be sufficient to elevate blood pressure *chronically*. Several experimental and clinical observations argue against this notion. Hyperinsulinaemia for 28 days in the dog only temporarily induces sodium retention followed by a »renal escape« associated with an increase in glomerular filtration rate and, if any, a decrease in blood pressure [18]. Chronic hyperinsulinaemia in rats does not raise blood pressure either [19]. Finally, patients with an insulinoma do not have an increased prevalence of hypertension and removal of the tumor does not affect blood pressure [20]. Notwithstanding these observations, insulin-induced sodium retention might still contribute to blood pressure elevation if the homeostatic responses to offset its potential pressor effect fail. Several studies that have examined segmental tubular sodium handling by utilizing the lithium clearance technique, reported an increase in distal tubular sodium

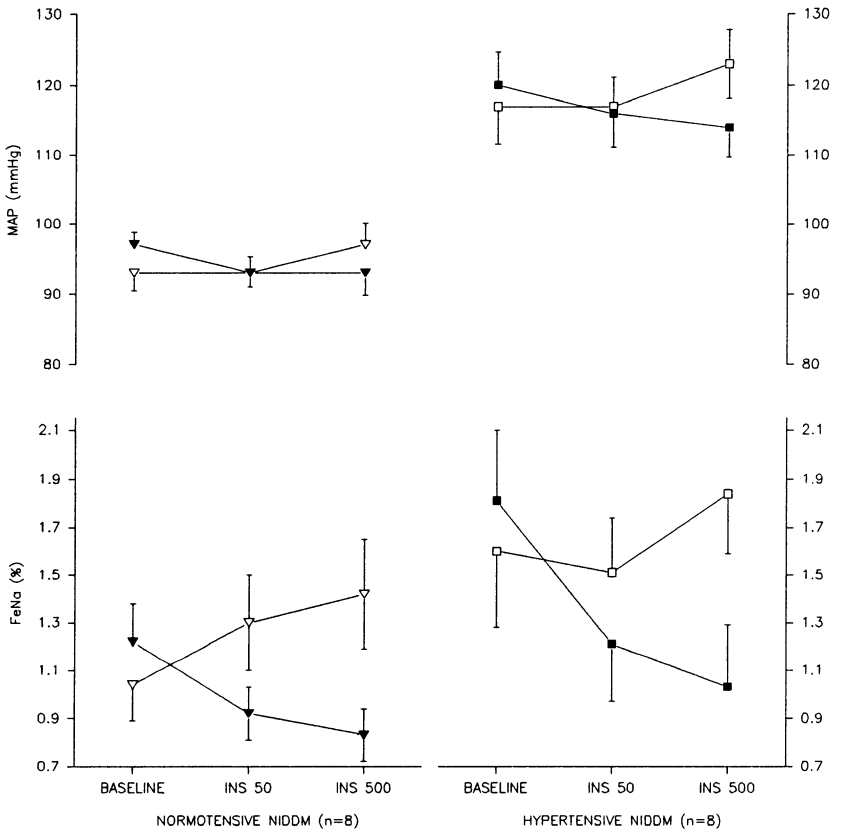

Figure 25-2. The effect of insulin infusion (50 and 500 mU/kg/h; closed symbols) or vehicle (open symbols) on fractional sodium excretion (FeNa) and mean arterial pressure (MAP) in NIDDM (adapted from ref 5).

reabsorption during insulin infusion which was associated with a fall in proximal tubular sodium reabsorption [14,16]. Interestingly, the latter was not observed during insulin infusion in a group of patients with the nephrotic syndrome, a condition that is not only characterized by avid sodium retention but also by insulin resistance [21]. Similar results were obtained in a group of *hypertensive* NIDDM patients. Compared with a normotensive control group of NIDDM, the fall in proximal tubular sodium reabsorption was attenuated or absent [22]. Despite possible limitations of lithium as a marker of proximal tubular sodium reabsorption, it is tempting to speculate that the decrease in proximal sodium reabsorption during acute

insulin infusion acts as a compensatory mechanism to counteract its sodium retaining action at a more distal site, and that this response is defective in the presence of insulin resistance.

3. CARDIOVASCULAR EFFECTS

Increased sympathetic drive has long been implicated as a cause of essential hypertension [23]. Thus, activation of the sympathetic nervous system (SNS) associated with a modest increase in systemic blood pressure and heart rate during administration of pharmacological, albeit supraphysiological amounts of insulin, has provided an attractive hypothesis to explain the link between hyperinsulinaemia and hypertension [15,24]. An implicit assumption in this view is that the insulin-induced increase in sympathetic noradrenergic activity increases peripheral vascular resistance. However, it has been repeatedly shown that during infusion of physiological amounts of insulin, vasodilatation and an increase in skeletal muscle blood flow occur despite marked increases in muscle sympathetic nerve activity and plasma norepinephrine levels [25,26]. If changes in arterial blood pressure did occur during those experiments, small *decreases* in blood pressure have been reported (figure 25-2) [5,26]. The mechanisms mediating the vasodilatation during insulin infusion have yet to be defined. Metabolic vasodilatation due to the increase in tissue metabolism i.e. glucose oxidation, is most likely of importance, but other local and systemic vasodilatator mechanisms also appear to be involved [25]. The increase in SNS activity may simply represent a baroreceptor reflex response to the slight decrease in arterial pressure, although a central neural action of insulin may contribute to the SNS activation. In one study among patients with essential hypertension systemic hyperinsulinaemia, but not local hyperinsulinaemia, resulted in increased SNS activity [27]. Interestingly, an impaired insulin-induced glucose uptake could only be shown in the hypertensive patients when SNS activation occurred at the same time.

The hypothesis that an increased sympathetic drive might *cause* insulin resistance and thus compensatory hyperinsulinaemia, is not without flaws either. Sympathetic vasoconstriction supposedly impedes diffusion of glucose and insulin to the cell, which will reflect itself as a state of functional insulin resistance. Epinephrine infusion indeed induced acute insulin resistance in normal subjects [28]. On the other hand, *chronic* beta-adrenergic stimulation may in fact increase insulin-induced glucose uptake [29]. This notion is supported by animal experiments. Although increased sympathetic activity and hyperinsulinaemia are features of spontaneously hypertensive rats, insulin resistance is not present in these animals [30]. In contrast, enhanced glucose disposal can often be shown [31]. Nonetheless, a putative role for increased noradrenergic drive as a cause of insulin resistance can not be entirely

discarded. There is evidence that sympathetic overactivity in the long-term may affect muscle fiber composition and, thereby, capillary density in a negative sense [32]. A negative relation between capillary density and insulin resistance has been reported [33].

4. INSULIN RESISTANCE

Although hyperinsulinaemia per se does not appear to be able to increase blood pressure *chronically*, it is possible that insulin resistance may elevate blood pressure, either by facilitating a hypertensive action of insulin or by mechanisms independent of hyperinsulinaemia. Vascular smooth muscle contraction as well as the release of insulin and the subsequent cellular events are dependent upon the balance between intracellular cyclic AMP- and Ca^{2+} content. It has, therefore, been proposed that the abnormality underlying the association between hypertension, hyperinsulinaemia and insulin resistance is a primary abnormality of divalent cation flux [34]. In this model hypertension and insulin resistance occur together because of a defect in a shared cellular mechanism. Alternatively, evidence accumulates suggesting a hemodynamic basis for the presence of insulin resistance in hypertension. The amounts of insulin and glucose that reach the target tissue are dependent on their transport across the capillary wall as well as on the intercapillary distance or capillary density of the tissue. In patients with obesity and NIDDM a decreased insulin-induced vasodilatation has been documented that correlated with the decrements in glucose uptake [35,36]. Interestingly, insulin-mediated glucose uptake as well as insulin-mediated increases in skeletal muscle blood flow were recently found to be inversely related to basal blood pressure in a group of normotensive subjects with a wide range of blood pressures [37]. Impaired insulin-induced vasodilatation might be due to a decreased glucose metabolism by the (muscle) cell as a result of receptor- and/or post-receptor defects and, thus, due to a diminished autoregulatory signal from the cell to its nourishing capillaries. Alternatively, if blood flow has difficulties to meet cellular demands because of microvascular dysfunction, insulin resistance is likely to ensue. It is noteworthy that in essential hypertension as well as in diabetes mellitus a decreased endothelium-(in)dependent vasodilatatory capacity has been found [38-40], suggesting that hemodynamic factors may determine insulin sensitivity and peripheral vascular resistance at the same time. One study in essential hypertensives, however, detracts from the importance of the vasodilatatory capacity with respect to insulin resistance [41]. Compared with normotensive controls, no appreciable differences as to baseline forearm blood flow and the rise in blood flow during insulin infusion could be discerned despite the presence of a markedly reduced glucose uptake. On the other hand, hypertension is characterized by so-called vascular rarefaction, a functional and structural disappearance of microves-

sels, that supposedly contributes to the rise in peripheral vascular resistance [42]. It has been argued that the increased vascular resistance serves to maintain substrate supply to the tissues at a level that matches metabolic demand in the presence of elevated systemic pressure, which tends to raise tissue blood flow [43]. Consistent with this view, a normal blood flow in tissues of hypertensives has been reported [43]. This does not, however, automatically imply reestablishment of adequate tissue nourishment. Vessel rarefaction affects the spatial distribution of flow with less homogenous capillary perfusion, which will hamper the efficacy of the capillary exchange and, possibly, insulin sensitivity [42]. Circumstantial evidence supports the notion that structural vascular abnormalities without appreciable differences in tissue blood flow may affect vascular resistance and insulin sensitivity in hypertension. The percentage of fast-twitch muscle fibers and, thus, capillary density have been found to be lower in untreated hypertensives compared to normotensive controls, and to correlate with intra-arterial blood pressure and peripheral vascular resistance [44]. In addition, capillary density has been shown to be inversely related to insulin resistance [33].

Functional and/or structural microvascular dysfunction per se, however, is unlikely to be able to elevate blood pressure. Numerous theoretical and experimental studies suggest that chronic hypertension can occur only if renal function is abnormal and a shift of the renal pressure-natriuresis relationship takes place [45]. In the absence of the latter, increased peripheral vascular resistance only transiently raise blood pressure, to be followed by an increase in renal sodium excretion and a return of arterial blood pressure to normal. Likewise, insulin-stimulated vascular smooth muscle growth [46,47] and hypertrophy of resistance vessels are not by itself a primary cause of hypertension.

A group of patients with asymptomatic atherosclerosis were recently found to be insulin resistant compared to a control group without peripheral vascular disease [48]. Blood pressure and plasma insulin levels were normal in both groups and, more importantly, did not differ between the two groups. A defective non-oxidative glucose metabolism identical to that observed in hypertension, was shown. These findings suggest that insulin resistance not necessarily coincides with hypertension and that a defect in glucose metabolism is the primary abnormality with hyperinsulinaemia being a secondary phenomenon.

In conclusion, hyperinsulinaemia is an unlikely primary cause of hypertension, but a facilatatory role for hyperinsulinaemia in blood pressure elevation remains possible. The association between insulin resistance and hypertension is intriguing but far from clear.

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26. CATION TRANSPORT, HYPERTENSION AND DIABETIC NEPHROPATHY

RUGGERO MANGILI

The hypothesis that diabetic nephropathy may not simply be a result of the metabolic abnormalities of diabetes, but may require the concomitance of a permissive genetic background, was initially suggested by the incidence pattern of proteinuria in insulin-dependent diabetes [1,2], and was later supported by the observation that renal destiny is often concordant among Type 1 diabetic siblings [3,4]. Family clustering of diabetic nephropathy may occur also in Type 2 diabetes, and closer evidence that this complication may reflect inheritance, independent of that of Type 2 diabetes, is restricted to Pima Indians [5]. Exploring parental history of diabetic nephropathy *per se* may not be feasible in Type 1 diabetes [6], but addressing the relevance of known genetic factors to renal prognosis is otherwise possible, in the hope to identify suitable markers of predisposition, and to provide clues to the molecular and cellular pathophysiology of diabetic kidney disease. Among the candidate issues, the genetic background predisposing to essential hypertension was more extensively explored and discussed in the past few years. As essential hypertension is known to cluster in families and to be characterised by abnormalities

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in erythrocyte sodium transport with established genetic components, the hypothesis was probed by examining these variables in diabetic nephropathy, in addition to revisiting the chicken-and-egg relationship of blood pressure with urinary albumin excretion.

1. BLOOD PRESSURE AND DIABETIC NEPHROPATHY

Diabetic nephropathy explains a large proportion of the excess cardiovascular morbidity and mortality characterising Type 1 diabetes [7], and arterial hypertension is a major risk factor for both outcomes [8]. Blood pressure is known to rise with urinary albumin excretion through the natural course of diabetic nephropathy, eventually reflecting the concomitant decline of glomerular filtration rate and renal failure [9,10]. The idea that arterial hypertension could not be entirely secondary to kidney disease among these patients was initially raised among the theoretical explanations to the higher systemic blood pressure characterising Type 1 diabetic patients with microalbuminuria, as glomerular filtration rate is still normal or elevated at this stage [11]. Clinical intervention studies have confirmed a central role for raised systemic blood pressure in the progression of microalbuminuria to overt nephropathy (Chapter 29), as well as through chronic renal failure (Chapter 31), but this wealth of data cannot represent intrinsic evidence that abnormalities in blood pressure may be relevant to the onset of diabetic kidney disease.

Indeed, raised blood pressure was found to predict clinical proteinuria in Type 1 diabetes [12], although the independence of this effect from the possible concomitance [11,13] and predictive value of microalbuminuria (Chapter 18) remained uncertain. Two longitudinal studies recently investigated the relevance of blood pressure to the onset of microalbuminuria in Type 1 diabetes, but came to opposite conclusions [14,15]. Importantly, parental hypertension has been traced more often in diabetic nephropathy than among Type 1 diabetic patients at low renal risk [16,17], suggesting a family clustering of the factors involved in the pathogenesis of essential hypertension with those predisposing to diabetic nephropathy. However, the initial controversy in this issue [18] was further established after analyses were extended to family history of cardiovascular disease [19,20]. While younger parental age may reflect lower rates of parental hypertension and cardiovascular disease and, theoretically, lower chance to observe the phenomenon [20], more contributions are awaited to solve this and the former issue.

Though blood pressure is already weighed by parental factors among teenagers [21] and among young Type 1 diabetic patients [22], phenotypic variables may have limited value in the categorical identification of susceptibility to hypertension early in the course of Type 1 diabetes, as the penetrance of hypertension and that of a relevant family history may be very low at the young age of these patients. On the

contrary, the detection of intermediate phenotypes of hypertension in diabetic nephropathy might better suggest the relevance of susceptibility to hypertension, and would also offer a perspective chance to mark predisposed individuals.

Distinct genetic components underlie the lower sodium/potassium pump and the higher sodium-potassium cotransport activities characterising essential hypertension [23,24], but those determining elevated rates of erythrocyte sodium-lithium countertransport (SLC) in hypertension [25-27] are known to be stronger [28] and were so given greater potential relevance in the approach to diabetic nephropathy. Up to 80% of the inter-individual variability of SLC is explained by the sum of a major gene effect with polygenes among Caucasian pedigrees of the general population [26,27], where SLC shows a bimodal distribution independent of age and sex [29]. Taken together, these observations strongly suggested the partial identity of the genetic determinants of hypertension with those of elevated SLC [30], which qualified then as an intermediate phenotype of essential hypertension. The dispersion of SLC values around each mode may reflect the confusing effect of environmental factors and polygenes around the central effect of a major gene; the resulting overlap may partly restrict the use of elevated SLC as a categorical marker of disease. Nonetheless, its prognostic relevance was recently supported by a prospective study of the incidence of hypertension [31].

2. Na/Li COUNTERTRANSPORT AND DIABETIC NEPHROPATHY

Evidence that SLC could be elevated in Type 1 diabetic patients with clinical nephropathy was simultaneously provided for the first time by two independent studies [17,32], whereas no abnormalities in the activity of the ouabain-sensitive Na/K pump and of the bumetanide-sensitive Na-K cotransport associated with nephropathy [17]. Median SLC was almost twice that of long-term normoalbuminuric patients with Type 1 diabetes of long duration, hence at low renal risk, though neither metabolic variables [17,32], nor renal failure [32] or presence of retinopathy [17] could explain this difference. In particular, measures of glycaemic control did not explain the inter-individual variability of SLC in either study, but retrospective indices of hyperglycaemia were found to interact positively and independently with elevated SLC to confer a poor renal prognosis [17]. Finally, both studies were backed by evidence that family history of hypertension, an established concomitant of elevated SLC in the general population [25,28,33,34], was also more common among the patients with nephropathy [16,17], thus qualifying the hypothesis that elevated SLC might express the genetic background of essential hypertension also in diabetic nephropathy.

The finding of comparably elevated SLC in microalbuminuria further supported its candidate role as a marker of susceptibility to nephropathy in Type 1 diabetes

[35], although three reports argued against this possibility either after missing the association [18] or by observing that SLC rates were largely comparable in diabetic nephropathy and in patients at low renal risk [36,37]. However, after the initial observations were extended to larger samples of patients [38-40] and one more independent set of results was made available [41], evidence that SLC can indeed be elevated in Type 1 diabetic patients with raised urinary albumin excretion seems to outweigh evidence of the contrary (figure 26-1).

The relative risk of having SLC higher than 0.4 mmol $\cdot$ l_{RBC}^{-1} $\cdot$ h^{-1} in diabetic nephropathy was in fact very similar in the Joslin Clinic study [17] and in the Steno study [18], though statistical significance was just missed by the latter. There were a few methodological differences in the technique for the measurement of SLC, which could account for this weak but critical difference in findings between these two studies. That this may be the mere explanation for the controversy is also suggested by the finding of highest relative risk where the original method [25-27,29] was carefully reproduced [32,35,41], and by the several points at methodological variance conversely characterising studies where no association was detected [37,40]. Though changing single technical steps may be of little relevance (e.g.[40,42,43]), it cannot be excluded that several changes may partly compromise the final estimate of SLC rates, as recently discussed elsewhere [42,44].

Environmental factors underlie 20% of the inter-individual variability of SLC in the general population, and have been often postulated [18,37,40,45] to drive the finding of elevated SLC in diabetic nephropathy [17,32], though there is no evidence that this may be the case. All studies have investigated Type 1 diabetic patients in ordinary glycaemic control, and no straight association of SLC with blood glucose, glycated haemoglobin levels or daily insulin dose was detected. No patients with known thyroid disorders [46], nor pregnant women [47] were ever considered, and the hypothesis that hyperlipidaemia [48,49] might independently explain elevated SLC in diabetic nephropathy has been recently ruled out [41], though both conditions eventually do coexist. On the contrary, systemic blood pressure remained a positive predictor of elevated SLC in all of the studies which addressed this association [17,35,39,50], and, importantly, independent of the presence of nephropathy [38,41]. Furthermore, a positive correlation of midparental SLC with that measured in their Type 1 diabetic offspring has been described, though observations in proteinuric and non-proteinuric patients were pooled altogether [51]. In line with similar observations in non-diabetic families [25,28,52], SLC did not show correlation between spouses, i.e. genetically unrelated individuals, thus suggesting that inherited components more than shared family environment may contribute to the inter-individual variability of SLC also in Type 1 diabetes. While confirming these findings, another study failed to observe elevated parental SLC in

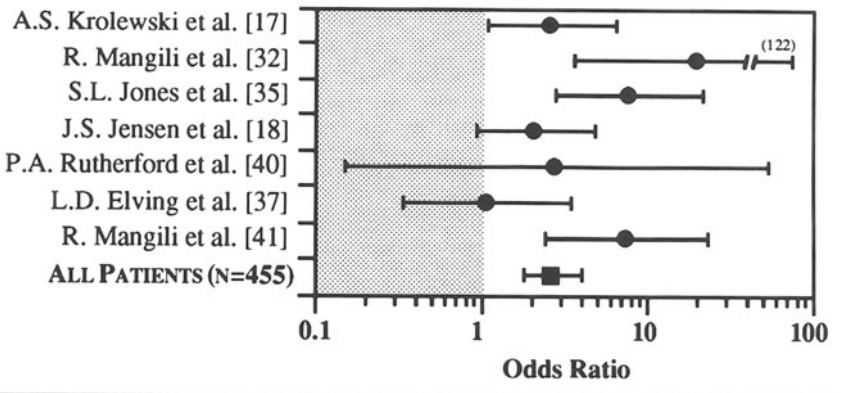

Figure 26-1. Odds ratio of having SLC activity higher than 0.4 mmol · l_{RBC}^{-1} · h^{-1} in Type 1 diabetic patients with microalbuminuria or macroalbuminuria vs. age, sex and duration of diabetes -matched patients with normoalbuminuria, in 7 independent studies (filled circles) and in their 455 cumulative observations (filled square; OR=2.72, χ^2=25.8, $p<0.00001$). Studies where the 95% confidence intervals partly range through the shaded area consistently failed to detect higher SLC in diabetic nephropathy.

diabetic nephropathy, arguing against the heritability of elevated SLC in diabetic nephropathy [18]. However, the extension of this second analysis to several families where only one of the parents could be ascertained may have partly confused data, and the statistical power of this comparison was calculated without accounting for the residual variability of parental SLC as predicted by that measured in the diabetic offspring. This circumstance may restrict chances to reject the hypothesis, and the central question may then turn to the above mentioned reasons for the borderline difference in SLC between proteinuric patients and their normoalbuminuric controls in the same study [18].

3. Na/Li COUNTERTRANSPORT: NATURE AND FUTURE

Taking together current evidence, it seems possible to conclude that SLC is elevated in Type 1 diabetic patients with nephropathy, and shows major concomitants which mirror those described in the general population, putatively accounting for part of the genetic abnormalities of essential hypertension. Indeed, some of the concomitants of elevated SLC in essential hypertension, mostly some degree of insulin resistance [53] and cardiorenal hypertrophy [54], were also observed in hypertensive Type 1 diabetic patients without clinical proteinuria [55-57], although the possible independent contribution of microalbuminuria could not be always singled out. An

association of elevated SLC with glomerular hyperfiltration has also been suggested [58], but soon turned as controversial [34] as it is in essential hypertension [59,60].

Altogether, these associations should conservatively remain statistical, as there is no molecular or cellular evidence that SLC may be either involved directly in the mechanism of hypertension [61,62] or even in that of diabetic kidney disease. Indeed, the nature of the membrane transport mediating SLC remains poorly understood. Evidence that lithium can compete for the internal proton site of the amiloride-sensitive, sodium-hydrogen exchanger (NHE) in vesicle preparations from non-erythroid cells [63-66] stands at variance with the observation that SLC may not always mediate proton efflux [67], and is totally insensitive to amiloride in the erythrocyte [68-70], where the amiloride-sensitivity of NHE was otherwise confirmed [71]. Whether this functional heterogeneity may be explained either by the allosteric properties of a single transporter [44,72] or by the structural and biological independence of distinct sodium exchangers remains to be seen. Enhanced NHE activity may have straightforward pathophysiological implications, and was described in leucocytes and skin fibroblasts from patients with nephropathy (Chapter 18), but the relationship with the genetic component of SLC is also unclear [73].

While longitudinal studies are eagerly awaited to understand whether SLC may reflect renal prognosis in Type 1 diabetes [74], the use of the standard technique [25] is recommended to warrant the collection of comparable data. Though the activity of SLC is usually quantified by measuring sodium-driven lithium efflux in the presence of physiological amounts of extracellular sodium [25,75-77], and though it was under these conditions that the relevance of SLC to the genetics of human hypertension was established, the external sodium site may not be always saturated by physiological concentrations, and kinetic studies of SLC may allow, in principle, further insight in its pathophysiology [37,44].

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27. MICROALBUMINURIA IN YOUNG PATIENTS WITH TYPE 1 DIABETES

HENRIK BINDESBØL MORTENSEN

Diabetic nephropathy is the main cause of the increased morbidity and mortality among patients with Type 1 diabetes [1,2,3]. In recent years it has been shown that a slightly elevated urinary albumin excretion rate (microalbuminuria) is an early predictor for later development of manifest diabetic nephropathy [4,5,6]. The presence of hypertension in the diabetic individual markedly increases the risk and accelerates the course of the diabetic kidney disease [7]. Given the poor prognosis for patients developing manifest diabetic nephropathy emphasize the need for a uniform intervention programme for treatment of microalbuminuria in children and adolescents with Type 1 diabetes.

MEASURE FOR ALBUMIN EXCRETION

In 1989 a nation-wide screening for microalbuminuria in Denmark was performed in 22 paediatric departments treating children with Type 1 diabetes [8]. To assess the prevalence of microalbuminuria in this group of patients, timed overnight urine collection was used. This urine fraction avoids the effect of posture, physical

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exercise, major blood pressure variations and the acute effect of diet on albuminuria [9,10] and it is a convenient and practical method for most children. If the urinary albumin excretion rate (AER) was >20 μg min^{-1} in one of the two samples from a diabetic patient, a third sample was taken to determine whether the child had elevated albumin excretion, microalbuminuria. This limit was chosen as the lowest albumin excretion rate predicting diabetic nephropathy on the basis of investigations of the upper 95th percentile for albumin excretion in the control group of 209 healthy children [8].

ALBUMIN EXCRETION RATE AMONG CHILDREN WITH AND WITHOUT DIABETES

The ranges for albumin excretion rate in urine samples collected overnight in both non-diabetic and diabetic children 12 years or less and adolescents from 12 to 19 years are given in table 27-1. The geometric mean for albumin excretion was significantly elevated ($p<0.001$) in adolescents compared to children for both groups. There were no significant differences ($p>0.05$) in albumin excretion rates between the sexes.

These findings are consistent with the results on night-time urines reported by Davies et al. [11] and by Rowe et al. [12]. In non-diabetic adolescents the relationship between AER, body surface area and level of maturity was nearly constant. By contrast in diabetic adolescents AER was positively correlated with body surface area and age. This correlation was independent of the current HbA_{1c} level, suggesting that specific metabolic changes other than poor blood glucose control might affect AER, particularly in the diabetic subjects in the pubertal period.

TYPE 1 DIABETIC CHILDREN WITH ELEVATED ALBUMIN EXCRETION RATE

A prevalence of 4.3 % for persistent microalbuminuria (>20-150 μg min^{-1}) was revealed in 957 Danish children and adolescents aged from 2 to 19 years with Type 1 diabetes and mean diabetes duration of 6 years [8]. This is considerably lower than the prevalence reported in other studies of smaller groups of diabetic children and adolescents. In a previous study, Mathiesen et al. [13] using timed overnight urine collections reported a prevalence of 20% for microalbuminuria, investigating 97 children and adolescents, age range 7-18 years, with a mean diabetes duration of 10 years. In another study Nørgaard et al. [14] observed a prevalence of 15 % based on 24-h urine collection in 113 Type 1 diabetic patients, age range 1-18 years, with a mean diabetes duration of 9 years. D'Antonio et al. [15] reported a prevalence of 21 % using 24-h urine collections in 62 patients, age range 5.8 to 20.9 years, with a diabetes duration of 5 years. In a recent study Joner et al. [16] observed a

Table 27-1. Timed overnight urinary albumin excretion rates in healthy children and adolescents, and in children and adolescents with Type 1 diabetes and AER ≤ 20 μg min^{-1}

	Children $\leq$12 years		Adolescents >12-19 years	
	Boys	Girls	Boys	Girls
Normal children				
n	47	30	58	74
AER (μg min^{-1})	1.28×/÷2.75	1.37×/÷1.97	2.73×/÷2.18[a]	2.34×/÷2.14[a]
Diabetic children				
n	154	124	334	297
AER (μg min^{-1})	1.70×/÷2.11	1.72×/÷2.07	2.94×/÷2.38[a]	3.16×/÷2.23[a]

Geometric mean ×/÷ SD factor.
[a]$p < 0.001$ compared with younger age group.
Boys vs. girls all NS. [ref. 8, with permission]

prevalence of 12.5% based on timed overnight urine specimens in 371 Type 1 diabetic patients, age range 8-30.3 years, mean diabetes duration 10.5 years. The discrepancies in prevalence for persistent microalbuminuria in these studies may partly be explained by differences in age, diabetes duration and blood glucose control in the populations investigated. Still these studies are not strictly comparable in terms of prevalence of microalbuminuria, as the definition of microalbuminuria differs. This problem will remain until agreement is reached on definition.

In adolescent diabetic patients (above 16 years) the prevalence of microalbuminuria was 13-14 % in accordance with the previous investigations. The occurrence of microalbuminuria is extremely rare before puberty. Two prepubertal children were diagnosed with microalbuminuria in an earlier study of Nørgaard et al. [14], and Joner et al. [16] reported one case. In our study [8] two other girls were diagnosed, while none were detected in the study of Mathiesen et al. [13] or of Dahlquist et al. [17]. The prevalence of persistent microalbuminuria in different age groups and in groups with different duration of diabetes are shown in figures 27-1 and 27-2. Screening for microalbuminuria need only be recommended in paediatric care over 12 years of age in adolescents with a diabetes duration of 4 years or more.

OVERNIGHT ALBUMIN EXCRETION RATE AND BLOOD GLUCOSE CONTROL

Several previous reports have suggested a relationship between poor blood glucose control and increased urinary albumin excretion [18,19]. We found that only females with microalbuminuria had significantly elevated HbA_{1c} values compared to diabetic

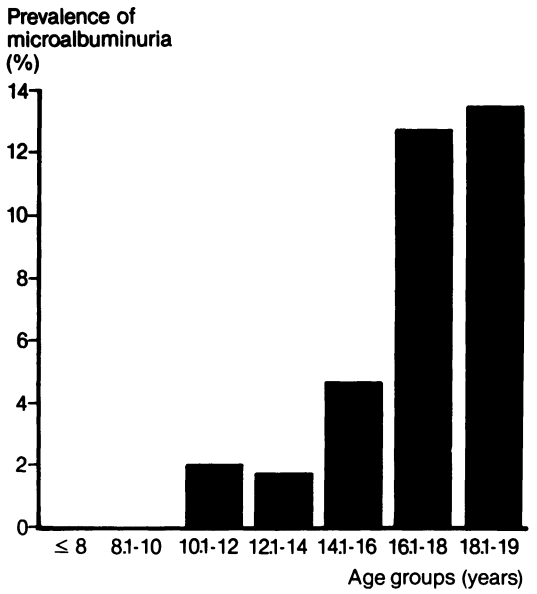

Figure 27-1. The prevalence of microalbuminuria in different age groups in 909 children and adolescents with Type 1 diabetes [8, with permission].

patients with normoalbuminuria, in agreement with the results reported by D'Antonio et al. [15]. In previous nationwide investigations [20,21] we have shown that blood glucose control is poorer during puberty, particularly in adolescent females compared to males. This observation may be explained by changed hormonal and/or lifestyle factors. An impaired linear growth observed in females with microalbuminuria may also be associated with long-term poor blood glucose in these patients. Recent studies have shown that improved metabolic control could retard but not prevent the progression of incipient diabetic kidney disease [22,23].

OVERNIGHT ALBUMIN EXCRETION RATE AND ARTERIAL BLOOD PRESSURE

The normal range for diastolic blood pressure in diabetic boys and girls aged 8 to 18 years with normoalbuminuria are shown in figures 27-3 and 27-4. The figures also include data from the patients diagnosed with micro- and macroalbuminuria. Ten out of 16 boys had diastolic blood pressure above the upper quartile while eight out of 14 girls with microalbuminuria had diastolic blood pressure above this quartile. Three boys with macroalbuminuria had diastolic blood pressure below the

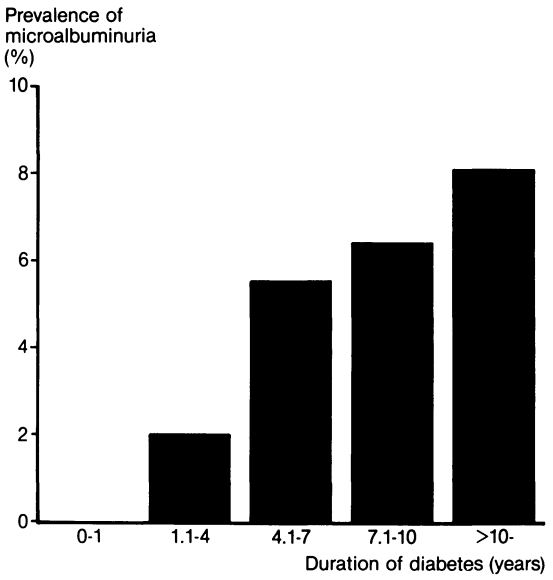

Figure 27-2. The relationship between duration of diabetes and prevalence of microalbuminuria in 909 children and adolescents with Type 1 diabetes [8, with permission].

upper quartile while two girls had values above. Consequently 60% of adolescents with microalbuminuria had diastolic blood pressure in the upper quartile for normoalbuminuria [24]. Thus excess prevalence of raised blood pressure in Type 1 diabetic patients could be explained by the presence of elevated blood pressure in adolescents with micro- and macroalbuminuria as suggested by Nørgaard et al. [14]. Re-examination of 15 adolescents with microalbuminuria 2 years after identification revealed that two of these (13%) had developed overt proteinuria during this period. They had initially an overnight albumin excretion rate of 62 and 115.7 μg min^{-1} increasing to 184.4 and 448.3 μg min^{-1}, respectively (unpublished data). Without treatment a more marked increase in the yearly progression rate to overt diabetic nephropathy can be seen for some individuals than previously reported [22]. Altered glomerular haemodynamics with increased glomerular plasma flow and transcapillary pressures are considered key factors in the initiation and progression of diabetic nephropathy [25-27]. Therapy with an angiotensin converting enzyme (ACE) inhibitor has been shown to lower albumin excretion rate and mean arterial blood pressure in normotensive adolescents [28] and adults [29] with IDDM and microalbuminuria on the short term. Recently long-term studies have suggested that

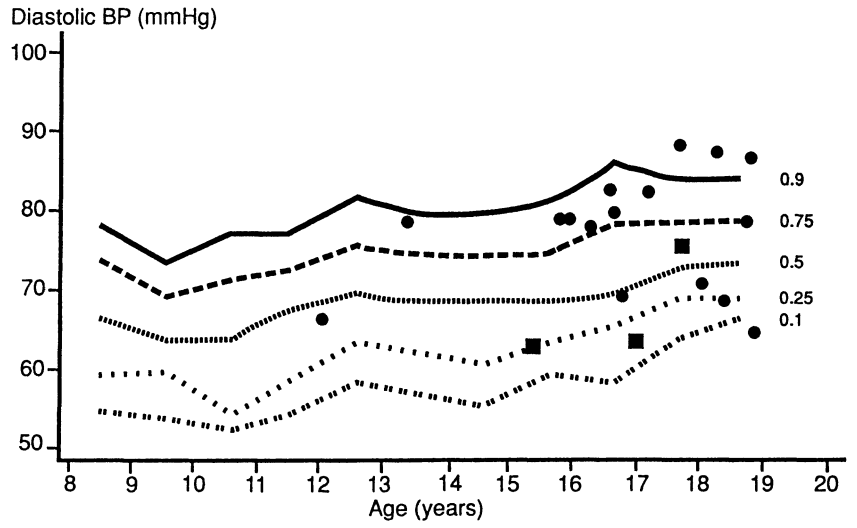

Figure 27-3. Percentile distribution of diastolic blood pressure in 487 boys aged 8 to 18 years with Type 1 diabetes. The dots represents diastolic blood pressure for the 16 boys with microalbuminuria; the squares the three boys with macroalbuminuria [24, with permission].

ACE-inhibition delays progression to diabetic nephropathy in normotensive Type 1 diabetic patients with persistent microalbuminuria [30,31]. Previous investigations in adults with Type 1 diabetes have shown that at the time of recognition of microalbuminuria the blood pressure is often within the normal range [32], and tends to increase in parallel with the extent of micro-/macroalbuminuria [33-36]. Only two out of five adolescents with macroalbuminuria had elevated blood pressure. This may be a selection bias because 2 patients with macroalbuminuria were excluded due to antihypertensive treatment. However, shorter duration of diabetes and lower body mass index compared to an adult population could explain the observed discrepancies.

These findings suggest that elevated arterial blood pressure may be related to the increased prevalence of elevated albumin excretion rate observed in adolescents with Type 1 diabetes and it suggests that hypertension plays an important role for the initiation and the progression of diabetic nephropathy in keeping with previous reports [37-39].

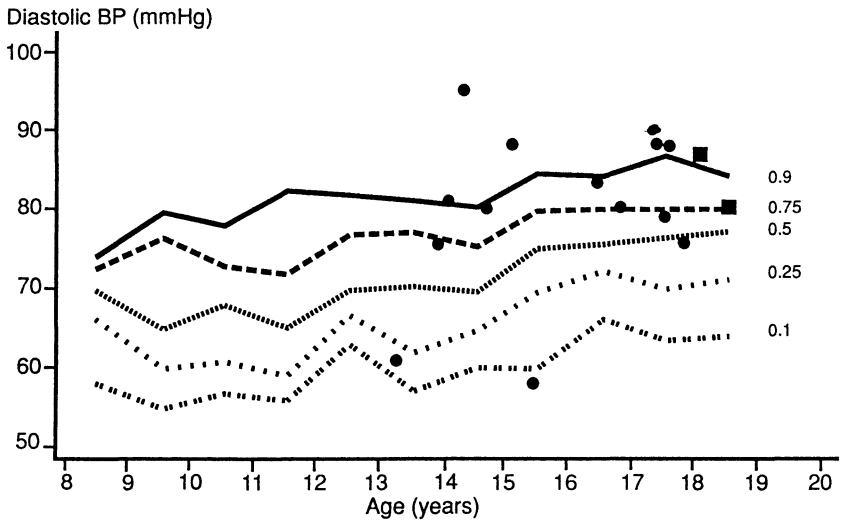

Figure 27-4. Percentile distribution of diastolic blood pressure in 425 girls aged 8 to 18 years with Type 1 diabetes. The dots represents diastolic blood pressure for the 14 girls with microalbuminuria; the squares the two girls with macroalbuminuria [24, with permission].

INTERVENTION PROGRAMME FOR TREATMENT OF MICROALBUMINURIA IN CHILDHOOD

In children with microalbuminuria ($>$20-150 $\mu g\ min^{-1}$) blood glucose control should be improved during a period of 6 months and simultaneously the status of microalbuminuria should be monitored closely. If microalbuminuria disappears or improves there is no indication for pharmacologic intervention. However, if the status of microalbuminuria deteriorates even if the blood glucose control improves and blood pressure is within the normal limits, antihypertensive treatment by an ACE-inhibitor should be instituted. The ACE-inhibitors have potential therapeutic advantages over other antihypertensive drugs because they may selectively reduce efferent arteriolar pressures, and thereby glomerular capillary pressure, by lowering angiotensin II levels [39,40]. Besides there is a wide experience with its use in the paediatric age group and therapy has been associated with very few side effects at low doses in the presence of normal renal function [41,42]. However, long-term follow up studies in children are required to evaluate whether intervention at an early stage with ACE-inhibitors will slow down rather than prevent progression to established diabetic nephropathy.

CONCLUSION

The prevalence of persistent microalbuminuria was only 4.3% in a study consisting of a large fraction of all Danish children and adolescents. Elevated AER occurs mainly after the onset of puberty, and screening for microalbuminuria should only be recommended in children over 12 years of age with a duration of diabetes at least 4 years. Sixty percent of adolescents with microalbuminuria had diastolic blood pressure above the upper quartile for normoalbuminuric patients. Therefore elevated blood pressure in childhood should lead to careful observation of the blood pressure level in the long term and examination of the urinary albumin excretion rate to prevent development of end-organ damage.

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28. EARLY RENAL HYPERFUNCTION AND HYPERTROPHY IN IDDM PATIENTS INCLUDING COMMENTS ON EARLY INTERVENTION

MARGRETHE MAU PEDERSEN

Since diabetic nephropathy constitutes the principal background for reduced survival in insulin-dependent diabetes, much interest is being paid to early alterations in kidney function and structure, and to the possible relationship between such early abnormalities and later development of diabetic nephropathy. A modest increase in urinary albumin excretion, microalbuminuria, has been identified as an early marker of diabetic nephropathy, and interventions postponing the onset of overt nephropathy has been introduced. In this chapter the earliest renal changes in IDDM, glomerular hyperfunction and renal hypertrophy, will be addressed.

GLOMERULAR HYPERFUNCTION

From the onset of IDDM kidney function is characterized by elevation of glomerular filtration rate (GFR) and renal plasma flow (RPF). Using precise measurements e.g. renal clearance of inulin or iothalamate, mean GFR in groups of short-term IDDM patients (diabetes duration less than 12-15 years) has consistently been found increased by approximately 15-25% - to values around 135-140 ml/min/1.73m^2

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

during 'usual metabolic control' [1-5]. Previous to the start of insulin treatment (but in the absence of ketoacidosis) glomerular hyperfiltration is even more pronounced, often showing elevations of approximately 40% [6,7]. RPF seems to be elevated synchronously with the increase in GFR, but less pronounced [1,3]. Although questioned, estimation of RPF from renal clearance of hippuran appears to be a reliable measure also in the diabetic state [8].

Glomerular hyperfunction remains a characteristic feature of diabetic kidney function during the first one or two decades of diabetes. In cross-sectional studies patients with microalbuminuria - typically developed after 10 to 15 years of diabetes - show more pronounced hyperfiltration than normoalbuminuric patients [5,9]. Until now, however, no prospective studies have described the individual course in GFR during transmission from normo- to microalbuminuria. With further increase in albumin excretion and development of nephropathy, GFR and RPF starts to decline, whereas in patients with persistent normoalbuminuria a moderate degree of glomerular hyperfunction seems to persist [10].

The characteristic glomerular hyperfunction in early stages of human diabetes in some degree parallels early renal changes in experimental diabetes. As described in Chapter 22, besides hyperperfusion, increased intraglomerular hydraulic pressure is an important factor in experimental hyperfiltration. In humans the proportionally larger increase in GFR than RPF - that is an increased filtration fraction - may suggest the presence of similar glomerular hypertension. However an elevation of the ultrafiltration coefficient due to an increase in filtration surface might offer an alternative or a contributing mechanism for the high filtration fraction [11].

RENAL HYPERTROPHY

Kidney volume, estimated from ultrasonic technique or roentgenographically, like GFR shows marked increases from the debut of diabetes. During initial insulin-treatment kidney hypertrophy is somewhat reduced (the reduction apparently being 'delayed' and of relatively smaller size compared to the lowering of GFR [12]), but mean size remains elevated by approximately 20-30% during short-term IDDM [3,13-15]. At this stage kidney volume is strongly correlated to GFR - corresponding to the state in non-diabetic subjects and in most forms of non-diabetic renal hypertrophy [16]. Later in the course of diabetes this association vanish, possibly with further increase in kidney volume in the microalbuminuric state [17] and with persistent hypertrophy also after the onset of overt nephropathy. Morphological studies concerning the initial renal enlargement show glomerular and tubular hypertrophy [18,19]. Subsequent deposition of PAS-positive material in the glomerular tuft and further enlargement of open glomeruli does not play a significant role to whole kidney size. As discussed below both GFR and kidney volume in early

diabetes are associated to glycemic control. However results are conflicting with respect to whether kidney size may still be modulated after years of diabetes and e.g. during the microalbuminuric state [17,20,21].

DETERMINANTS FOR GLOMERULAR HYPERFUNCTION AND HYPERTROPHY

The question why - or by which pathophysiological mechanisms - glomerular filtration rate and renal plasma flow are increased still remains unclarified. A number of intervention studies have been performed often suggesting the specific importance of abnormalities concerning one particular substance. In table 28-1 such factors with a probable involvement in glomerular hyperfunction are listed, many of which may 'only' represent normal modulators of kidney function influenced by an abnormal metabolic milieu and changes in fluid homeostasis. Furthermore many of these factors are interrelated and/or represents different steps in regulatory mechanisms.

Alterations in carbohydrate metabolism no doubts are of primary importance to glomerular hyperfunction. An increase in blood glucose concentration apparently creates vasodilation in a number of tissues including the glomerular capillaries [22,23]. Suggested mechanisms includes an osmotic effect on cells lining small vessels [24], an increase in formation of kallikrein and endothelium-derived-relaxing-factor (EDRF) [25,26], and modulation through renal prostaglandins [27]. Furthermore increased tubular sodium reabsorption linked to increased amount of filtered glucose may suppress the tubuloglomerular feedback system and thereby contribute to hyperfiltration [25,28]. Both earlier intervention and cross-sectional studies [29-32] and a recent investigation we performed on determinants for intra-individual variation in diabetic kidney function [33] suggest that the 'acute' level of glycemia is of main relevance to variation in RPF while long-term metabolic control (e.g. represented by HbA_{1c}) is closer related to variation in GFR. It may be that e.g. biochemical membrane properties are important to the long-term influence of glycemic control. Controversies exist, however, with respect to the degree of influence on GFR from acute hyperglycemia [34,35], and it may be that subgroups of diabetics patients react differently to changes in blood glucose [34].

Another aspect of hyperglycemia is enhanced glucose metabolism through the polyol pathway in tissues with insulin-independent glucose uptake. High activity of the enzyme aldose reductase leads to sorbitol accumulation and probably changes in the redox state. These alterations, which appear to be rather closely linked to depletion of myoinositol [36], have been related to development of late diabetic complications in different tissues and lately also to the presence of glomerular hyperfiltration [37,38].

Table 28-1. Factors with probable involvement in early diabetic glomerular hyperfunction including suggested intermediary steps [ ].

Metabolic factors:	Blood glucose Long-term glycemic control ($HbA1_c$) Activity of polyol pathway Ketone bodies	[bradykinin, EDRF, prostaglandins]
Hormonal/peptide substances:	GH, IGF-I Glucagon Insulin (peripheral hyperinsulinemia, hepatic insulinpenia) Atrial natriuretic peptide Catecholamines (reduced effect) Arginine vasopressin	[prostaglandins] [?, no direct effect on renal vessels] [restraining effect from adenosine]
Other vasoactive substances:	Prostaglandins Kallikrein, bradykinin, kinin Endothelial derived relaxing factor (EDRF)	
Dietary factors other than carbohydrates	Protein intake (/phosphate?)	[glucagon, prostaglandins, kallikrein, adenosin, dopamine, nitric oxide]

References : 22-27,29-33,37-40,42-46,49-56.

Increase in the concentration of ketone bodies accompany also fairly well-regulated diabetes and may be of some significance to hyperfiltration and hyperperfusion. Intervention studies points towards such influence [39], however no statistical correlations have been demonstrated between the concentration of ketone bodies and GFR or RPF.

Besides an indirect effect of insulin deficiency on renal hemodynamics through the blood glucose level, it has been suggested that inadequate hepatic delivery of insulin is associated with increased production of renal vasoregulatory factors [40]. Furthermore insulin seems to be of importance to calcium entry into renal vascular smooth muscle cells [25]. Insulin deficiency might accordingly compromise vascular

contraction and give rise to glomerular hyperfunction. However during conventional insulin treatment a peripheral hyperinsulinaemia is often present.

A consequence of hyperglycemia and peripheral hyperinsulinaemia appears to be an increase in total exchangeable body sodium and a tendency towards extracellular volume expansion [4,41]. Apart from the influence on tubuloglomerular feedback system, this condition may induce hyperfiltration through a reflectoric increase in atrial natriuretic peptide (ANP). A significant role for ANP in hyperfiltration is strongly suggested by experimental studies showing marked reductions in GFR during treatment with anti-ANP serum [27,42] or an ANP-receptor antagonist [43]. In the above mentioned study on individual variation in kidney function such influence of ANP in human diabetes was indicated by the finding of a close co-variation (figure 28-1) between GFR and ANP.

Growth hormone (GH) and glucagon have long been known to represent probable mediators of diabetic hyperfiltration. Both hormones are capable of inducing elevation in GFR (though GH not acutely) [44,45]; increased plasma levels of the hormones are brought about by the diabetic state, and with respect to GH a statistical correlation between plasma levels and GFR has been reported [46]. The influence of GH is apparently indirect - acting through insulin-like growth factor I (IGF-I) [47]. Glucagon may be relevant especially secondary to changes in protein intake [48].

Protein intake plays a special role in diabetic hyperfiltration in the sense that it represents a 'iatrogenic' stimulator of GFR. Diabetic diets typically have a protein content of approximately 18-20% of total energy intake compared to a protein intake around 14% in non-diabetic (Danish) subjects. By lowering protein intake from 19 to 12% we observed a decrease in mean GFR from 146 to 132 ml/min/1.73m^2 in a group of normoalbuminuric IDDM patients [49]. The type of protein ingested seems to be of importance to the magnitude of influence on GFR [50]. Furthermore the content of phosphate may be relevant [51].

With respect to renal hypertrophy it is largely unknown to which extent the above mentioned factors may be involved in parallel to the influence on GFR. However modulation of renal volume - if possible - is likely to occur slowly. Besides the important influence of glycemic control, experimental studies strongly points towards GH/IGF-1 as contributors to especially very early kidney growth [47].

POSSIBLE ROLE OF HYPERFILTRATION AS A RISK MARKER FOR DIABETIC NEPHROPATHY

By noticing the quite often marked hyperfiltration in certain IDDM patients, and the fact that such condition is usually seen in patients with poor metabolic regulation,

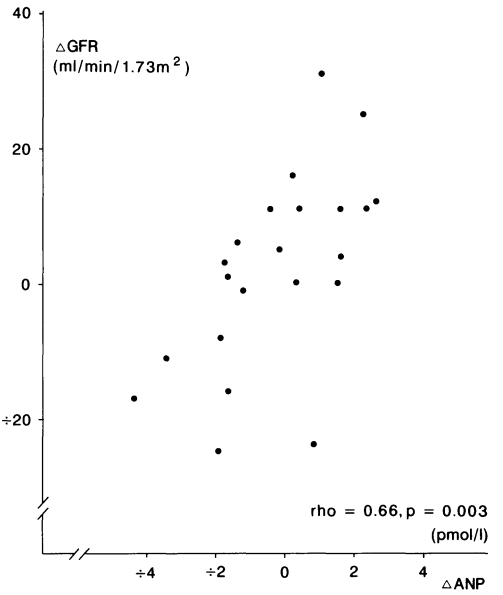

Figure 28-1. Intra-individual variation in glomerular filtration rate (ΔGFR) in relation to variation in plasma concentration of atrial natriuretic peptide (ΔANP) in 22 patients with IDDM. $\sigma = 0.66$, $p = 0.003$. From Mau Pedersen et al. [33, with permission].

is has been logic to suggest hyperfiltration as a pathogenetic factor for later development of diabetic nephropathy. The apparent analogy between the characteristic early renal hemodynamic changes in IDDM and early renal involvement in experimental diabetes has nourished this suspicion. Thus in experimental models a lowering of high GFR and/or high intraglomerular hydraulic pressure by pharmacological or dietary means clearly has attenuated progression of renal disease [57]. In human diabetes retrospective data have indicated that marked hyperfiltration may be a risk factor for later nephropathy [10,58], and from a recent prospective study glomerular hyperfiltration has been reported as the only independent predictor identified for the outcome of incipient or overt nephropathy [59]. Normoalbuminuric adolescent diabetic patients (with diabetes duration >8 years) were followed for 8 years. As possible independent predictors for nephropathy duration of diabetes, albumin excretion rate, blood glucose, and HbA_{1c} were included besides GFR. Meanwhile other studies have not been able to demonstrate such predictive value of a high GFR [60,61]. Designing the 'ideal' study however enclose many problems. Basically it needs to be of long-term prospective design, probably to include a

complete cohort of patients, and to use either repeated GFR measurements as baseline values or to characterize conditions for measurement rather strictly.

Indirect evidence for a pathogenetic role of abnormal renal hemodynamics may be found in the marked slowing of early renal disease observed during antihypertensive treatment, - maybe especially when applying ACE-inhibitors, which are considered to reduce intraglomerular pressure more specifically than other antihypertensives. Interestingly, in essential hypertension a recent study has suggested high GFR to be an indicator of early target organ damage expressed as increased left ventricular mass also when accounting for the blood pressure level [62].

Yet not extensively studied, also kidney hypertrophy have been implicated in development of diabetic nephropathy. Especially if more exact measurements for kidney volume became possible a hypothesis might be tested that enlargement of the kidneys and/or sustained marked hyperfiltration afflict diabetic subjects, who for some (unknown) reason are more strained by the diabetic state than others, and who might accordingly be at high risk of developing nephropathy.

POSSIBILITIES FOR INTERVENTIONS

As it appear from above, hyperfiltration per se does not constitute an established indication for intervention - leaving out though, the obvious goal of optimizing glycemic control also in order to decrease the risk of late complications. Moreover a priori it appears rational to avoid inducing additional hyperfiltration by recommending higher protein intake in diabetic than non-diabetic diet.

Possibilities for pharmacological intervention includes administration of aldose reductase inhibitors, aiming at normalizing polyol pathway activity [37,38], and treatment with somatostatin analogues, which may act on GFR through a lowering of GH (or IGF-I) and/or a suppression of glucagon secretion [63,64]. Until now these interventions have been tested only in rather short term studies and the possible long-term benefits awaits further investigations.

Also ACE-inhibitors deserves to be mentioned along with propositional early interventions. Although these agents have not generally been found to reduce GFR, their ability to reduce filtration fraction and maybe intraglomerular pressure [65] may prove valuable also before the onset of microalbuminuria. In addition to hemodynamic effects, ACE-inhibitors (or angiotensin II antagonists) may be relevant due to the possible growth stimulating effect of ANG II (including glomerular hypertrophy) [66].

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29. THE CONCEPT OF INCIPIENT DIABETIC NEPHROPATHY AND EFFECT OF EARLY ANTIHYPERTENSIVE INTERVENTION

MICHEL MARRE, GILLES BERRUT and BÉATRICE BOUHANICK

1. INTRODUCTION

Diabetic nephropathy is the main cause for premature death among type 1, insulin-dependent diabetic subjects [1]. To date, aggressive antihypertensive treatment is the only intervention able to improve prognosis of these patients [2]. The term diabetic nephropathy designates glomerular injury attributable to diabetes [3]. As in all glomerular diseases, its diagnosis is based upon three functional abnormalities: proteinuria (mainly, albuminuria), elevated blood pressure, and reduced glomerular filtration rate. Technical improvements lead to early detection of glomerular dysfunction in type 1, insulin-dependent diabetic subjects: the first ones were sensitive assays for urinary albumin measurement [4,5], also sensitive techniques to detect glomerular hyperfiltration early in the course of diabetic renal disease, and only recently automatic blood pressure monitoring to detect minimal blood pressure changes [6,7]. The concept of incipient diabetic nephropathy was validated by 4 follow-up studies of patients whose urinary albumin was measured serially with sensitive techniques [8-11]. These studies indicated that minimal increases in urinary

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

albumin excretion (UAE) (called microalbuminuria) can have a prognostic value. Therefore, the concept of incipient diabetic nephropathy is based upon the premise that persistent microalbuminuria can already indicate initial glomerular injury, and not only glomerular dysfunction [Chapter 16].

2. DESCRIPTION AND NATIONAL HISTORY OF INCIPIENT DIABETIC NEPHROPATHY

2.1. Description

2.1.1. UAE

By definition, UAE is elevated in the microalbuminuria range. Although UAE values predictive for diabetic nephropathy varies from 15 to 70 μg/min among the four pilot studies [8,11], a consensus was proposed to define microalbuminuria as UAE ranging 30-300 mg/24 h, or 20-200 μg/min, 2-3 times over 1-6 month period [12]. The Steno group proposed to subdivide into micro-microalbuminuria (30-99 mg/24 h) and macro-microalbuminuria (100-300 mg/24 h), because the prognosis was poorer for the latter than for the former values [13]. However, these differential prognostic values were not confirmed on an individual basis [14,15].

2.1.2. Blood pressure

The mean blood pressure values of subjects with incipient diabetic nephropathy are higher than those of healthy controls, or of diabetic subjects with normal UAE, but lower than those of subjects with established diabetic nephropathy. There is a good correlation between blood pressure and UAE values. However, diagnosis of incipient diabetic nephropathy cannot be based upon cut-off values for blood pressure, because of large inter-group overlaps. Only the upper limit for blood pressure values can be fixed, namely those defining permanent hypertension: 160/95 mmHg or more, and/or concurrent hypertensive treatment. This upper limit has practical implications to delineate different causes for microalbuminuria: microalbuminuria with permanent hypertension indicates severe hypertension, but not incipient diabetic nephropathy, and regression lines between blood pressure and UAE are not superimposable for one case and for the other [16].

Automatic devices can improve blood pressure recording precision, but probably not sensitivity to classify subjects with incipient diabetic nephropathy [17]. Nocturnal recordings can ameliorate sensitivity [6,7,17], but this may be attributable either to concomitant autonomic dysfunction, or to nocturnal blood pressure rise secondary to glomerular disease.

In summary, blood pressure values are not in the permanent hypertension range during incipient diabetic nephropathy; they must be recorded precisely and uniformly for follow-up purposes [Chapter 24].

2.1.3. Glomerular filtration rate

In incipient diabetic nephropathy, GFR can be normal, or elevated, but rarely below normal values. The prognostic significance of glomerular hyperfiltration is discussed elsewhere in this book [Chapter 28]. However, it is not clear by which UAE values within the microalbuminuria range GFR starts declining in normotensive diabetic individuals. Mogensen and Christensen proposed that the initially positive relationship between UAE and GFR values becomes negative for UAE ranges above 30-50 μg/min [11]. In figure 29-1, we traced a parabolic regression line between individual UAE and GFR values obtained in 84 type 1, insulin-dependent diabetic subjects without antihypertensive treatment. The calculated top of the line was found for UAE 34 mg/24 h and GFR 130 ml/min/1.73 m^2. Hence,it is possible that glomerular filtration surface is reducing from the lowest UAE values within microalbuminuria, even though GFR values are in the normal, or supra-normal ranges. This biphasic relationship between UAE and GFR suggests that the phenomenon observed by Starling [18] on heart muscles is applicable to changes in glomerular function of type 1, insulin-dependent diabetic subjects. This analogy in modelization can have a physical basis, as mesangial cells are of muscular origin.

2.2. Natural course of incipient diabetic nephropathy

2.2.1. incidence of, and factors predisposing to diabetic nephropathy

Incidence of persistent microalbuminuria in normotensive type 1, insulin-dependent diabetic subjects was studied by several groups [19,20] over 4 or 5 year-periods. It approximates 1-2% cases/year. The main risk factor for microalbuminuria onset is diabetes duration, which is 5 years minimally. It was recently outlined that subjects with microalbuminuria and long diabetes duration may display a better prognosis than those with diabetes duration shorter than 15-17 years [21]. However, this result must be interpreted cautiously, because the slope of UAE progression can vary widely from one individual to another, and because early interventions can alter the course of the disease, especially with ACEIs. Glycaemic control is of paramount importance to prognose microalbuminuria: subjects with HbA1c below 7.5% have a low risk for microalbuminuria [19-20]. Results from the DCCT indicated that optimized insulin treatment reduced risk for microalbuminuria onset by 21-52% [22].

Genetic factors can affect risk for incipient or established diabetic nephropathy. The role for familial hypertension and for its possible intermediate phenotype Na+ Li+ countertransport is discussed elsewhere in this book. Another candidate for affecting genetic predisposition to diabetic nephropathy is angiotensin I converting enzyme (CE) intra-renal levels: plasma and cellular ACE levels are genetically determined by an insertion/deletion (I/D) polymorphism of ACE gene (23); the ACE

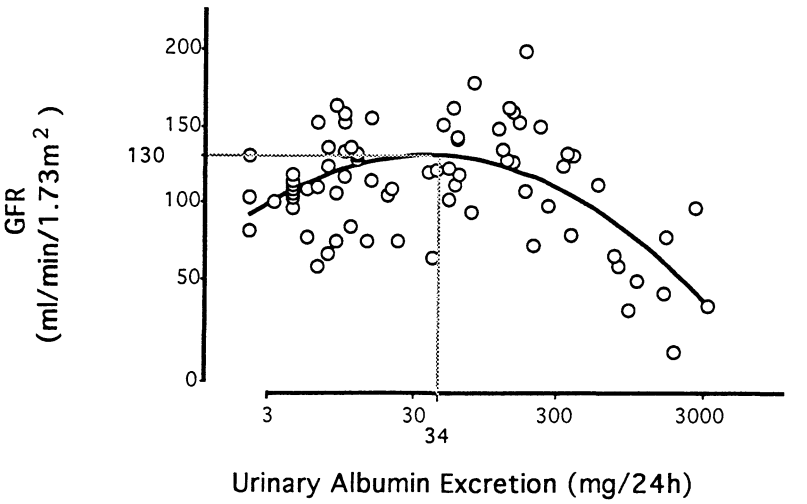

Figure 29-1. Observed relationship between UAE (the mean of 3 consecutive 24-hour urine collections) and GFR (^{51}Cr-EDTA plasma disappearance technique) values measured in 84 consecutive type 1, insulin-dependent diabetic subjects without antihypertensive treatment: r=0.576; p=0.0001; GFR (ml/min/1.73 m^2)=70+78 (SD 16) log UAE (mg/24 h) - 26 (4) [log UAE]^2 - Calculated top of parabolic curve was UAE=34 mg/24 h and GFR=130 ml/min/1.73 m^2.

levels may be a rate-limiting step for angiotensin and kinin metabolism, and angiotensin II can mimic diabetes effect on glomerular capillary pressure. We recently observed a low proportion of II ACE genotype in a case-control study on diabetic nephropathy [24]. This imbalance in ACE genotype distribution can account for elevated plasma ACE activity previously observed in subjects with incipient diabetic nephropathy [25].

2.2.2. Duration of incipient diabetic nephropathy

Duration of incipient diabetic nephropathy is not determined precisely from large group follow-up. Some studies indicate a 5-15 year duration [13]. Nonetheless, incidence of established diabetic nephropathy may be high: in control groups of clinical trials performed in normotensive subjects with microalbuminuria, it ranged between 8 and 30% cases/year [14,15,26,27].

3. EFFECT OF EARLY ANTIHYPERTENSIVE INTERVENTION IN INCIPIENT DIABETIC NEPHROPATHY

3.1.Rationale

There is a proportional increase of UAE and of blood pressure during the course of diabetic nephropathy from the incipient sage [28]. Follow-up studies indicated that early, aggressive antihypertensive treatment reduces effectively both albuminuria and the rate of GFR decline in patients with established diabetic nephropathy [29,30]. These were pragmatical studies, in which classical antihypertensive drugs were used, of them the beta-blocker metoprolol. Then, Christensen and Mogensen reported a six-year follow-up of 6 patients with incipient diabetic nephropathy before and during metoprolol treatment [31]. UAE was reduced, and GFR maintained unchanged with metoprolol. Taken together, these studies [29-31] supported the concept that reducing blood pressure is an effective mean to reduce microalbuminuria and protect GFR in incipient diabetic nephropathy. However, clinical and experimental data supported that increased UAE results from increased glomerular capillary pressure, which is determined not only by systemic blood pressure, but also by pre-/post glomerular vasoconstriction/dilation [32]. This latter determinant is strongly regulated by the activity of the renin-angiotensin-aldosterone system. Beta-blockers can modify glomerular haemodynamics, because they reduce renin secretion, in addition to their actions on cardiac output and blood pressure [33]. In the above mentioned studies [29-31], changes in glomerular haemodynamics were not studied in relation to those of renin secretion.

Conversely, experimental studies to reduce glomerular capillary hypertension of diabetic rats with ACEI lead to prevention of albuminuria and glomerulosclerosis [34], but systolic blood pressure was lower on ACEI than on placebo. Similarly, we set-up a double-blind, placebo-controlled trial demonstrating prevention, or postpone of diabetic nephropathy with enalapril in normotensive diabetic subjects with microalbuminuria [14]. However, blood pressure was reduced by enalapril compared to placebo, which made interpretation of this trial difficult, since reducing blood pressure reduces UAE in hypertensive subjects [35].

Thus, confusion rose from these two types of observations, because alterations in systemic blood pressure and in glomerular haemodynamics were not controlled simultaneously with changes in activity of the renin angiotensin system. Anderson et al. demonstrated later on that ACEI effacy to prevent albuminuria in diabetic rats was due to both hypotension and reduction of intra-glomerular capillary pressure [36]. In a double-blind, double-dummy, one year parallel trial comparing enalapril to hydrochlorothiazide (two drugs with similar hypotensive effects but symmetrical actions on angiotensin II production) to reduce UAE or normotensive insulin-dependent subjects with microalbuminuria, we demonstrated that reducing systemic

blood pressure reduces UAE in the long-term only if the renin-angiotensin system effectiveness is simultaneously blocked on glomerular haemodynamics [37].

3.2. Elligibility for antihypertensive treatment in incipient diabtic nephropathy

Should subjects with incipient diabetic nephropathy be assigned to antihypertensive treatment on the basis of UAE, or of blood pressure values? Certainly on the basis of a persistent microalbuminuria, because definition of incipient diabetic nephropathy is based on this biological abnormality. Second, microalbuminuria is probably an early sign of, rather than a factor predictive for diabetic nephropathy [38]. In this connection, UAE >20 μg/min (or 30 mg/24 h) is clearly abnormal: more than fifty per cent of healthy subjects excrete less than 5 mg/24 h [39]. Also, GFR can start declining from the lowest range of microalbuminuria, as illustrated in figure 29-1. Finally, UAE reduction can be obtained independently of blood pressure reduction, as detailed below.

3.3. Evidence for a superiority of ACEIs over other available hypotensive drugs to reduce UAE in incipient diabetic nephropathy

Several studies indicated that microalbuminuria of normotensive type 1, insulin-dependent diabetic subjects could be reduced by ACEIs, while blood pressure was not modified significantly [15,40]. We reported in a short-term double-blind study that small doses of ramipril can reduced microalbuminuria as effectively as hypotensive doses. This UAE reduction was obtained independently of blood pressure reduction, but it was related to the degree of ACE inhibition and to changes in filtration fraction [41]. Comparison of enalapril to hydrochlorothiazide to reduce microalbuminuria of normotensive type 1, insulin-dependent diabetic subjects lead to similar conclusions; both drugs were not different for their hypotensive effects, but only enalapril reduced microalbuminuria; UAE changes were related to those of filtration fraction, not to those of blood pressure [37]. Thus, dose-response curves for the renal and the hypotensive effects of ACEIs may not be superimposable. A recently published mea-regression analysis supports a preferential role for ACEIs to reduce UAE and to Protect GFR of diabetic subjects [42]. The Melbourne Diabetic Nephropathy Study Group reported no difference between the ACEI perindopril and the calcium-antagonist nifedipine in diabetic subjects with microalbuminuria [43]; a type 2 error may account for this observed lack of difference.

3.4. Which primary outcome for antihypertensive treatment in subjects with incipient diabetic nephropathy?

Certainly GFR preservation is the only clinically significant outcome for intervention studies in diabetic nephropathy. Microalbuminuria is a surrogate end-point.

However, intervention studies with antihypertensive drugs in incipient diabetic nephropathy indicated that drug efficacy on microalbuminuria was accompanied by GFR preservation, while subjects who progressed to macroalbuminuria displayed significant GFR reduction [14,15]. In this respect, microalbuminuria may be a valid surrogate end-point. The assumption that macroalbuminuria prevention (or microalbuminuria reduction) with ACEIs means GFR preservation lead to encouraging simulations on cost-benefit of early antihypertensive treatment indicated by microalbuminuria in type I, insulin-dependent diabetic subjects (44, see Chapter 7). However, several questions remain unanswered on ACEIs used of for diabetic nephropathy prevention: 1) intervention studies in normotensive subjects are still required with GFR preservation as primary end-point to demonstrate their effacy in this respect; 2) do ACEIs prevent, or post-pone diabetic nephropathy?; 3) does early treatment with ACEIs prevent cardio-vascular events (the mean death cause for these patients), in addition to GFR preservation?; 4) should primary prevention of diabetic nephropathy be considered with ACEIs? Further studies are then required in these respects.

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30. COMPARATIVE STUDY OF THE EFFECT OF ACE-INHIBITORS AND OTHER ANTIHYPERTENSIVE AGENTS ON PROTEINURIA IN DIABETIC PATIENTS

M. DE COURTEN, L. BÖHLEN and P. WEIDMANN

INTRODUCTION

The incidence and prevalence of renal failure secondary to diabetes mellitus has steadily increased over the past decade in the United States [1], so that diabetes is now the leading cause of end-stage renal failure [2]. Microalbuminuria (30-300 mg/24 h) predicts overt nephropathy (proteinuria >300 mg/24 h) and chronic renal failure in diabetic subjects [3] and has a powerful association with macrovascular disease unexplained by simultaneous existing cardiovascular risk factors [4].

Hypertension contributes to the progression of diabetic nephropathy in insulin dependent diabetes mellitus (IDDM) [5]. Blood pressure (BP) is usually normal in the absence of nephropathy, tends to rise before or concomitantly with the onset of incipient nephropathy and increases further when renal damage progresses to the stages of clinical nephropathy and renal failure (6-8). In patients with non insulin dependent diabetes mellitus (NIDDM), the temporal relationship between onset of hypertension and nephropathy is more variable; hypertension most often precedes and sometimes follows diabetes, and it may also be aggravated further by

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nephropathy [9,10]. Moreover, once nephropathy is present, a high BP may also promote and accelerate the development of renal failure [9]. Compared with the general population, relative mortality from cardiovascular disease is increased about 2.5 to 7.2-fold in diabetics with hypertension [11,12] and up to 37-fold in diabetics with clinical nephropathy [5,13].

Therapeutic attempts at slowing progression of diabetic nephropathy have included dietary modifications and antihypertensive therapy. Several studies over the past 15 years have shown that antihypertensive therapy with different types of drugs can reduce microalbuminuria or clinical proteinuria and retard the progression toward end stage renal failure [5,6,14-18]. Antiproteinuric and renoprotective effects were initially observed with conventional antihypertensive therapy, including diuretics and β-blockers [14,15], the exception being monotherapy with diuretics which was suspected to accelerate diabetic nephropathy [19].

Concerning the choice of antihypertensive agents, a new argument was introduced by some studies suggesting disparate renal protective effects of different antihypertensive drugs in diabetic animals [17,20-23] and humans [24]. In an attempt to resolve the controversy surrounding this possibility, we reported a meta-analysis of published studies in diabetics with microalbuminuria or overt proteinuria treated with conventional agents, ACE-inhibitors or Ca^{2+}-antagonists [25,26]. In this chapter, we present an updated meta-analysis of treatment-effects on proteinuria as well as glomerular filtration rate (GFR).

METHODS

Studies - experimental groups

The literature was screened for clinical trials using any antihypertensive agents in diabetic patients. The search was performed using MEDLINE and bibliographies in publications. Studies fulfilling the following criteria were included in our previous reports [25,26] and the present analysis: 1) diabetic patients receiving conventional antihypertensive drugs (diuretics and/or β-blockers and sometimes vasodilators) or a monotherapy with ACE-inhibitors or Ca^{2+}-antagonists, 2) measurements of albuminuria or total proteinuria and blood pressure before and after therapy lasting $\geq$4 weeks, 3) pre-treatment albuminuria (proteinuria) $\geq$30 mg/day. In addition the following exclusion criteria was applied: repetitive reports of partly similar patient groups (from such series, only the most complete report with the largest N was included).

Since the literature so far contains only a few double-blinded studies with a parallel placebo control group, this analysis could not be done without inclusion of studies which were uncontrolled but fulfilled all of the above mentioned criteria.

Table 30-1. Antiproteinuric action of antihypertensive drugs in diabetics: meta-analysis. Mean (95% CI). * $p < 0.05$

Type of Therapy	N		Mean Study Duration (Month)	Average Changes (%) in		
	Reports	Subjects		Mean Systemic BP	Urinary Albumin or Protein	
Diuretics and/or β-Blockers	21	258	15.5	-10(-12/-8)	-23(-35/-11)	
ACE-Inhibitors	68	1061	8.2	-12(-19/-5)	-45(-64/-25)	*
CA^{++}-Antagonists						*
all	27	398	5.4	-12(-15/-10)	-17(-33/-2)	
Nifedipine	12	166	5.9	-13(-17/-9)	+5(-21/+31)	*
all except Nifedipine	15	232	5.0	-11(-14/-7)	-35(-47/-24)	
Verapamil/ Diltiazem	5	56	7.2	-11(-14/-7)	-32(-47/-17)	

STATISTICAL ANALYSIS

Study end points were mean arterial pressure (mmHg), GFR (ml/min), urine protein excretion defined as either albumin or total protein excretion (μg/min). Treatment effects were weighted by the number of patients in each report in relation to the total number of patients and number of reports, and mean values ±95% confidence intervals (CI) were calculated. Differences between the drug specific classes were tested by analysis of variance and were considered significant at $p < 0.05$ (two-tailed). Multiple regression analysis was applied to determine the influence of different independent explanatory variables on study end points. Type of medication, initial mean blood pressure, initial urinary albumin or total protein excretion, type of diabetes, duration of the study and number of patients investigated were considered as independent variables. Forward stepwise regression analysis was then performed for each treatment group to identify which of the independent variables could be explanatory for renal effects. Linear regression analysis was carried out using change in mean blood pressure, initial mean blood pressure or initial level of albumin or total protein excretion as independent variables and change in urinary albumin or total protein excretion and change in glomerular filtration rate, as dependent variables.

RESULTS

Study characteristics

Out of 260 publications identified by the literature search, 93 fulfilled the inclusion criteria and contained 116 treatment groups. Of these, 68 treatment groups were allocated to the ACE-inhibitor category [25,27-58], 27 [25,33,34,41,49,53,57,59] to the Ca^{2+}-antagonist category and 21 [25,38,54,57,60-65] to the conventional (diuretic and/or β-blocker) treatment category (table 30-1).

The analysis included in total 1710 patients with a mean age of 46 ± 11 years in all reports. The mean proportion of men in all reports was $62 \pm 23\%$. The reported type of diabetes was 39% for type I, 37% type II and in 11% a mixture of both types; In 13% of the reports no indication was given. Age, gender, type of diabetes, and mean duration of therapy did not differ significantly between the treatment groups.

Urine albumin or total protein excretion

Albuminuria or total proteinuria tended to decrease on average more on ACE-inhibitors than on conventional therapy or all Ca^{2+}-antagonists together, but the difference did not reach statistical significance. Moreover, albuminuria or total proteinuria tended to increase on nifedipine, despite similar average BP reductions (table 30-1, figure 30-1).

ACE-inhibitor-induced changes in albuminuria or proteinuria correlated significantly with decreases in BP ($p<0.01$, figure 30-1). The decrease in albuminuria or proteinuria averaged -20.5% at zero BP change (y-intercept), and varied 1.8% for each % BP change. The slope and intercept describing reduction of albuminuria as a function of the decrement in BP differs between ACE-inhibitors and the other antihypertensive therapies ($p<0.05$). The effects of structurally different ACE-inhibitors were similar (data not shown).

On therapy with conventional antihypertensive agents, changes in albuminuria-proteinuria and BP were also correlated ($r = 0.61$, $p<0.005$, slope 3.6, y-intercept 12.5, figure 30-1). However, albumin or total protein excretion started to decrease only at a BP reduction of >5%, and the slope was steeper (3.6% change in albuminuria-proteinuria per % BP change) than on ACE-inhibitors. The regression line differed from the ACE-inhibitors regression line but not in comparison with the regression line on treatment with Ca^{2+}-antagonists other than nifedipine.

Although the distribution of data points did not obviously differ between reports using diuretic monotherapy, β-blocker monotherapy or their combination, differences between mono- or combination therapy in this category are not excluded as the limited number of reports precludes a separate analysis.

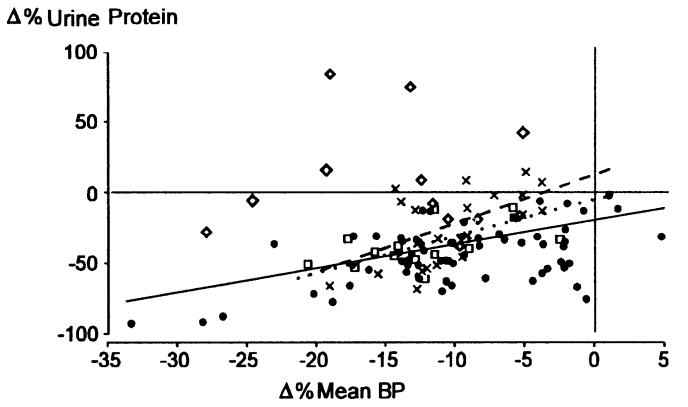

Figure 30-1. Percentage changes in albuminuria - proteinuria as related to blood pressure changes in diabetics on antihypertensive drugs. ● ,----- ACE inhibitors, $r=0.77$, $p<0.01$. ×,- - - - 'conventional' drugs (β-blockers and/or diuretics), $r=0.61$, $p<0.005$. □ , ... Ca^{2+}-antagonists other than nifedipine, $r=0.78$, $p<0.001$. ◇ nifedipine.

In the treatment group including all Ca^{2+}-antagonists, changes in albuminuria or proteinuria were unrelated to BP changes (figure 30-1). Further stratification of this group into two subgroups treated with either nifedipine or Ca^{2+}-antagonists other than nifedipine (including verapamil, diltiazem and the dihydropyridines nicardipine, nitrendipine and isradipine), revealed a significant relationship between changes in BP and albumin or total protein excretion in the latter ($r= 0.78$, $p<0.001$, slope 2.8, y-intercept -5.2, figure 30-1), but not in the nifedipine subgroup. Choosing another subgroup assignment, namely Ca^{2+}-antagonists of the dihydropyridine type vs. non-dihydropyridines, revealed no statistical relationship between the reduction in albuminuria and decrease in mean BP.

Glomerular filtration rate

70 reports contained data on GFR [18,19,25,28,32,34,35,37-39,42,45,47,48,50-52, 59,63,65,66] (table 30-2). The latter was measured by the clearances of inulin, ^{99}Tc-DTPA, ^{125}I-iothalamate or ^{51}Cr-EDTA in 53 studies and was estimated by the clearance of creatinine in 17 studies.

Over the observation period, GFR was on average unchanged on ACE-inhibitors and tended to decrease minimally on conventional therapy or all Ca^{2+}-antagonists analyzed together (table 30-2). The tendency for decrease in GFR appeared to be more pronounced, although not significantly, on nifedipine.

Table 30-2. Effects of antihypertensive therapy on GFR in diabetics: meta-analysis. Mean (95% CI).

Type of Therapy	N		Mean Study Duration (Month)	Average Changes (%) in	
	Reports	Subjects		Mean Systemic BP	Glomerular Filtration Rate
Diuretics and/or β-Blockers	16	190	16.4	-11(-13/-8)	-1.9(-10/-1)
ACE-Inhibitors	38	604	6.8	-16(-28/-4)	-0.01(-6/+6)
CA^{++}-Antagonists					
all	16	205	6.6	-14(-17/-10)	-2.2(-11/+7)
Nifedipine	8	107	7.4	-14(-20/-9)	-9.9(-25/+5)
all except Nifedipine	8	98	5.8	-13(-17/-8)	+5.8(-4/+15)
Verapamil/ Diltiazem	5	58	7.2	-12(-13/-11)	-1.3(-7/+4)

ACE-inhibitor-induced changes in GFR correlated inversely with changes in mean BP, so that GFR tended to increase with progressive BP reduction (figure 30-2). On Ca^{2+}-antagonists or conventional therapy, variations in GFR were unrelated to changes in BP.

DISCUSSION

These findings demonstrate a predominance of drug-specific over systemic BP-dependent mechanisms in the antiproteinuric action of ACE-inhibitors in diabetic patients. In contrast, as the example of nifedipine illustrates, drug-specific intrarenal effects may antagonize a BP-dependent antiproteinuric action and even counteract the effect of lowering systemic pressure. However, with progressive lowering of blood pressure, the antialbuminuric effect increases less on ACE-inhibitors than on conventional antihypertensive therapy or Ca^{2+}-antagonists other than nifedipine. It is obvious from figure 30-1, that a difference or no difference between ACE-inhibitors and these alternative antihypertensive agents may occur depending on how markedly BP has been lowered. This explains some controversies in the literature.

This meta-analysis also reveals that with progressive BP reduction GFR tended to increase on ACE-inhibitors, but not on conventional antihypertensive therapy or Ca^{2+}-antagonists (figure 30-2). This complements the disparate renal profile of different antihypertensive agents in diabetics with incipient or overt nephropathy.

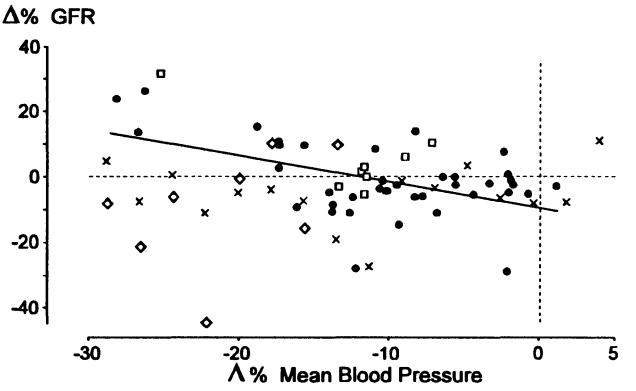

Figure 30-2. Percentage changes in GFR as related to blood pressure changes in diabetics on antihypertensive drugs. ●,----- ACE inhibitors, r=-0.55, p<0.00001. × 'conventional' drugs (β-blocker and/or diuretics). □ Ca^{2+}-antagonists other than nifedipine. ◇ nifedipine.

Renal effects of antihypertensive agents obviously are mediated at least in part by direct intrarenal actions. Intrarenal hemodynamics, tubular function or mesangial cell metabolism may be modified.

ACE-inhibitors block the generation of angiotensin II, a potent inducer of intrarenal vasoconstriction. Furthermore, ACE-inhibitors increase levels of vasodilatory prostaglandins PGI2 and PGE2 through inhibition of kininase II, an enzyme identical to angiotensin converting enzyme [67]. Therefore, these agents dilate both afferent and efferent arterioles and consequently reduce glomerular capillary pressure. Since they preferentially dilate efferent over afferent glomerular arterioles [68], a fall in systemic BP will cause a greater decrease of glomerular capillary pressure. More controversy exists with regard to the intrarenal hemodynamic effects of Ca^{2+}-antagonists. Although their ability to induce substantial afferent arteriolar vasodilatation is well demonstrated, their effect on efferent arteriolar resistance remains controversial. In animal and human studies verapamil and diltiazem have been noted to exert renal hemodynamic effects comparable to those of ACE-inhibitors. Both agents have been shown to lower glomerular capillary pressure [20,69]. The majority of studies investigating the renal hemodynamics of dihydropyridines showed no effect of nifedipine on efferent arteriolar resistance [70]. Therefore, a beneficial influence of lowered systemic BP on glomerular pressure may be antagonized by preferential afferent over efferent glomerular vasodilatation, which occurs with certain Ca^{2+}-antagonists [71].

Considering non-hemodynamic actions, certain Ca^{2+}-antagonists may tend to inhibit renal hypertrophy associated with diabetes [21]. Both Ca^{2+}-antagonists and ACE-inhibitors may beneficially influence metabolism of mesangial cells [21,72], while ACE-inhibitors also may decrease glomerular permeability for proteins [23,73], probably by affecting charge and size selectivity of the glomerular capillary barrier in humans [74]. ACE-inhibitors also limited the development of glomerular structural lesions as well as tubular interstitial damage. The biological mechanisms which could prevent these lesions are not completely understood, but studies in mesangial cells suggested the involvement of nitric oxide [75], which itself could be influenced by ACE-inhibitors via inhibition of local bradykinin degradation [22,75]. On the other hand, the lack of effect of nifedipine on albumin excretion may perhaps in part depend on proximal tubular interactions [42]. Nifedipine caused a marked reduction in fractional lithium reabsorption and a corresponding increase in lithium clearance [76]. β-2-microglobulin, a freely filterable protein and therefore also used as a marker of proximal tubular function [79] was also significantly increased during nifedipine treatment compared with lisinopril therapy [42,78]. The inhibitory effect of nifedipine on several proximal tubular function markers is consistent with the possibility that it might also inhibit proximal tubular albumin reabsorption, thereby promoting albuminuria despite its systemic antihypertensive effect.

As ACE-inhibitors exert a specific antiproteinuric effect even without a change in systemic BP, they are superior to other agents in treating microalbuminuria or overt proteinuria in initially normotensive or borderline hypertensive diabetic patients. On the other hand, when systemic BP is lowered by 10-20%, as it is desirable in hypertensive patients, ACE-inhibitors, conventional therapy, and several Ca^{2+}-antagonists all have a distinct antiproteinuric action.

Nevertheless, effects of agents on the kidney can not be the sole criterion in selecting an antihypertensive drug for diabetic patients. The influence of drugs on serum lipid levels and glucose and potassium metabolism as well as their ability to reduce left ventricular hypertrophy, should also be considered [25,79]. The challenge remains, therefore, to prove whether different antihypertensive drugs have also a disparate effect on the long-term evolution of renal function and, most importantly, on mortality. Until then the approach to pharmacotherapy in diabetic nephropathy will be largely empirical.

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31. CLINICAL TRIALS IN OVERT DIABETIC NEPHROPATHY

STAFFAN BJÖRCK

There is only limited data showing if and how the kidney benefits from antihypertensive treatment in non-diabetic renal disease. In contrast to this, several studies have shown that aggressive antihypertensive treatment is probably the most important factor to determine the rate of decline in kidney function in diabetic nephropathy. The evidence that antihypertensive treatment can preserve renal function is based on the much reduced rate of renal disease progression after effective blood pressure control [1,2]. These studies compare the rate of decline in glomerular filtration rate during intervention with retrospective data. This is not ideal since uncontrolled factors might influence the outcome. However, the effect of antihypertensive treatment is so profound that it is obviously very important for the kidney in diabetic nephropathy. Anyone that treats these patients observe that end-stage renal failure is postponed by antihypertensive treatment and that the disease runs an accelerated course during uncontrolled hypertension.

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1. DIFFERENCES BETWEEN ANTIHYPERTENSIVE DRUGS

It has been debated whether all antihypertensive drugs confer the same benefit to the kidneys in diabetic nephropathy. In early uncomplicated type 1 diabetes distinct changes have been found in renal function [Chapter 26]. The glomerular filtration rate is increased, renal blood flow is increased to a smaller extent and the filtration fraction is increased. These findings might indicate an increase in glomerular filtration pressure. The finding of this early disturbance in renal haemodynamics in a group of patients of which one third develops kidney disease has led to the hypothesis that an increased glomerular pressure is harmful to the diabetic kidney. Since the renin-angiotensin system modulates renal pressures and flows, it has been speculated that angiotensin-converting enzyme inhibition can protect the kidneys by an effect independent of its effect on systemic blood pressure. This class of agents have been shown to increase renal blood flow and decrease filtration fraction while glomerular filtration rate usually remains unchanged which points to a reduction in glomerular pressure by these agents [3]. Many studies have tried to determine if there is a specific, blood-pressure independent renal protective effect of angiotensin converting enzyme (ACE)-inhibitors in diabetic nephropathy. The end-points in these studies have been the urinary excretion of proteins and the effect on the natural decrease in renal function.

2. EFFECT ON PROTEINURIA

Reducing blood pressure by any measure leads to a reduction in the urinary excretion of proteins in patients with type 1 diabetes and nephropathy. Therefore, is it difficult to separate an effect of ACE-inhibitors from the non-specific effect of blood pressure reduction. In a short-term study, Taguma et al. first showed that captopril treatment induced a reduction in proteinuria even though blood pressure was relatively unchanged [4]. This was an uncontrolled study in patients with concomitant diseases. A dissociation between the hypotensive and the antiproteinuric effect of ACE-inhibitors has recently been shown by others [5,6].

Randomised controlled studies with other classes of antihypertensive drugs serving as controls have been performed with contradictory results. Calcium antagonists for example have been shown to decrease, to have no effect or to increase proteinuria [7,8,9]. ACE-inhibitors in these studies more consistently reduce proteinuria [10]. In comparisons with betablocking agents, both a superior and an equal antiproteinuric effect has been found [11,12]. Differences between studies regarding experimental design, concomitant treatment, level of blood pressure control and patient selection makes interpretation of results difficult. In a recent meta-regression analysis of 100 available studies, Kasiske et al. concluded that ACE-inhibitors decreased proteinuria independently of changes in blood pressure

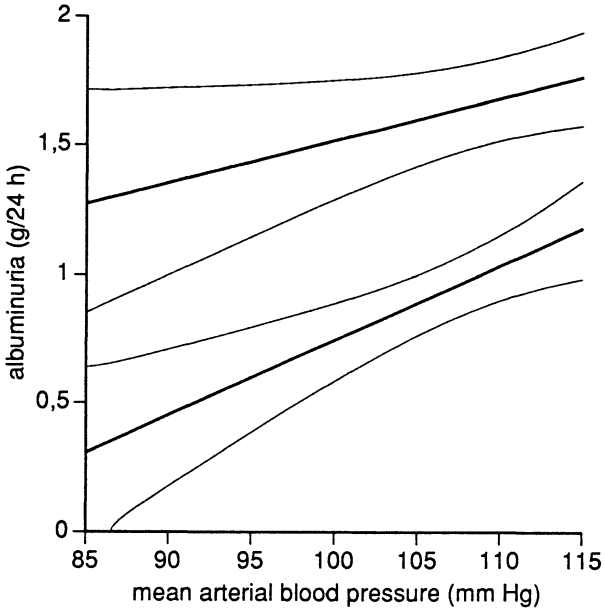

Figure 31-1. Regression lines with 95% confidence intervals for the relationship between supine mean arterial blood pressure and urinary albumin excretion in patients treated with metoprolol (top line) and enalapril (bottom line). Regression lines are based on 417 simultaneous measurements of blood pressure and 24 hour excretions of albumin in 36 patients.

while reductions in proteinuria with other antihypertensive agents could be entirely explained by changes in blood pressure [13].

We have compared the antiproteinuric effect of enalapril and metoprolol on albuminuria in patients with type 1 diabetes and nephropathy [11]. We found that the antiproteinuric effect of enalapril was superior to that of metoprolol. During two years treatment, there was a continuous fall in albuminuria during enalapril treatment but not with metoprolol. The mean reduction in albuminuria was 63% during enalapril treatment while there was no change during metoprolol treatment. In this group of patients, the difference does not seem to be explained by differences in blood pressure. The blood pressure was similar in both groups. The large number of simultaneous determinations of urinary albumin excretion and blood pressure allows a further analysis of the relationship between blood-pressure and albuminuria (figure 31-1). Throughout the range of ordinary blood pressure levels, enalapril-treated patients excrete less albumin than metoprolol-treated patients.

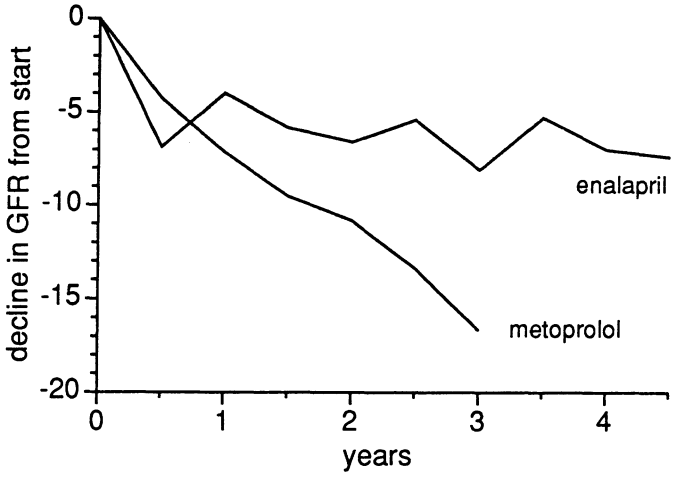

Figure 31-2. Decline in kidney function in 36 patients with type 1 diabetes and nephropathy treated with enalapril or metoprolol [14].

3. LONG-TERM EFFECT ON RENAL FUNCTION

A few studies have investigated the long-term effect on renal function of ACE-inhibitors. In 1986 we reported on a reduction in the rate of decline in kidney function in captopril-treated patients with diabetic nephropathy despite a rather small effect on treatment resistant hypertension [3]. The study was uncontrolled however, and the study group was small. In our two year study of the effect enalapril or metoprolol we have also investigated the glomerular filtration rate [11]. There was a slower fall rate in glomerular filtration rate in patients treated with enalapril than in those with metoprolol. The mean ($\pm$SD) decline in glomerular filtration rate was 2.0 ± 3.2 ml/min/year in the enalapril-treated and 5.6 ± 5.9 ml/min/year in the metoprolol-treated patients (figure 31-2). The study has been stopped but the enalapril treated patients have been followed for four years and we have found a stabilisation of renal function during the last years [14]. The main fall in glomerular filtration rate that occurred during the first six months was 7.5 ± 9.8 ml/min/1.73 m2. During the following three and a half years the fall was only 0.3 ± 3.9 ml/min/year.

Contrary to this Parving et al., in two separate studies on captopril and other antihypertensive agents found that both treatments had a similar effect on proteinuria and rate of decline in kidney function [1,15]. In a carefully controlled study, the rate of decline in kidney function was not different during treatment with a calcium antagonist or an ACE-inhibitor [7]. In this one year study, the authors found a rapid

decline in ACE-inhibitor treated patients during the first month followed by a later stabilisation of renal function. Ferder et al., studied creatinine clearance in patients with type 1 diabetes and nephropathy during one year treatment. They found that the renal function remained stable and that albuminuria decreased in the enalapril treated but not in the nifedipine treated patients [16]. The longest reported treatment time is reported by Ravid et al. who found that five years treatment of patients with type 2 diabetes and microalbuminuria resulted in unchanged renal function and proteinuria in contrast to the non-ACE-inhibitor treated control group that exhibited a rise in albuminuria and a fall in renal function measured as serum-creatinine [17].

Recently, a three year randomised comparison of captopril and placebo have been completed in 409 patients with type 1 diabetes and nephropathy [18]. Details of the study are still to be published but it has been preliminary reported that there was a 42% risk reduction regarding the time to doubling of serum-creatinine by captopril treatment when the effect of differences in blood pressure had been statistically corrected.

4. PROBLEMS RELATED TO STUDIES OF RENAL EFFECTS

Similar blood pressure levels in study groups are essential for conclusions due to the influence of the blood pressure level both on the proteinuria and on the rate of deterioration in kidney function. Comparisons between different drugs regarding their renal effects are frequently confounded by the difficulty to achieve a similar blood pressure control in the different groups. ACE-inhibitors are often more efficient in reducing blood pressure than other drugs and differences in blood pressure have to be corrected statistically. This makes results more unreliable in small samples. In larger patient samples such calculations become more accurate and studies about to be published will provide important information [18]. In clinical studies, blood pressure determinations are usually done in the supine position in the morning, a few hours after the intake of the medication. The representativity of such isolated measurements may be questioned due to the variability in blood pressure and since differences in duration of action of different drugs are largely unknown. The effects on standing and on supine blood pressure may also differ between drugs. We found that metoprolol was more effective than enalapril in reducing upright blood pressure and we therefore used the mean of supine and standing blood pressure in our evaluation [11]. Twentyfour-hour measurements of blood pressure will probably add to the precision of conclusions.

Proteinuria or albuminuria is frequently used as a measure of the renal effects of antihypertensive drugs. It seems plausible that a reduction in proteinuria indicates an improved renal prognosis. In many circumstances gross proteinuria is correlated to a worse renal prognosis. However, changes in proteinuria does not only represent

an effect on glomerular function and integrity. It is possible that different antihypertensive agents have different effects on the tubular handling of proteins [8]. It is also uncertain whether a reduction in proteinuria by any means will benefit the kidneys in the long-term.

Methods to determine renal function differ greatly between studies. Serum creatinine or creatinine clearances are frequently used. Creatinine clearance overestimates true glomerular filtration rate in diabetic nephropathy due to the tubular secretion of creatinine and it is not known whether blood pressure reduction and different drugs can affect this secretion.

The use of diuretics has varied markedly between studies. It has been shown that the antiproteinuric effect of ACE-inhibitors is highly dependent on sodium balance and that the activity in the renin-angiotensin system determines the renal hemodynamic response to ACE-inhibitors [19]. The largest reduction in proteinuria was found in a study using high dose diuretic treatment [11].

The follow-up time has to be extensive since the effect of intervention may be delayed [1,11]. Many studies base their conclusions on studies over only weeks or months. In the study by Ravid over 5 years, a distinct separation of the enalapril and the placebo-treated group appeared during the last years [17].

In conclusion, ACE inhibitors seem to have an antiproteinuric effect independent of the effect on systemic blood pressure. Clinical studies with the aim to determine if the decline in kidney function can be arrested more effectively with ACE-inhibitors show conflicting results. So far however, no class of agents has been shown to be more effective than ACE inhibitors.

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32. ANTIHYPERTENSIVE TREATMENT IN NIDDM, WITH SPECIAL REFERENCE TO ABNORMAL ALBUMINURIA

PAUL G. MCNALLY and MARK E. COOPER

The deleterious effects of systemic blood pressure on glomerular structure were reported more than twenty years ago in a patient with NIDDM and unilateral renal artery stenosis, in which characteristic nodular diabetic glomerulosclerosis was present in the non-ischaemic kidney only [1]. Nevertheless, to date the impact of antihypertensive therapy on renal injury in NIDDM has received little attention even though the cumulative incidence of persistent proteinuria and microalbuminuria in NIDDM subjects is comparable in frequency to IDDM subjects of similar duration [2-5]. The clinical relevance of these figures is reflected by statistics which now show that over 50% of patients entering renal replacement programs have NIDDM [6-8]. Furthermore, in NIDDM the relationship between nephropathy and hypertension is more complex than in IDDM, since hypertension is not necessarily linked to the presence of renal disease, and often precedes the diagnosis of diabetes.

This review focuses on the role of antihypertensive agents in NIDDM subjects with abnormal albuminuria (microalbuminuria and macroalbuminuria), the

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significance of albuminuria in NIDDM and the consequences of treatment with these agents.

1. THE USE OF ANTIHYPERTENSIVE AGENTS IN NIDDM SUBJECTS WITH ESTABLISHED DIABETIC NEPHROPATHY (Table 32-1)

The impact of angiotensin converting enzyme inhibitors (ACEI), calcium channel blockers (CCB) and conventional antihypertensive agents on renal function has been evaluated in both normotensive and hypertensive NIDDM subjects with persistent proteinuria and variable degrees of renal impairment for a maximum period of 18 months [9-17]. Administration of low dose enalapril (5 mg/day) for 6-12 months to normotensive subjects with persistent proteinuria reduced albuminuria without affecting systemic or renal haemodynamics [9,10]. Similarly, in hypertensive NIDDM subjects with persistent proteinuria studied for periods of up to 6 months, ACEI [11,12] and certain CCB [12,13,14] reduced albuminuria. Comparable responses were also obtained with the beta-blocker, atenolol, but not with the thiazide diuretic, chlorthalidone, despite similar reduction in blood pressure [15]. However, administration of captopril to NIDDM subjects with moderate renal impairment (GFR 57 ± 17 ml/min/1.73 m^2) for up to 6 months failed to alter albuminuria or renal haemodynamics, despite satisfactory blood pressure control [16].

There have been significant differences in the effect on albuminuria obtained with various CCB, which has been attributed by Bakris and coworkers to the particular class of CCB [12,14,17]. Bakris [12] initially demonstrated in hypertensive, nephrotic NIDDM that diltiazem, a benzothiazepine CCB, had a comparable response to lisinopril in decreasing albuminuria. In contrast, nifedipine, a dihydropyridine CCB, given for 6 weeks to 14 hypertensive NIDDM patients with baseline renal impairment, precipitated an increase in albuminuria and a deterioration in renal function, despite equivalent blood pressure reduction to diltiazem [14].

The longest running study to date is a randomized parallel group study comparing diltiazem, lisinopril and conventional therapy (atenolol and frusemide) in hypertensive NIDDM subjects with marked albuminuria (>2.5 g/24 hours) and renal insufficiency (creatinine clearance <70 ml/min/1.73 m^2) [17]. After 18 months of therapy the rate of decline of glomerular filtration rate was attenuated with either diltiazem or lisinopril (-0.22 ± 0.07 and -0.29 ± 0.06 ml/min/month/1.73 m^2 respectively), when compared to the conventional therapy group (-0.52 ± 0.08 ml/min/month/1.73 m^2) despite comparable blood pressure reduction. The beneficial changes on glomerular filtration rate were paralleled by changes in albuminuria with significant reductions in the diltiazem and lisinopril groups, but no change in the conventionally treated group.

Table 32-1. The effect of antihypertensive agents on albuminuria, renal function and blood pressure in NIDDM subjects with established nephropathy

Agent	Duration of study	n	Δ in AER (%)	Δ in GFR	Δ in BP	Reference
Normotensive						
Enalapril	6 months	12	↓(-56)	→	→	Stornello et al. [9]
Placebo			→	→	→	
Enalapril	12 months	8	↓(-47)	→	→	Stornello et al. [10]
Placebo			→	→	→	
Hypertensive						
Captopril	6 months	12	→	→	↓	Valvo et al. [16]
Captopril	4 weeks	12	↓(-48)	→	↓	Stornello et al. [13]
Nicardipine			↓(-61)	→	↓	
Captopril & Nicardipine			↓(-75)	→	↓	
Enalapril	6 weeks	12	↓(-37)	→	↓	Stornello et al. [15]
Chlorthalidone			→	→	↓	
Atenolol			↓(-36)	→	↓	
Placebo			→	→	→	
Captopril	6 months	9	↓(-62)	→	↓	Stornello et al. [11]
Diltiazem	18 weeks	8	↓(-38)	→	↓	Bakris [12]
Lisinopril			↓(-43)	→	↓	
Nifedipine	6 weeks	14	↑(+89)	↓*	↓	Demarie and Bakris [14]
Diltiazem			↓(-52)	→	↓	
Lisinopril	18 months	10	↓(-42)	→	↓	Slataper et al. [17]
Diltiazem		10	↓(-46)	→	↓	
Frusemide & Atenolol		10	→	↓†	↓	

Statistically significant decreases (↓), increases (↑) or no change (→). AER, Albumin excretion rate. GFR, glomerular filtration rate. BP, Blood pressure. * Median increase in creatinine 53.1 μmol/l after 14 weeks treatment. †Higher rate of decline in GFR vs other 2 groups.

2. THE USE OF ANTIHYPERTENSIVE AGENTS IN HYPERTENSIVE NIDDM WITH NORMOALBUMINURIA AND MICROALBUMINURIA (Table 32-2)

The use of antihypertensive therapy in NIDDM subjects with hypertension and microalbuminuria has been evaluated in relatively few studies [18-22]. Gambardella and coworkers [18,19] showed that indapamide 2.5 mg daily did not alter albuminuria or glomerular filtration rate over a 24 month period in hypertensive normoalbuminuric patients despite a significant reduction in blood pressure. In contrast, in the microalbuminuric patients indapamide reduced albuminuria after 6 months and was sustained at 36 months [19]. Recently, a double blind study compared captopril with conventional therapy (metoprolol and hydrochlorothiazide) in normoalbuminuric and microalbuminuric hypertensive NIDDM subjects over a 3 year period [20]. Both regimens reduced blood pressure without altering albuminuria in the normoalbuminuric NIDDM subjects. However, their findings in hypertensive NIDDM patients with microalbuminuria indicated that despite a comparable reduction in blood pressure, only the ACEI induced a persistent decline in albuminuria during the 36 months of therapy. Although albuminuria decreased at 9 months in the conventional therapy group, by 36 months it had returned to baseline levels. Furthermore, whereas an increase in albuminuria was prevented in most patients treated with captopril (8/9), it rose in 8/12 patients on conventional therapy, with macroalbuminuria developing in 2 cases from this diuretic/metoprolol treated group. Although these findings suggested that the ACEI conferred a beneficial renoprotective effect long-term, these data are potentially biased by the fact that the conventionally treated group had a lower baseline glomerular filtration rate than the captopril treated group (87 versus 99 ml/min) and hence, possibly a greater potential to progress to macroalbuminuria. Also, the lack of a placebo group makes it difficult to determine if the effects of the conventional treatment could still represent a beneficial effect.

There is a discrepancy in the effects of CCB on albuminuria in patients with hypertension and microalbuminuria compared to studies in established nephropathy [14]. In the Melbourne Diabetic Nephropathy Study, nifedipine was shown to produce a similar response to perindopril in decreasing albuminuria rate over 12 months in the NIDDM subjects with microalbuminuria [22]. Nicardipine, another dihydropyridine CCB, reduced albuminuria over 4 weeks in microalbuminuric patients but this finding was not observed in patients with macroproteinuria [21].

Table 32-2. The effect of antihypertensive agents on albuminuria, renal function and blood pressure in NIDDM with normo- and microalbuminuria

Patients	Agent	Duration of study	n	Δin AER (%)	Δin GFR	Δin BP	Reference
Normo HT	Indapamide	24 months	10	→	→	↓	Gambardella et al. [18]
Micro HT			10	↓(-66)	→	↓	
Micro HT	Indapamide	36 months	10	↓(-64)	→	↓	Gambardella et al. [19]
Normo HT	Captopril	36 months	25	→	→	↓	Lacourcière et al. [20]
	Metoprolol or HCTZ alone or in combination		28	→	→	↓	
Micro HT	Captopril		9	↓(-65)	→	↓	
	Metoprolol or HCTZ alone or in combination		12	→	→	↓	
Normo HT	Nicardipine	4 weeks	6	→	→	↓	Baba et al. [21]
Micro HT	Nicardipine	4 weeks	6	↓(-29)	→	↓	
Micro NT	Nifedipine	12 months	13	→	→	→	Melbourne Diabetic Nephropathy Study Group [22]
	Perindopril		11	→	→	→	
Micro NT	Captopril	6 months	13	↓(-36)	→	↓	Romero et al. [23]
	Untreated		13	→	→	→	
Micro NT	Enalapril	5 years	49	→	→	→	Ravid et al. [25]
	Placebo		45	↑(+152)	↓*	→	

Statistically significant decreases (↓), increases (↑) or no change (→). Normo, Normoalbuminuria. Micro, Microalbuminuria. HT, Hypertensive. NT, Normotensive. AER, Albumin excretion rate. GFR, glomerular filtration rate. BP, Blood pressure. HCTZ, hydrochlorothiazide. * 13% decline in 100/serum creatinine compared to 1% decline in the enalapril-treated group (figure 32-2).

3. THE USE OF ANTIHYPERTENSIVE AGENTS IN NORMOTENSIVE NIDDM WITH MICROALBUMINURIA (Table 32-2)

The possibility that early therapy will postpone or retard progression of renal injury in diabetes has led to the use of antihypertensive agents in normotensive subjects. Albuminuria over a 6 month period was reduced in a group of normotensive NIDDM patients with microalbuminuria treated with captopril, whereas the untreated group had no change in albuminuria [23]. In the Melbourne study [22] there was no change in albuminuria after 12 months treatment with either nifedipine or perindopril in normotensive microalbuminuric patients, despite a small but significant reduction in blood pressure (4 mmHg). Nonetheless, on stopping therapy at 12 months a dramatic increase in albuminuria was detected in the NIDDM but not in the IDDM subjects (figure 32-1), which was independent of mode of treatment [24]. The inability of either agent to reduce albuminuria in the normotensive cohort coupled with the rapid rise after stopping therapy needs to be considered in the setting of the natural history of microalbuminuria. Albuminuria would be anticipated to rise by an average rise of 20 to 50 per cent if left untreated for 12 months in microalbuminuric NIDDM subjects. This phenomenon of a rapid rise in albuminuria was not as clearly apparent in the IDDM patients and may indicate a difference in the underlying etiology and pathogenesis of albuminuria in NIDDM as compared to IDDM. It is possible that there are differences in the sensitivity to structural damage incurred from blood pressure between IDDM and NIDDM.

The first long-term (5 years) placebo controlled double blind randomized study to evaluate the effect of an antihypertensive agent in normotensive microalbuminuric NIDDM with normal renal function (as assessed by a serum creatinine < 123 μmol/l) was recently reported by Ravid et al [25]. During the first year of treatment albuminuria decreased in the enalapril treated group from an initial mean of 143 mg/24 hours to a mean of 122 mg/24 hours (figure 32-2). Thereafter, a small but steady increase in albuminuria occurred in the enalapril treated patients to 140 mg/24 hours after 5 years. Conversely, in the placebo treated patients a gradual increase in albuminuria occurred form a baseline of 123 to 310 mg/24 hours over the 5 years. Albuminuria exceeded 300 mg/24 hours in only 6/49 (12.2%) of the enalapril group compared to 19/45 (42.2%) of the placebo treated group. Renal function remained unchanged in the enalapril group during the first 2 years of follow up, but from the third year a small but non-significant decrease was evident, in the order of 1% after 5 years, in contrast to 13% in the placebo treated group (figure 32-2). Although the assessment of renal function (assessed by 100/serum creatinine) was rather crude this is the first long-term study to demonstrate both an antiproteinuric effect of an ACEI in normotensive NIDDM patients with microalbuminuria and preservation of renal function.

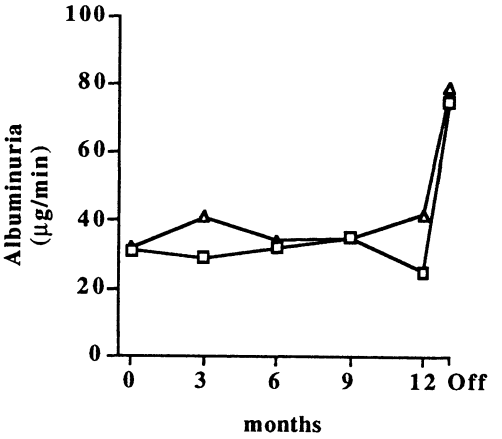

Figure 32-1. Effects of perindopril (□, n=11) or nifedipine (△, n=13) on albuminuria (geometric means) over 12 months of treatment and after 1 month of treatment (Off) in normotensive microalbuminuric NIDDM patients from the Melbourne Diabetic Nephropathy Study, adapted from [22].

4. THE USE OF ANTIHYPERTENSIVE AGENTS IN PATIENTS WITH NIDDM

The choice of an antihypertensive agent in the management of abnormal albuminuria in NIDDM depends not only on its potential renoprotective effect but must take into consideration other factors which could be deleterious to the patient. Microalbuminuria in the NIDDM patient is more closely linked to subsequent death from cardiovascular disease than from nephropathy [26,27]. Therefore, it is important that any antihypertensive intervention in the NIDDM patient with abnormal albuminuria does not exacerbate existing hypertriglyceridaemia or further reduce HDL-cholesterol, lipid abnormalities associated with NIDDM [28]. Furthermore, reduced sensitivity to insulin after administration of thiazides [29] and various beta-blockers may be detrimental [30]. In contrast, improved insulin sensitivity is seen after captopril and minimal or neutral effects are observed with CCB [30,31]. Also, in contrast to beta-blockers and thiazide diuretics, neither CCB nor ACEI affect glucose tolerance deleteriously [31].

5. WHICH AGENT TO USE?

The limited evidence so far published on the effects of antihypertensive agents in NIDDM with abnormal albuminuria concur with findings in IDDM [32]. Both ACEI and CCB may possess beneficial effects over and above simple blood pressure control, although in most studies the small numbers of subjects included may have

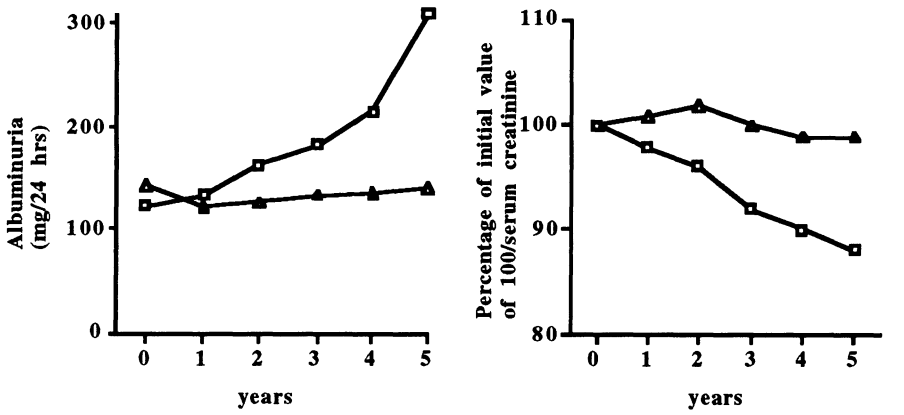

Figure 32-2. These graphs are adapted from Ravid et al. [25] and compare the effects of placebo (□) and enalapril (△) on albuminuria (left hand panel) and renal function (right hand panel) over 5 years in normotensive microalbuminuric NIDDM patients. [Reproduced with permission from Annals of Internal Medicine].

introduced a Type II statistical error. A recent meta-analysis of 91 trials involving patients with either IDDM or NIDDM demonstrated the salutary effects of ACEI on proteinuria and renal function compared to other classes of antihypertensive agent, whether or not the patient had Type I or Type II diabetes, hypertension, normoalbuminuria, microalbuminuria or macroproteinuria [33].

6. ABNORMAL ALBUMINURIA IN NIDDM: WHAT DOES IT SIGNIFY?

Microalbuminuria predicts not only nephropathy in NIDDM subjects but also is a strong predictor of all-cause mortality, particularly from cardiovascular diseases [26,27]. Although the principal endpoint in evaluating the influence of an antihypertensive agent on renal function in diabetes is its ability to alter the progression of the disease, it is clear that abnormally elevated albuminuria is also associated with progressive renal injury [34]. Although many of the short-term trials that have been performed in subjects with NIDDM only document a reduction in albuminuria in the absence of a change in glomerular filtration rate, long-term studies in IDDM subjects suggest that the severity of proteinuria also correlates with the rate of progression of renal disease [35]. Thus abnormal albuminuria in NIDDM may not only be a marker of renal damage but also constitute an independent risk factor. Nonetheless, studies involving renal structural assessment are warranted to more accurately determine the response to antihypertensive agents.

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33. THE COURSE OF INCIPIENT AND OVERT DIABETIC NEPHROPATHY: THE PERSPECTIVE OF MORE OPTIMAL INSULIN TREATMENT

BO FELDT-RASMUSSEN

The long-term objective of insulin treatment of insulin dependent diabetes mellitus (IDDM) is prevention of late complications. Through the years it has been a widely accepted hypothesis that development of such microvascular complications should be, at least in part, due to the lack of good glycaemic control. This hypothesis has been unduely hard to prove but results from a number of small scaled intervention studies and the result of the larger scaled American Diabetes Control and Complication Trial (DCCT) has now decisively documented, that development and progression of diabetic complications is closely associated with poor glycaemic control. The design and outcome of a number of these studies will be presented and discussed in this chapter as will the practical consequences of this newly gained knowledge.

1. THE CONCEPT OF MICROALBUMINURIA

Much of our recent knowledge has been obtained because it is now possible in a very early stage to identify patients at risk of clinical diabetic nephropathy as

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recently reviewed in a number of dissertations and elsewhere [1-6]. The proteinuria of clinical diabetic nephropathy is classically defined as a total urinary protein excretion of 0.5 g per 24 h or more, equivalent to a urinary albumin excretion rate (UAER) of approximately 300 mg/24h or 200 μg/min (figure 33-1). It has been documented that a UAER raised above a certain lower level is a good predictor of the development of clinical diabetic nephropathy. Patients at high risk of diabetic nephropathy have a UAER above the normal range but below that of clinical nephropathy. In 1986 a general consensus was made stating that this range of microalbuminuria should be defined as a UAER between 30 to 300 mg/24 h (20 to 200 μg/min) in a 24h or a short term, timed urine collection [7]. At early onset of nephropathy (UAER just above 300 mg/24 h) when the GFR is mainly within the normal range, an annual decline in GFR of approximately 3 to 4 ml/min can be demonstrated. Furthermore patients with microalbuminuria share a number of cardiovascular risk factors with patients with nephropathy [1-7]. Therefore the variations of the UAER have been an important endpoint to study in many of the recent studies of effects of glycaemic control in diabetes.

2. EFFECT OF IMPROVED GLYCAEMIC CONTROL?

2.1 The Scandinavian experience

Following the introduction of intensified insulin treatment regimens with multiple injections or continuous subcutaneous infusion of short-acting insulins, it became possible to establish and maintain a long-term improvement of the glycaemic control. On this basis a number of prospective randomized studies of the effect of improved glycaemic control on development and progression of late diabetic complications were initiated as recently reviewed [8,9, Chapter 34]. Among the early but smaller scaled studies including from 36 to 91 patients, three Scandinavian studies will be briefly summarized.

In the Steno studies 1 and 2, a total of 70 patients with IDDM had been included and randomized to either unchanged conventional insulin treatment or to intensified treatment using portable insulin infusion pumps [10-12].

The long-term glycaemic control given as the mean of all HbA_{1c} readings during the entire follow up period had been significantly improved in the insulin infusion groups during the 5 to 8 years of follow-up: HbA_{1c} at entry - HbA_{1c} mean of all; (insulin infusion group vs control group), (%)) Steno I: 2.0 $\pm$ 0.6 versus 0.7 $\pm$ 1.2; Steno 2: 1.8 $\pm$ 1.2 versus 0.4 $\pm$ 1.3 ($p < 0.01$). In Steno I with the longest follow-up, the decline rate of glomerular filtration rate was reduced from -3.7 (-5.4 to -2.0) (mean, 95% confidence interval) to -1.0 (-2.1 to -0.1) ml/min/1.73m^2 ($p < 0.05$). More patients had progressed to clinical nephropathy during conventional insulin treatment than in the insulin infusion groups. Also among the 19 patients

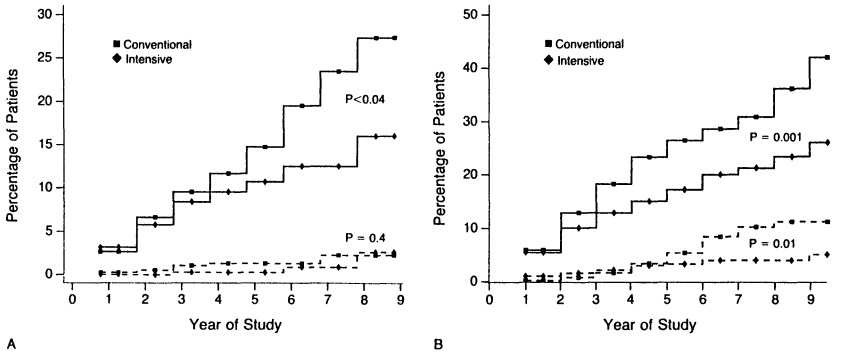

Figure 33-1. Cumulative incidence of urinary albumin excretion ≥300 mg per 24 hours (dashed line) and ≥40 mg per 24 hours (solid line) in patients with IDDM receiving intensive or conventional therapy. In the primary-prevention cohort (Panel A), intensive therapy reduced the adjusted mean risk of microalbuminuria by 34% ($P<0.04$). In the secondary-interventioncohort (Panel B), patients with urinary albumin excretion of ≥40 mg per 24 hours at baseline were excluded from the analysis of the development of microalbuminuria. Intensive therapy reduced the adjusted mean risk of albuminuria by 56% ($P=0.01$) and the risk of microalbuminuria by 43% ($P=0.001$), as compared with conventional therapy.

with an initial UAER in the high range from 100 to 300 mg/24h, a significant treatment effect was observed. Thus clinical nephropathy (10/10 versus 2/9, $p<0.01$) and arterial hypertension (7/10 vs 1/9, $p<0.01$) were diagnosed more often in the conventional treatment group.

In the Oslo study [13,14] 45 IDDM patients had been included. In general the patients had less severe microangiopathy than the patients of the Steno Studies. After four years of continuous subcutaneous insulin infusion, UAER was reduced from 26 ± 5 (SEM) to 16 ± 4 mg/24h ($2p<0.01$). No change was observed in the conventional treatment group: 21 ± 4 to 22 ± 6 mg/24h. After 4 years the randomization had been broken. The follow up after 7 years analyzed the patients according to their long-term glycaemic level in terms of 7 year mean HbA_{1c} values [14]. None of the patients received antihypertensive treatment and the protein intake had been unchanged. The patients increasing their UAER by more than 300 mg/24h had significantly higher HbA_{1c} values during the 7 years of study. The diastolic blood pressure was unchanged in patients with a mean $HbA_{1c}<10\%$, but increased slightly in patients with $HbA_{1c}>10\%$ (NS). The changes in glomerular filtration rates were not associated to the glycaemic control, but the changes had only been minor in the study groups with a mean change of -1.1 ml/min/year or less [14].

In the Stockholm Study [15,16] all the patients had to have a poor glycaemic control at entry. The control was improved by means of intensified treatment regimens without the use of insulin infusion pumps. Ninety-five patients had been included and randomized to an unchanged regimen (n=51) or intensified treatment (n=44). They all had non-proliferative retinopathy and a normal s-creatinine and had been followed for 5 years or more. Antihypertensive treatment was added if needed but was not accounted for in the paper [15]. Eight in the control group developed diabetic nephropathy in contrast to none in the intensified treatment group ($p < 0.05$). The changes in UAER was related to the mean HbA_{1c} levels in a dose-related manner. Manifest nephropathy after 3 years was seen almost exclusively in patients with HbA_{1c} levels above 9%. The glomerular filtration rate decreased by a mean of 7 ml/min during three years of study with no differences between the groups (intensified treatment group: 122 ± 3 to 115 ± 3 ml/min, $p < 0.05$).

A meta regression analysis of the results from 16 prospective randomized studies including the Scandinavian studies was performed [8]. In these studies, the mean reduction of HbA_{1c} had been 1.45% (as an example, a reduction of HbA_{1c} from 9.2% to 7.8%). After more than two years of intensified therapy the risk of retinopathy progression was lower (odds ratio 0.49 (95% confidence interval 0.28-0.85, $p=0.011$). The risk of nephropathy progression was also decreased significantly (odds ratio 0.34 (0.20-0.58, $p < 0.001$). The incidence of severe hypoglycaemia was increased by 9.1 episodes per 100 patient years in the intensively treated patients. The incidence of diabetic ketoacidoses increased by 12.6 episodes per 100 patient years (95 confidence interval 8.7-16.5) in the patients treated with continuous subcutaneous insulin infusion.

2.2 The Diabetes Control and Complication Trial (DCCT)

The American Experience

The DCCT study is a multicenter study performed in the period 1983 to 1993. The data were published in New England Journal of Medicine in september 1993 [17]. It comprised 1441 IDDM patients of whom only 19 patients dropped out. They had been randomized to either conventional insulin treatment with 1 to 2 daily insulin injections or to intensified treatment with more than 3 daily injections. This group also had to measure blood-glucose 4 times a day (and the adherence to this regimen had been documented). If so wished they could choose to be treated with portable insulin infusion pumps. The aims were:

1. To study if intensified treatment can prevent development of retinopathy (primary intervention of complications, 726 patients).
2. To study if intensified treatment can delay or stop the progression of retinopathy (secondary prevention of complications, 715 patients).

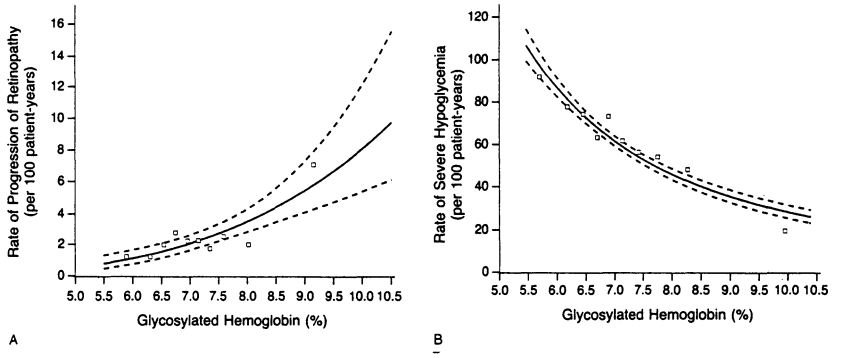

Figure 33-2. Risk of sustained progression of retinopathy (panel A) and rate of severe hypoglycaemia (panel B) in the patients receiving intensive therapy, according to their mean glycosylated haemoglobin values during the trial. In panel A, the glycosylated haemoglobin values used were the mean of the values obtained every six months. In panel B, the mean of the monthly values was used. Squares indicate the crude rates within deciles of the mean glycosylated haemoglobin values during the trial; each square corresponds to more than 400 patient-years. The solid lines are regression lines estimated as a function of the log of the mean glycosylated haemoglobin value in panel A and the log of the lines are regression lines estimated as a function of the log of the mean glycosylated haemoglobin value in panel A and the log of the glycosylated haemoglobin value in panel B; the dashed lines are 95 per cent confidence intervals.

Other indicators of diabetic complications as for instance the UAER and blood pressure were carefully monitored as well.

The main results were:

The mean HbA_{1c} at baseline had been between 8.8 and 9.0% in the study groups. in the intensified treatment group the mean HbA_{1c} was maintained at about 7.0% throughout the study i.e. for a mean of 6.5 years. The upper reference level of HbA_{1c} was 6.05%. Only 5 % of the patients on intensified treatment were consistently treated to a level below or equal to that level.

Intensified treatment had reduced the risk of developing the first microaneurism by 27% (95% confidence interval; 11-40) (primary intervention) and of developing moderate retinopathy by 76% (62-85) (secondary intervention). In the secondary intervention study, the risk of progression to severe non-proliferative - or proliferative retinopathy had been reduced by 47% (14-67). A positive correlation between HbA_{1c} and development of retinopathy was observed (figure 33-2). This was taken by the authors to indicate that any reduction of HbA_{1c} should reduce the risk of retinopathy. The figure may to my mind however also be taken as an indication of the existence of a cut off point of HbA_{1c} of about 7.5% below which very little extra protection against complications can be obtained.

Table 33-1. Target of B-glucose levels during intensified treatment regimens.

Fasting	4-7 mmol/l
Post prandial	5-10 mmol/l
Avoid values	below 3 mmol/l
Avoid values	above 10 mmol/l

In the intensified treatment groups, the risk of developing microalbuminuria (UAER > 40 mg/24h) were reduced by 39% (21-52) and for developing clinical nephropathy (UAER > 300 mg/24h), by 54% (19-74).

The risk reductions of development and progression of neuropathy was 60 % (38-74).

The most serious side-effects of intensified treatment had been the risk of severe hypoglycaemia which had been increased by a factor 3.5. An inverse correlation between HbA_{1c} and severe hypoglycaemia was observed (figure 33-2). The risk of ketoacidoses were similar in the groups, 1.8 versus 2.0 cases per 100 patient year respectively.

3. INTENSIFIED INSULIN TREATMENT. PRACTICAL GUIDELINES

The intensified treatment regimens operates with at least three important principles.

First, frequent or continuous administration of fast-acting insulins and little or no (infusion pumps) use of intermediate or long-acting insulins. The advantages of this is (a) small differences between the administered and absorbed amounts of insulin over 24 h, (b) postprandial insulin peaks and (c) a stable overnight insulin level (at least when administered by insulin infusion pumps).

Second, frequent blood glucose readings before meals and bedtime, making it possible to adjust the injected amount of insulin, not only according to experience (size and character of meal, physical exercise etc.) but also according to actual glycaemic level, and

Third, educational programmes making possible all the above.

Practical guidelines for optimal B-glucose levels during intensified insulin treatment are presented in table 33-1.

4. FINAL REMARKS

The development and progression of all late diabetic complications are closely associated with the quality of long-term glycaemic control, and improving the control significantly reduces the risk of complications. The major challenge in the

time to come will be to implement this knowledge without causing acute deleterious complications in terms of hypoglycaemia and ketoacidoses and without placing a too heavy burden of guild on the many patients who will eventually develop complications after all.

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34. META-ANALYSIS OF THE EFFECT OF INTENSIVE THERAPY ON NEPHROPATHY IN TYPE I DIABETES MELLITUS

PING H. WANG, JOSEPH LAU and THOMAS C. CHALMERS

The large-scale Diabetes Control and Complication Trial (DCCT) has convincingly demonstrated the benefits of intensive therapy on diabetic nephropathy, neuropathy, and retinopathy [1]. A meta-analysis of several smaller studies also reached the same conclusions on nephropathy and retinopathy [2]. Decades of debate over whether normalization of hyperglycaemia may retard or delay microvascular complications came to an end [3,4]. As more randomized-controlled trials in diabetic patients are being conducted, meta-analysis will be a useful tool to study interventions in the prevention of diabetic complications. In this chapter, we review the principle, strengths, and limitations of meta-analysis and the results of meta-analysis of intensive glycaemic control on diabetic nephropathy. The clinical implications of intensive therapy, based on the results of DCCT and meta-analysis, are also discussed.

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1. META-ANALYSIS

Increasing number of meta-analyses are being published in the medical literature, brought about by the necessity of making sense of the thousands of clinical studies published each year in various domains. Many of the studies are often too small to provide statistical significant results and are at times contradictory. Meta-analysis is a method to critically evaluate relevant clinical studies and uses statistical methods to pool the results [5]. Disparate results from individual studies when pooled may reveal statistical significance that is clinically important [6]. The use of randomized-controlled trials in meta-analysis increases the reliability of the results by removing many of the biases associated with non-randomized studies.

The first step in performing a meta-analysis involve defining a protocol stating the question being addressed, specifying the inclusion and exclusion criteria, and choosing the outcomes to be studied. An exhaustive literature search is performed usually using the computerized Medline database, bibliography of retrieved articles and other sources. An assessment of the retrieved studies are performed to determine the quality [7]. Extracted data are then statistically pooled to give an overall estimate of the effect size and a confidence interval [8].

2. CUMULATIVE META-ANALYSIS

Cumulative meta-analysis is performed by updating the pooled results every time with the appearance of a relevant new clinical study [9]. For example, the first pooling combines the first two published trials and the second pooling add the next trial to the first two, and so on. Using this method, the impact of an individual study on the overall results and the trends can readily be assessed. Accumulating studies chronologically by their publication years provide information on the year when a treatment could have been found to be effective. Cumulative meta-analysis has shown the lack of concordance of experts in tracking the development of clinical trials in their own field, therefore reliable consensus rarely developed in a timely fashion [10]. A dramatic example is the use of thrombolytic therapy in acute myocardial infarction. Expert recommendations and FDA approval of thrombolytic agents did not occur until the late 1980's, whereas a cumulative meta-analysis would have shown a statistically significant reduction of overall mortality in 1973 [10].

3. STRENGTHS AND LIMITATIONS OF META-ANALYSIS

The gold standard for assessing the therapeutic efficacy has traditionally been large randomized control trials. Increasing number of meta-analyses of smaller randomized-controlled trials are showing results similar to that of studies with larger number of patients. The great majority of the randomized-controlled trials in diabetes are usually too small in size thus lacking the power to provide definite

conclusions, an important use of meta-analysis is to pool the results of these studies so that more reliable conclusions can be obtained. In addition to recognizing efficacious or harmful therapy, meta-analysis is also useful in highlighting deficiencies of existing clinical studies, gaps of medical knowledge, and in the planning of future clinical trials.

Meta-analysis has been applied to many medical fields over the past 15 years. The full impact of meta-analysis on patient care is yet to be fully realized. The results of many clinical trials in different medical fields needs to be summarized. The Oxford Database of Perinatal Trials is an example of a comprehensive approach to reviewing clinical studies of a domain where all available randomized control trials in the perinatal field has been evaluated and their results pooled. Such database of clinical trials with meta-analysis awaits to be established in the field of diabetes.

Like any other research tools, meta-analysis is not without limitations [5,6]. Most meta-analyses have been performed on published data retrospectively, thus it may subject to the limitations of retrospective research. Meta-analysis may combine data from different patient populations and different study protocols. If one study protocol is vastly different from the others, valid data combination could be difficult to obtain. Another potential problem is publication bias, this is because researchers and journal editors tend to selectively publish positive studies. Failed to include unpublished negative studies may result in erroneous conclusions [11].

4. META-ANALYSIS OF THE INTENSIVE THERAPY TRIALS ON NEPHROPATHY

Several randomized-controlled trials were conducted to examine the effect of intensive therapy on nephropathy progression among type I diabetic patients [12-20]. Most patients on entry in these studies have either normal serum creatinine, normal urinary albumin excretion, or microalbuminuria. Since renal failure usually does not occur until decades after the onset of diabetes [21], in these studies the most commonly used marker to monitor the progression of nephropathy is urinary albumin excretion [22]. The results from the smaller trials published before the DCCT were not conclusive. A meta-analysis performed on these randomized-controlled trials of intensive therapy yielded the following results [2,23]. The effect of intensive therapy significantly reduced the risk of nephropathy progression by approximately 50% (odds ratio 0.34, 95%CI 0.2-0.58) (figure 34-1). This is similar to the 39 to 54% risk reduction shown by the DCCT [1]. Using the same technique of analysis, there is a parallel risk reduction in retinopathy progression in patients treated intensively. Intensive therapy was achieved by either multiple daily injections or insulin pump in these studies. The estimated reduction of glycosylated haemoglobin from these studies, albeit different methods of assay, was approximately 1.4%

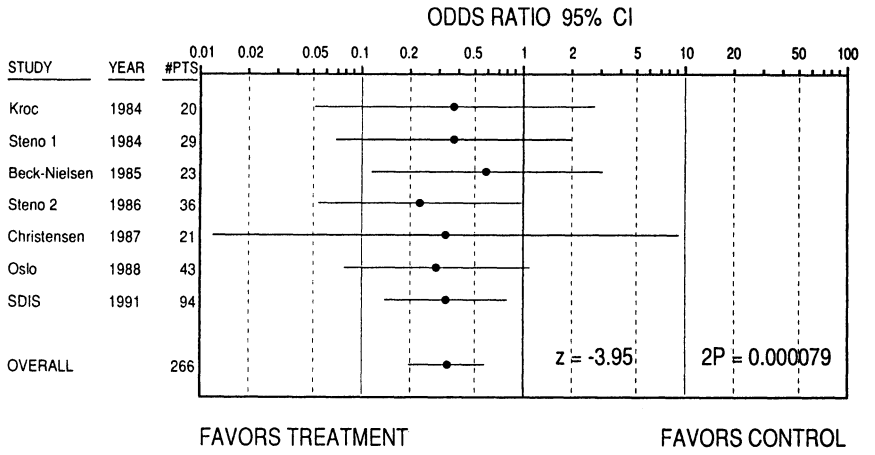

Figure 34-1. Meta-analysis of the effect of intensive therapy on nephropathy progression. [Adapted from Wang PH et al. Lancet 1993; 341: 1308]. Data represent the odds ratios of nephropathy progression with 95%CI.

(95%CI 1.1-1.8). A comparable reduction of glycosylated haemoglobin (1.5 to 2%) was reported by the DCCT [1]. In the case of intensive therapy and microvascular complication progression, meta-analysis of previous smaller trials was able to provide conclusions similar to the DCCT.

The effect of intensive therapy in delaying nephropathy progression is impressive, but the magnitude of reductions in glycosylated haemoglobin were modest in both the DCCT and the meta-analysis. Compared to the general diabetic population [24], many patients of the control groups in these studies had average or better than average glycaemic control. Since the incidence of nephropathy increases with higher glycosylated haemoglobin [24], it is tempting to speculate that the protective effect of tight glycaemic control may be even greater in patients with higher levels of glycosylated haemoglobin. However, further studies are needed to provide more direct evidence.

5. CUMULATIVE META-ANALYSIS OF THE INTENSIVE THERAPY TRIALS

A cumulative meta-analysis of the intensive therapy trials published between 1979 and 1993 were shown in figure 34-2. When urinary albumin excretion was used as a marker, the protective effect of intensive therapy on nephropathy progression first became statistically significant in 1986. This effect has remained statistically significant with smaller p values in later years as the ranges of 95%CI narrowed.

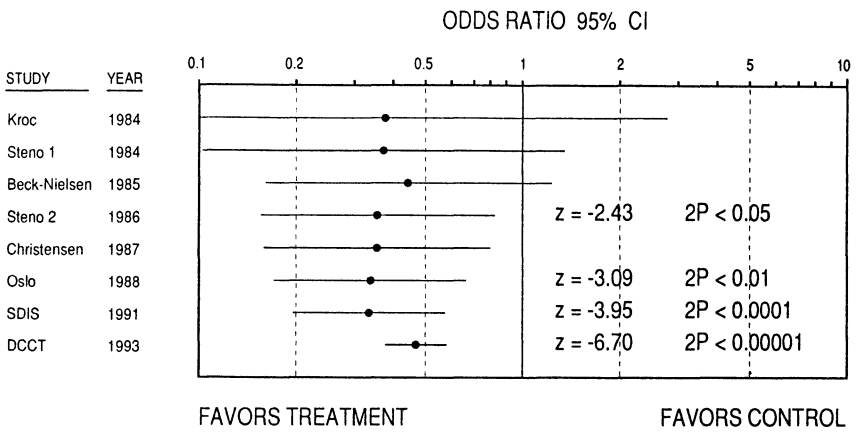

Figure 34-2. Cumulative meta-analysis of the effect of intensive therapy on nephropathy progression. Data represent the cumulative odds ratios of nephropathy progression with 95%CI.

The addition of later studies, including DCCT, did not alter previous conclusion. Because of the lack of consistency in each independent trial, intensive therapy, as an effective way to reduce the risk of diabetic nephropathy progression, were not recommended by some of the most popular endocrinology textbooks published between 1986 and 1992 [25,26].

6. CLINICAL IMPLICATIONS

Intensive therapy represents a vigorous effort to control blood glucose by intensified insulin therapy, frequent home blood glucose monitoring, defined dietary plan, extensive patient education, and close follow-up with doctors and nurses. The major side effects of intensive therapy are severe hypoglycaemia and ketoacidosis [1,2].

Ideally, all type I DM patients should be treated with intensive therapy if there is no contraindication. The patient's diabetic history, general medical conditions, and psychosocial status should be carefully reviewed before starting intensive therapy. The following groups of patients will not be good candidates for intensive therapy: 1) young children, because it is difficult to administer tight glycaemic control in this age group; 2) those who have a history of frequent severe hypoglycaemia or hypoglycaemia unawareness [27]; 3) patients with ischemic heart disease or severe arrhythmia because severe hypoglycaemia potentially may precipitate acute cardiac events; 4) patients with end-stage microvascular complications; 5) patients with severe systemic illness such as metastatic cancer; 6) those who physically or mentally incapable of practising intensive therapy. In those patients considered

unsuitable for intensive therapy but the risk of microvascular complications remains a concern, appropriate insulin treatment should be given to ensure reasonable glycaemic control. Although intensive therapy may delay the progression of microvascular complications, the optimal level of glycaemic control to gain maximal protection with minimal side effects awaits to be defined. The target level of glycaemic control and risk/benefit ratio ought to be individualized for each patient, no universal guidelines can be generalized to all patients.

The progression of nephropathy can be delayed but not completely stopped by intensive glycaemic control, some patients will still develop severe nephropathy and/or retinopathy despite meticulous glycaemic control. This suggests that other genetic or environmental factors are possibly involved in the pathogenesis of microvascular complications. Besides glycaemic control, blood pressure control and other investigational methods of preventing nephropathy progression such as low protein diet or angiotensin II converting enzyme inhibitors [also see Chapters 30 and 35] may provide additional protection. Thus, when indicated, a nephropathy prevention regimen consist of some or all of these elements should be designed for each type I diabetic patients.

Finally, although cumulative meta-analysis might have identified the beneficial effect of intensive therapy in 1986, individual physicians or investigators rarely have the resources to acquire and analyze all studies. Thus there is a need to establish a database of diabetes trials with cumulative meta-analysis. The establishment of such database accompanied with periodical cumulative meta-analysis will expedite the verification of efficacious new interventions in preventing or reversing diabetic nephropathy and other diabetic complications.

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35. NON-GLYCAEMIC INTERVENTION IN DIABETIC NEPHROPATHY: THE ROLE OF DIETARY PROTEIN INTAKE

JAMES D. WALKER

By the time clinical diabetic nephropathy is diagnosed by persistent proteinuria and a declining glomerular filtration rate (GFR), treatment options to preserve renal function are limited. Improving glycaemic control at this stage of the disease process is difficult and has little influence on the rate of decline of the GFR [1-3] whereas treatment of a raised blood pressure (BP) is more efficacious [4-8]. Dietary protein restriction has long been known to influence renal function [9] and numerous studies have tested the effect of dietary protein restriction in various renal diseases [10]. Additionally in animal models of chronic renal failure dietary protein restriction lessens proteinuria, mesangial expansion and glomerulosclerosis and preserves GFR [11-14]. This chapter discusses the influence of dietary protein on renal function and examines the effects of the therapeutic manoeuvre of restricting dietary protein in diabetic nephropathy.

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DIETARY PROTEIN AND RENAL FUNCTION

Normal humans

Vegans who eat less total protein than omnivores (0.95 vs. 1.29 g/kg/day) and 100% of their protein intake is the form of vegetable protein, have glomerular filtration rates that are 11% lower than matched omnivores [15]. In addition, urinary albumin excretion and blood pressure levels are lower [15]. A similar effect of diet on blood pressure is seen after a 6 week period of a lacto-ovo-vegetarian diet in healthy habitually omnivorous subjects independent of changes in weight and sodium or potassium intake [16]. In normal humans consuming a usual diet GFR increases by 7-18% and urinary albumin excretion by 100-300% in response to a meat meal of 80 g of protein as lean cooked beef [17,18]. In contrast a 3 week period of low protein diet (LPD) (43 g/day) causes a 14% reduction in baseline GFR, a 9% reduction in renal plasma flow (RPF) and a 50% reduction in the urinary albumin excretion rate [17].

In diabetic patients

Normoalbuminuric insulin-dependent patients completing 3 weeks of LPD (45 g/day) had a reduction in GFR with no difference in RPF and thus a reduction in filtration fraction (FF) (FF=GFR/RPF) [19]. This contrasts to the effect of LPD on FF in non-diabetics [17]. Glycaemic control and blood pressure levels were unchanged while the fractional clearance of albumin was lower on LPD. A larger study involving 35 normoalbuminuric insulin-dependent diabetic patients investigated the response to a 100 g/1.73 m^2 protein load in the form of a meat meal [18]. The area under the glomerular filtration rate curve rose more in normals than in the diabetic patients by a factor of 3.8. The impaired response of glomerular filtration rate to the meat meal in the diabetic patients was not due to differences in absorption of the meal since plasma levels of branched-chain amino acids were not different between normals and diabetics. Possible mechanisms of the differing responses included glucagon-mediated increases in the vasodilatory prostaglandins, prostaglandin E_2 and 6-keto prostaglandin $F_{1\alpha}$, which were impaired in diabetics.

A similar study employing a cross-over design tested the renal effects of 10 days of a diet of 0.9 g/kg/day or 1.9 g/kg/day of dietary protein. GFR and FF were lower on the diet containing the lesser amount of protein with a more marked fall in GFR in those patients with glomerular hyperfiltration (GFR > 127 ml/min) [20].

At the stage of microalbuminuria a reduction in GFR, urinary albumin excretion rate and fractional clearance of albumin was seen after 3 weeks of a low protein diet (47 g/day) [21]. These changes were independent of changes in glycaemia or blood pressure. In insulin-dependent diabetic patients with diabetic nephropathy 3 weeks of LPD was associated with an improvement in glomerular permselectivity while no

differences were seen in renal haemodynamics (GFR, RPF, and FF) between the two diet periods [22,23]. The reabsorption rate of B_2 microglobulin was similar in both diet periods, suggesting that tubular function was not influenced by the different diets.

Thus in both normals and diabetic subjects with microalbuminuria and glomerular hyperfiltration, short-term dietary protein restriction leads to a reduction in albuminuria and GFR whereas in diabetic patients with proteinuria although urinary protein loss is diminished in the short-term, this intervention has no effects on renal haemodynamics.

MEDIATORS OF RENAL EFFECTS OF DIETARY PROTEIN

In order to define some of the determinants of the change in glomerular filtration rate in response to different dietary protein intakes, Krishna and colleagues administered a 1 g of protein/kg body weight as beef steak, to 9 healthy males [24]. The renal haemodynamic studies were repeated on three separate occasions after pretreatment with either placebo, indomethacin (to inhibit renal prostaglandin synthesis) or enalapril (to inhibit angiotensin II synthesis). Following placebo GFR increased by 29% with an accompanying increase in RPF and a fall in renal vascular resistance (RVR). Pretreatment with indomethacin attenuated the rise in the GFR (12% rise) whereas treatment with enalapril was not different to placebo. Urinary excretion rates of prostaglandin E_2 fell significantly in the indomethacin group, levels of plasma renin activity were increased in the enalapril group while plasma noradrenaline and adrenaline were unchanged in all groups. From these data it appears that the protein-mediated elevation in glomerular filtration is in part associated with prostaglandin levels. In diabetic patients the attenuated glucagon response to a protein challenge may mediate the reduced prostaglandin effect [18].

The effects of similar amounts of animal and vegetable protein ingestion on renal haemodynamics were investigated in a short-term study of 10 normal males [25]. GFR, RPF and the fractional clearance of albumin were all lower on the vegetable protein diet while renal vascular resistance (RVR) was higher compared to the animals protein diet. In a separate experiment, seven normal subjects were given an 80 g protein load of animal protein (lean cooked beef) and subsequently 80 g of diluted soya powder (vegetable protein). While an elevation in GFR and RPF and a reduction in RVR was seen after animal protein no changes occurred after soya. The incremental glucagon area was greater for meat than soya and whereas the vasodilatory prostaglandin 6-keto $PGF_{1\alpha}$ rose significantly after the animal protein, it did not change after soya challenge. From these data, it appears that the same quantity of vegetable protein causes different renal effects compared to animal protein, and that this difference is associated with a smaller glucagon and

vasodilatory prostaglandin response. These hormonal mediators have been also implicated from a study in which infusion of somatostatin diminished the renal response to amino-acid infusion [26].

Elevated levels of plasma renin activity on high protein diets have been observed in man and experimental animals [22,27]. This difference could not be explained in terms of differences in sodium or potassium intakes, which were identical between the two diets. As prostaglandins are known to mediate renin release [27,28] the elevated levels of prostaglandins may have caused the elevated renin levels. Although there were no changes in mean arterial pressure between the two diet periods the elevated renin levels may have resulted in increased levels of angiotensin II to cause constriction of both the afferent and efferent glomerular arterioles. The role of angiotensin II in the physiological and pathophysiological response to low protein feeding may be important since in the rat captopril reverses the reduced GFR and RPF and increased renal vascular resistance seen with LPD [29].

Other mediators in addition to glucagon, prostaglandin and the renin/angiotensin/aldosterone system may be involved in the renal response to dietary protein. Recently increased levels of mRNA for PDGF-A and -B chains and TGF-ß genes have been shown to correlate with glomerulosclerosis in a rat model [30]. Low protein feeding reduced the prevalence of glomerulosclerosis and attenuated the abnormally high expression of the PDGF-A and -B and TGF-ß genes. These data suggest that growth factors may play a role in the development of glomerulosclerosis and can be modulated by LPD.

LONG-TERM CLINICAL STUDIES OF LOW PROTEIN DIETS IN PATIENTS WITH DIABETIC NEPHROPATHY

Most studies designed to test the effects of a diet restricted in protein in insulin dependent patients with diabetic nephropathy have used creatinine clearance or the reciprocal of the serum creatinine to assess renal function (table 35-1). This is not an accurate or precise measure of GFR compared to isotopic clearance methods, such as the plasma clearance of ^{51}Cr EDTA, which give nearly identical values to inulin clearances. In addition changes in the creatine pool and creatinine intake seen in low protein diet studies further render such measurements unreliable for the assessment of GFR [31-34].

Study designs have varied. Evanoff used patients as their own control [35]. After a 12 month observation period a LPD of 0.6 g/kg/day was instituted and, using creatinine clearance and the reciprocal of the serum creatinine to assess renal functional response, 11 patients were studied for 2 years [35]. The period of LPD was associated with a slowing in the rate of decline of the reciprocal of the serum creatinine and no change in the creatinine clearance levels during the 2 years of

Table 35-1. Clinical studies of low protein diet in patients with diabetic nephropathy

AUTHOR/ YEAR	STUDY DESIGN	DIETARY PRESCRIPTION	DIETARY ASSESSMENT	GFR ASSESSMENT	DURATION OF LPD	OUTCOME
Zeller, 1991	Randomised controlled, 68 pts.	0.72 g/kg/day in pts. 1.08 g/kg/day in controls	Weighed food records Urinary urea nitrogen	Iothalamate clearances	37 months	Iothalamate clearances 0.26 ml/min/mo in pts. 1.01 ml/min/mo in controls MBP 102 in pts., 105 in controls
Walker, 1989	Self controls 19 tps.	1.1 g/kg/day on NPD→0.66 g/kg/day on LPD	Weighed food records Urinary urea nitrogen	Plasma clearance of ^{51}Cr EDTA	29 months on NPD 33 months on LPD	GFR 0.61 ml/min/mo on NPD, 0.14 ml/min/mo on LPD MBP 106 on NPD, 102 on LPD
Evanoff, 1989	Self controls 11 pts.	1.2 g/kg/day on NPD→0.95 g/kg/day on LPD	Dietary recall urinary urea nitrogen	Creatinine clearance 1/serum creatinine	24 months	Δ 1/serum creatinine -0.18/yr on NPD -0.03/yr on LPD Systolic BP 147 LPD→126 NPD
Barsotti, 1988	Self controls 8 pts.	1.3 g/kg/day on NPD 0.3 g/kg/day on LPD (supplemented with essential amino- and ketoacids)	Urinary urea nitrogen	Creatinine clearance	17 months	Decrease in TUP Increase in TPP Rate of decline in CrCl on NPD 1.38 ml/min/mo on LPD 0.03 ml/min/mo
Ciavarella, 1987	Randomised controlled 16 pts.	0.71 g/kg/day in pts. 1.44 g/kg/day in controls	Dietary interview Blood urea nitrogen Urinary urea nitrogen	Creatinine clearance	4.5 months	Decrease in AER in LPD group

AER = Urinary albumin excretion rate; TUP = Urinary total protein excretion rate; LPD = Low protein diet; CrCl = Creatinine clearance; NPD = Normal protein diet; TPP = Total plasma protein level; Δ = Delta (change in); All blood pressure values are in mmHg; MBP = Mean blood pressure

study. However, 9 of the 11 patients had antihypertensive agents initiated during the study and systolic blood pressure levels fell significantly. No attempts were made to correct for the substantial fall in systolic blood pressure (about 20 mmHg) and it is therefore difficult to separate the effects of the blood pressure reduction from those of LPD making interpretation of the effects of LPD in this study difficult. Using the same study design Barsotti followed 8 patients with more severe renal impairment for 16 months on a normal protein diet (NPD) (1.2 to 1.4 g/kg/day) and then instituted a more restrictive protein prescription of 0.25 to 0.35 g/kg/day with essential amino acid supplementation for a mean duration of 17 months [36]. Urinary urea and urinary protein levels fell during the diet, body weight, triceps skin thickness, mid-arm muscle circumference and plasma albumin levels were

unchanged and insulin requirements fell despite an increase in the carbohydrate intake. The rate of decline of creatinine clearance was slowed on LPD in a heterogeneous manner.

A 6 month controlled study involving 7 patients in a LPD and 9 in a control group revealed no changes in creatinine clearance but a reduction in urinary albumin excretion on LPD [37]. The majority of patients in both groups had serum creatinine levels that were within the normal range indicating well preserved renal function and thus it was not surprising that no change in creatinine clearances were observed in this short-term study.

A larger controlled trial that employed an isotopic clearance method for measurement of GFR demonstrated a significant reduction in the rate of decline of GFR after 37 months on a low protein diet (0.72 g/kg/day) compared to a control group on a normal protein diet (1.08 g/kg/day) for this period [38]. Blood pressure was lower in the group on the low protein diet but when included as an independent variable in a stepwise regression analysis with change in glomerular filtration rate as the dependent variable, it was found to exert no significant effect. Interestingly, the rate of decline of GFR was only significantly different between the patients on the two diets when those with initial glomerular filtration rates above 45 ml/min were considered. This may be taken to suggest that dietary intervention should be introduced early in the course of diabetic nephropathy before significant reductions in glomerular filtration rate occur. There was no indication that the LPD had any nutritional adverse effect. Serum cholesterol and triglyceride levels were increased during the LPD period but the changes failed to reach statistical significance.

The only other prospective study employing an isotopic clearance method to assess GFR investigated the effect of LPD in 19 insulin-dependent diabetic patients with nephropathy. Patients were followed for 29 months on NPD (1.11 g/kg/day) and subsequently for 33 months on LPD (0.66 g/kg/day). GFR decline was slowed by an average of 0.47 ml/min/month (figure 35-1) and the rise in albuminuria halted independent of changes in glycaemia or blood pressure [39]. The effect of LPD on the decline in GFR was heterogeneous with 10 of the 19 patients exhibiting a significant slowing yet in the remaining 9 the rate was either non-significantly slower or in some cases faster. No identified factors separated the responders from the non-responders. This study quantitated and emphasised the heterogeneity of the GFR response with has also been observed in a trial of antihypertensive therapy in patients with diabetic nephropathy [5].

PROBLEMS WITH LOW PROTEIN DIETS

Two main problems are associated with the prescription of a LPD namely protein/calorie malnutrition and compliance [40-43]. Protein intakes below 0.6

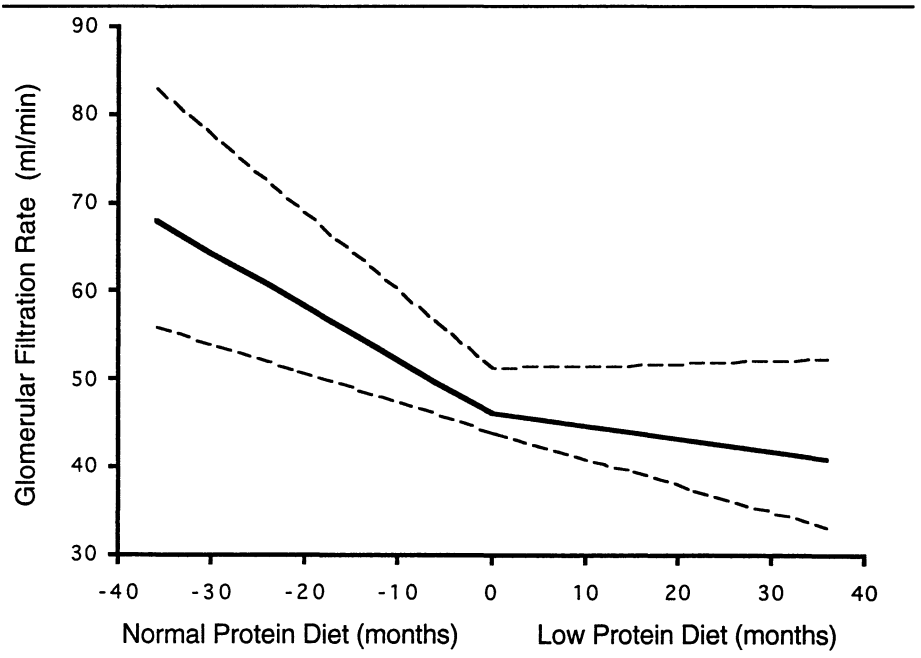

Figure 35-1. GFR decline (mean - solid line and 95% confidence intervals - dashed lines) in 19 insulin-dependent diabetic patients with nephropathy on a normal and subsequently a low protein diet. Data taken from reference 39.

g/kg/day have been associated with protein malnutrition [40,41] and the aim of a LPD should be reduce protein intake to a non-harmful yet achievable level by the majority of patients. Despite increased carbohydrate intake, necessary to compensate for the calorie reduction caused by a reduction in dietary protein, energy intake has been reported to fall and a small degree of weight loss occur on LPD in some studies [36,39]. However, stable or increased serum albumin levels and no change in mid-arm muscle circumference are reassuring parameters and suggest that the levels of protein reduction in reported studies are not associated with muscle loss and protein malnutrition [38,39].

Compliance is a prerequisite for this form of treatment and 2 recent studies, one involving patients with diabetes and microalbuminuria, have demonstrated how difficult this can be to achieve. Locatelli, in a large study, prescribed a LPD of 0.6 g/kg/day yet the achieved level of protein intake was 0.83 g/kg/day [42] - not a low protein diet. In patients with diabetes and microalbuminuria only 7 of 14 patients achieved the prescribed protein reduction of <0.8 g/kg/day during a 2 year study

[43]. The reasons for the poor level of compliance in this study may include the lack of concern of the patients about their renal condition at this early stage of renal disease.

BLOOD PRESSURE TREATMENT AND DIETARY PROTEIN RESTRICTION IN DIABETIC NEPHROPATHY

No study has tested the effects of blood pressure reduction **and** dietary protein restriction in diabetic nephropathy. In non-diabetic renal disease evidence for an additive effect is provided by a short-term study of 17 patients in whom addition of enalapril to a LPD resulted in a further decrease in proteinuria and a reversal of some acute renal haemodynamic changes associated with LPD [44]. In diabetic patients with nephropathy, the 2 clinical trials that used isotopic clearances to assess GFR found that the small reduction in mean blood pressure on LPD exerted a very small effect on the change in GFR [38,39]. In these studies mean blood pressure was only 4 mmHg lower on LPD [38,39]. This contrasts with the 12 mmHg fall in mean blood pressure caused by antihypertensive treatment in the study reported by Parving [5]. The achieved mean blood pressure level in the LPD studies was 102 mmHg a level similar to the level of 99 mmHg achieved in the study reported by Parving [5]. The reduction in the rate of GFR decline associated with LPD is similar to that seen with treatment of hypertension. However, as levels of mean blood pressure on NPD were considerably lower than the untreated blood pressures levels of Parving's patients (106 vs. 112 mmHg) the further slowing of GFR decline on LPD argues for an additional effect of this therapeutic manoeuvre.

CONCLUSIONS AND IMPLICATIONS

There is now enough evidence to strongly support the hypothesis that a reduction in the dietary intake of protein retards the rate of decline of renal functional loss in cases of established diabetic nephropathy in patients with insulin-dependent diabetes mellitus. Subjecting a patient to this dietary regime should not be undertaken lightly and needs full co-operation of the patient and full involvement of a nutritionist experienced in this field. GFR response to LPD appears to be heterogeneous thus making it is vital to assess whether an individual is benefiting from the intervention. It would thus be prudent for patients to have a run-in period on their usual diet and therapy with 3 isotopic measurement of GFR to establish a baseline rate of decline against which the response to LPD can be compared. Protein restriction of 0.6 g/kg/day appears to have no untoward nutritional effect.

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36. MICROALBUMINURIA AND DIABETIC PREGNANCY

CARL ERIK MOGENSEN and JOACHIM G. KLEBE

Renal and vascular damage, including blood pressure elevation, is often involved in complications of diabetic pregnancy. Therefore, sensitive methods for measuring elevated urinary protein excretion, especially of albumin (so-called microalbuminuria) [1-3], might be useful in early prediction of complications in diabetic as well as nondiabetic pregnancy. This is the case in nonpregnant diabetics [3-9], in whom microalbuminuria is a sensitive marker of generalized subclinical vascular disturbance and damage [6] and in whom it predicts overt nephropathy [3-6] as well as proliferative retinopathy [7]. This chapter deals with the pattern of urinary albumin excretion rate in diabetic pregnancy as studied with a sensitive radioimmunoassay for albumin using 24-h urine samples. Patients with overt nephropathy are discussed in Chapter 37.

1. PATIENTS, METHODS, AND CLASSIFICATIONS

We studied 52 insulin-dependent diabetic patients consecutively. One patient was pregnant twice. Patients were studied every second week when attending the clinic

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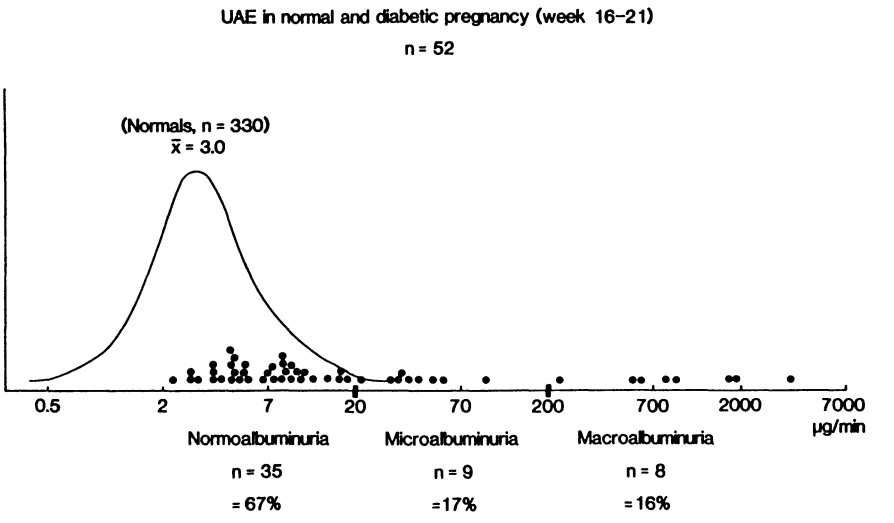

Figure 36-1. Urinary albumin excretion rate in normal and diabetic pregnancy (weeks 16-21). The *solid line* show the distribution curve for normal pregnancies (n = 330), and the *dots* indicate diabetics (n = 52).

for general obstetric control. About 10% of the diabetics were seen at prepregnancy consultations. In all pregnant diabetics, values were available from week 16. Blood glucose, HbA_{1c}, blood pressure, and urinary albumin excretion (UAE) (on 24-h urine samples collected at home) were determined [10].

No increase in UAE is seen either early or late in the course of normal pregnancy. In our laboratory, 330 normal pregnant women showed values of 3.0 µg/min $\times/\div$ 1.8 week 20 (geometric mean $\times/\div$ tolerance factor) (figure 36-1), corresponding to or lower than those in nonpregnant normals [10,11], and also no increase was seen late in pregnancy (weeks 38-41) in normal women (5.5 µg/ml $\times/\div$ 1.6 in morning urine samples, n = 35).

1.1. Classification of patients

Patients were classified according to a newly proposed classification system for renal involvement in insulin-dependent diabetics [12], as outlined in Chapter 1.

Group I included patients with diabetes diagnosed during pregnancy. Group II comprised patients with normal UAE around week 16 ($\leq$20 µg/min). This group had to be subdivided into groups IIa and IIb since a number of patients later in pregnancy showed values higher than 20 µg/min (IIb). Group III included patients with microalbuminuria early in pregnancy (UAE 20.1-200 µg/min), and group IV

Table 36-1. Patient data including number of patients, mean age, duration of diabetes, blood pressure, HbA_{1c} values and retinopathy data, creatinine clearance, number of total death, % Caesarean section, and mean birth weight

Patient data		*n*	Mean age (years)	Mean known duration of diabetes	Initial MAP (mmHg)	Mean HbA_{1c} values	Retinopathy (NIL/S/P)[a]	Creatinine clearance[b] ml/min	Fetal death (*n*)	% Caesarean section	Mean birth weight (g)
I	Diabetes diagnosed during pregnancy	4	26±2	-	77±8	6.0±1.4	4/0/0	111	0	0	3867
IIa	Normoalbuminuria	17	27±4	13±7	81±9	6.8±1.0	8/8/1	122	1	30	3570
IIb	Normo→Micro-alb.	14	25±4	11±6	85±10	6.2±0.7	7/6/1	130	2	69	3425
III	Microalbuminuria	9	27±7	14±6	91±6	7.1±1.1	0/8/1	98	1	37	3505
IV	Macroalbumin initially	8	26±3	16±7	100±10	6.9±1.0	1/1/6	82	0	87	2633

[a]S, simplex retinopathy; and P, proliferative retinopathy.
[b]Late in pregnancy.

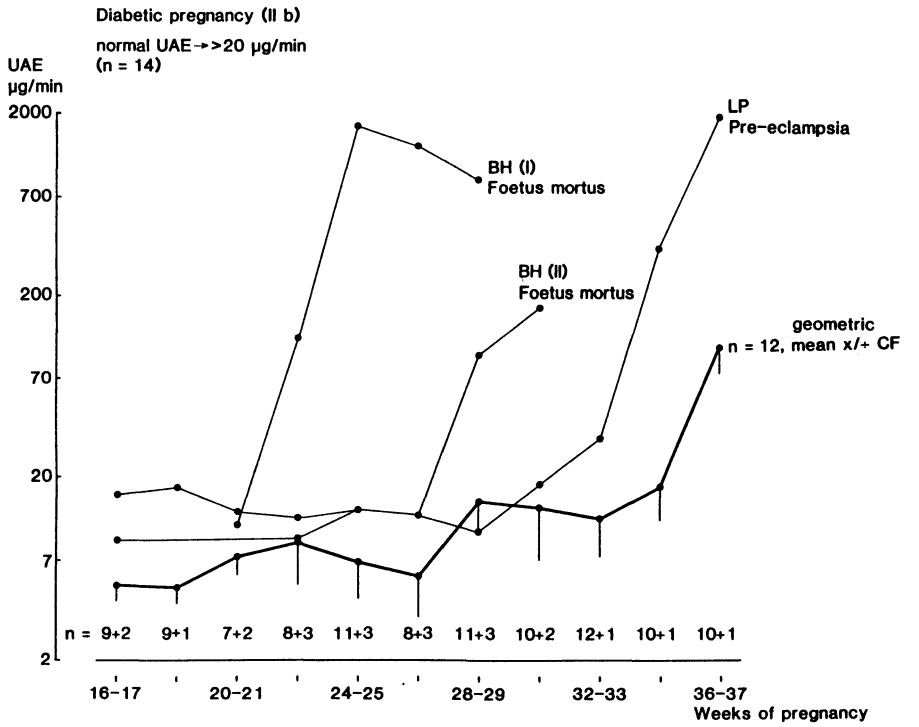

Figure 36-2. Urinary albumin excretion rate in diabetic pregnancy (group IIb). All patients started with normal UAE but increased to values above 20 µg/min. The *lower curve* shows data for 12 patients throughout pregnancy. The *upper three curves* shows data from patients with complications, namely, foetus mortus twice in one patient (B.H.). Patient L.D. developed preeclampsia.

included patients with clinical proteinuria, which corresponds to approximately >200 µg/min in UAE. According to this system, the 52 patients were classified as follows: I, 4; IIa, 17; IIb, 14; III, 9; and IV, 8 patients. Pertinent clinical data are presented in table 36-1, including age, duration of diabetes, initial blood pressure, and mean HbA_{1c} values, as well as information on retinal lesions and complications in general.

2. URINARY ALBUMIN EXCRETION DURING PREGNANCY

Figure 36-2 shows the longitudinal course of UAE in the group IIb, as just described. Mean values are shown, with the exception of data from three pregnancies in two patients with a complicated course. In four pregnancies (one in group IIa, two in group IIb, and one in group III), early or late intrauterine death was of

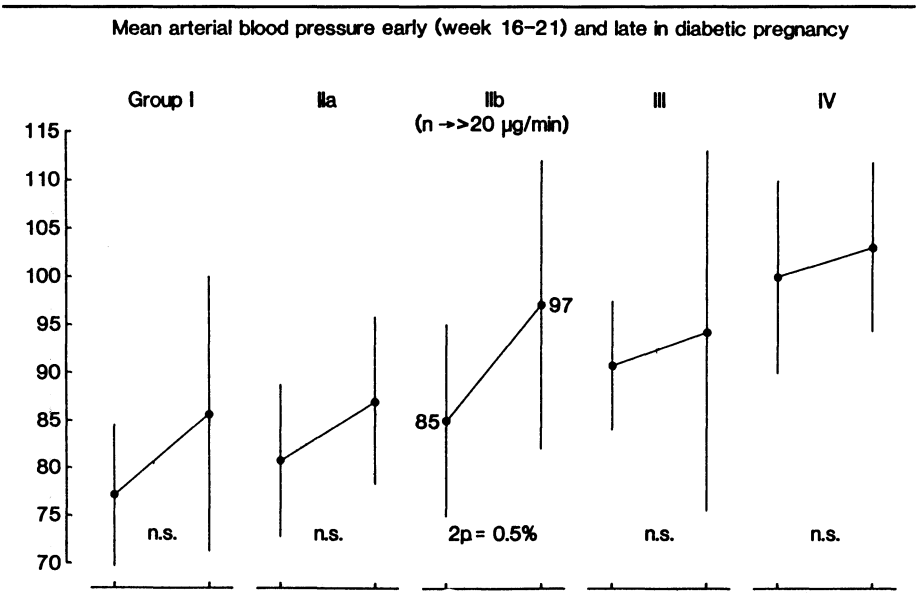

Figure 36-3. Mean arterial blood pressure early and late in diabetic pregnancy in groups I-IV. A significant increase is seen throughout groups I-IV. There is a tendency toward increase throughout pregnancy in each group, but this difference only became significant in group IIb, which was characterized by initial normal albumin excretion, but development of high values late in pregnancy (>20 µg/min).

recorded. One patient in group IIb developed preeclampsia. In one patient in group IIa with foetus mortus no change in UAE was seen. As table 36-1 14 shows, (45%) 31 patients changed from normoalbuminuria to microalbuminuria during pregnancy, a phenomenon generally not seen in normal pregnancy. Patients with microalbuminuria remained stable unless intrauterine death occurred. Urinary track infection unrelated to change in UAE occurred in two patients.

2.1. Blood pressure and creatinine clearance in the course of pregnancy

Figure 36-3 shows values of mean arterial pressure (MAP), defined as diastolic pressure plus one-third of pulse pressure, early (week 16) and late in pregnancy (the week before delivery). A tendency toward MAP increase in the last trimester is seen in all groups, but this increase becomes significant in only group IIb, which was characterized by an increase in UAE during pregnancy. Initial MAP increased throughout all of the groups. Creatinine clearance remained stable in all patients,

Table 36-2. Patients classified according to the White classification and according to renal involvement in diabetes

		White classes				
	Total	A	B	C	D	F/R
I	4		4			
IIa	17		3	3	10	1
IIb	14		3	2	8	1
III	9				8	1
IV	8		1(?)			7

(?) Nondiabetic renal disease

except in one patient in group IV whose clearance decreased dramatically (95→31 ml/min).

2.2. Urinary albumin excretion groups and White classification

Data are presented in table 36-2. No difference in the White classification is seen between groups IIa and IIb.

3. URINARY ALBUMIN EXCRETION IN THE MANAGEMENT OF DIABETIC PREGNANCY

This consecutive study shows that marked abnormalities in UAE are seen both early and late in the course of diabetic pregnancy. In many patients, an abnormal increase in UAE was seen during pregnancy (i.e., in 45% of patients with normal values around week 20). Such increases were generally not seen in normal pregnancy [13,15], also in accordance with our normal material. In several cases, UAE changes in the subclinical range were associated with a complicated course of pregnancy. We observed four pregnancies with late intrauterine death, and one with late abortion, a rather high percentage in 53 consecutive diabetic pregnancies. In normal pregnancies, the number is very small, around 0.5%, but it remains one of the significant problems in the management of diabetic pregnancy [16,17], where the figure now is generally around 1%-2%. The three pregnancies in two patients with early or late intrauterine death showed a gradual and marked increase in UAE in the preceding weeks, as seen from figure 36-2.

The increase in UAE may represent a form of subclinical preeclampsia with development of microalbuminuria and, alter, macroalbuminuria in some cases (i.e., more than 200 μg/min). Decreased placental blood flow is seen in diabetic

pregnancy and in preeclampsia, which is also associated with increased frequency of late intrauterine death [18,19]. Preeclampsia is seen more often in diabetic pregnancy than in nondiabetic pregnancy [17]. In fact, one patient in group IIb did develop the clinical picture of preeclampsia.

New prognostic markers, with possible therapeutic implications, are clearly needed so that the frequency of deleterious complications in diabetic pregnancy can be reduced to a level not higher than that in normal pregnancy. UAE, in conjunction with an established obstetric parameter, may qualify as one marker in this respect, but further studies are required. Rapid, inexpensive, and sensitive immunoassay are now available [20].

The White classification, subgrouping diabetic patients according to complication and duration of disease, is widely used in most centers. This classification is very useful, but additional information may be obtained by classifying patients according to UAE. Thus, patients starting with normal excretion rates who later develop increased UAE may be more prone to complications. This will not be detected by using the White classification criteria. It should also be borne in mind that many patients, e.g., in White classification D, show a normal albumin excretion rate throughout pregnancy and thus will not be prone to develop complications (group D is defined as insulin-dependent diabetes diagnosed between the age of 0-10 years, diabetes duration of more than 20 years, or background retinopathy). The present classification of diabetic patients in pregnancy is in accordance with a new classification system regarding renal changes in nonpregnant patients [12], and this system may also be useful in pregnant diabetics [21]. Large-scale studies on abnormal albuminuria in diabetic pregnancy are now being undertaken.

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37. DIABETIC NEPHROPATHY AND PREGNANCY

C. ANDREW COMBS and JOHN L. KITZMILLER

Every practitioner who cares for adolescent and young adult diabetic women has an obligation to recognize that these women may become pregnant, that pregnancy poses serious risks to mother and offspring, that most of these risks are related to poor glycaemic control, and that the risks may be reduced through special programs that achieve meticulous metabolic control before conception and throughout pregnancy.

With diabetic nephropathy, as with diabetes in general, the most common cause of perinatal death is major congenital malformation, as reviewed below. A major advance has been made in the past decade with the recognition that most malformations can be prevented by institution of strict metabolic control before conception. There are several interdisciplinary programs in North America and Europe for preconception diabetes management. Every diabetic woman should have instruction in contraception and should be referred to a specialized center when pregnancy is considered. Pregnancy should never be a surprise in a diabetic woman.

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Table 37-1. Improved pregnancy outcome with preconception care of diabetes

	Rate of Complications			
	Enroled before conception		Enroled after conception	
	N	(%)	N	(%)
Spontaneous Abortions				
Dicker et al. [3]	5/59	(8.5%)	10/35	(28.6%)
Rosenn et al. [4]	2/28	(7.1%)	17/71	(23.9%)
TOTAL	7/87	(8.0%)	27/106	(25.5%)
Major Malformations				
Fuhrman et al. [5]	1/128	(0.8%)	2/292	(7.5%)
Goldman et al. [6]	0/44	(0)	1/31	(3.2%)
Steel et al. [7]	2/114	(1.8%)	9/86	(10.5%)
Damm, Mølsted-Pedersen [8]	2/197	(1.0%)	5/61	(8.2%)
Kitzmiller et al. [9]	1/84	(1.2%)	12/110	(10.9%)
Rosenn et al. [4]	0/28	(0)	1/72	(1.4%)
Cousins [10]	0/27	(0)	23/347	(6.6%)
TOTAL	6/622	(1.0%)	73/998	(7.8%)

Until recently, women with diabetic nephropathy were generally advised to avoid pregnancy because there was a low probability of a healthy infant and a high probability that nephropathy would worsen. Although advances in obstetric and neonatal care have improved the outlook, nephropathy in pregnancy still presents a challenging situation requiring coordination between the patient, obstetrician, perinatologist, diabetologist, nephrologist, ophthalmologist, neonatologist, nurse-educator, dietitian, social worker, and other personnel. As reviewed in this chapter, women with nephropathy remain at high risk for many pregnancy complications in addition to congenital malformations, including preeclampsia, accelerated hypertension, preterm delivery, fetal growth retardation, and cesarean delivery.

1. EVALUATION BEFORE CONCEPTION

The risk of spontaneous abortions and major congenital malformations is highest in mothers with poor glycaemic control during embryonic organogenesis [1]. Because this critical period ends a few weeks after conception, often before pregnancy comes to clinical attention, the institution of strict glycaemic control immediately after diagnosis of pregnancy is inadequate to prevent adverse outcomes [2]. In contrast,

Table 37-2. Management of diabetic nephropathy before, during and after pregnancy

At all times
- Prevent hyperglycaemia
- Control hypertension
- Low protein diet
- Restrict exercise

Prior to pregnancy
- Measure renal function
- Ophthalmologic exam
- Cardiovascular evaluation (history, exam, EKG)
- Rubella immunization
- Thyroid evaluation
- Hepatitis B surface antigen
- Serologic testing for syphilis
- Counselling and education

First prenatal visit
- Measure renal function
- Ophthalmologic exam
- Sonogram for dating

Second trimester
- Measure renal function (12, 24 wks)
- Maternal serum alpha-fetoprotein (15-18 wks)
- Detailed sonogram
- Fetal echocardiogram (if indicated, 20 wks)

Third trimester
- Monthly sonogram
- Weekly nonstress test ($\geq$26 wks)
- Ophthalmologic exam
- Measure renal function (36 wks)
- Delivery planning

Postpartum
- Weekly follow-up
- Measure renal function (6 wks)
- Counselling
- Referral to appropriate specialists

when control is instituted *before* conception, there is a dramatic reduction in the risk of malformation and miscarriage, as summarized in table 37-1.

An outline of preconception management is included in table 37-2. Evaluation for diabetic microvascular disease and hypertension are critical. Albuminuria or proteinuria should be quantified, preferably with a 24-hour specimen [11,12]. If nephropathy is diagnosed, the patient must be thoroughly counselled regarding possible complications of pregnancy and regarding her own reduced life expectancy. She must then decide whether to attempt pregnancy.

Antihypertensive therapy is indicated for most patients with microalbuminuria or overt nephropathy. Angiotensin converting-enzyme (ACE) inhibitors are contraindicated during pregnancy because they may be teratogenic and are associated with neonatal renal failure [13]. This is unfortunate because there are extensive data,

Table 37-3. Changes in creatinine clearance in 44 women with diabetic nephropathy with measurements in both first and third trimesters of pregnancy.

First Trimester		Third Trimester		
CrCl	N	Increased >25%	Stable	Decreased >15%
>90 ml/min	14	3(21%)	5(36%)	6(43%)
60-89 ml/min	20	9(45%)	6(30%)	5(25%)
<60 ml/min	10	2(20%)	6(60%)	2(20%)
Total	44	14(32%)	17(39%	13(29%)

Data pooled from Kitzmiller et al. [16], Reece et al. [17], and Jovanovic and Jovanovic [18]

reviewed elsewhere in this volume, indicating that ACE-inhibitors may retard the development and progression of nephropathy. Diltiazem and other calcium-entry blockers are probably best avoided during the first trimester until there are adequate data regarding potential teratogenesis. Agents believed to be relatively safe for pregnancy include alpha-methyldopa, prazocin, clonidine, and beta-adrenergic antagonists.

Ophthalmologic examination is especially important for women with nephropathy because most also have retinopathy. Rapid normalization of blood glucose may cause worsening of retinopathy [14]. With background or proliferative disease, we allow several weeks to normalize blood glucose before pregnancy. Proliferative retinopathy should be in remission or laser-treated before pregnancy.

Glycaemic control is achieved with diet and intensive insulin therapy. The diet prescription for pregnancy is 25-35 kcal/kg ideal body weight. With nephropathy, protein intake should be restricted, but 60 g/day is probably required for fetal development. The preferred insulin regimen includes a mix of short and intermediate-acting human insulins. The optimal doses and timing are determined by self-monitored capillary blood glucose determinations before and after each meal.

2. COURSE OF NEPHROPATHY DURING PREGNANCY

GFR rises by 40-80% in normal pregnancy, as reflected by increasing creatinine clearance and decreasing serum creatinine [15]. With diabetic nephropathy, however, the normal rise in GFR is seen in only about one-third of patients, as summarized in table 37-3. In another one-third, GFR actually decreases, probably reflecting the underlying natural progression of nephropathy. Jovanovic and

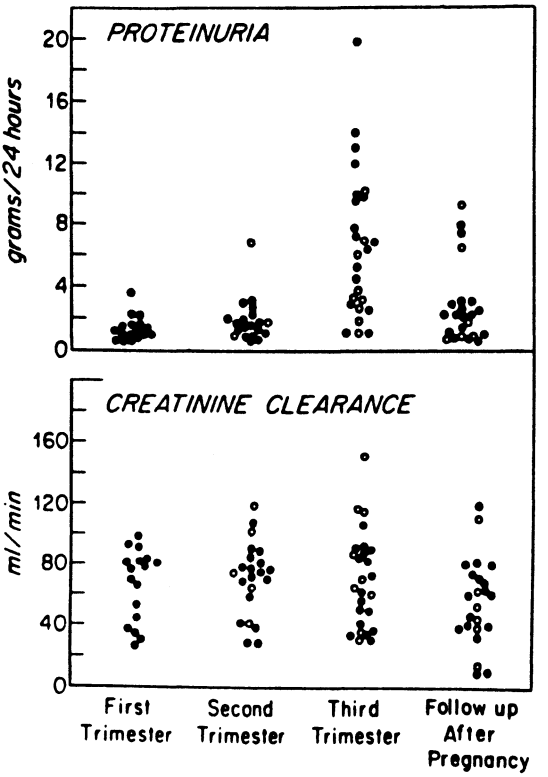

Figure 37-1. Distribution of levels of proteinuria and creatinine clearance in women with diabetic nephropathy in each trimester of pregnancy and at follow-up 9-35 months after pregnancy. *Closed circles* indicate women studied in each trimester. *Open circles* indicate women not seen in the first trimester. From Kitzmiller et al. [16], with permission.

Jovanovic found that prevention of hyperglycaemia and hypertension allowed a normal rise in GFR during pregnancy.

The excretion of albumin and other proteins increases by 80-120% in normal pregnancy, presumably due to increased GFR [19,20]. With diabetic nephropathy, proteinuria often increases dramatically, frequently exceeding 10 g/day in the third trimester (figure 37-1). Though some of this increase may reflect the underlying progression of nephropathy, protein excretion usually subsides after delivery [16].

Nephropathy can progress to end-stage renal disease during pregnancy, although this is unusual. Of the 44 women summarized in table 37-3, none progressed to end-stage disease during pregnancy. There is some experience with both haemodialysis

Table 37-4. Pregnancy complications with diabetic nephropathy.

Complication	N	%	References
Preeclampsia	88/192	46%	16,17,18,23,24,25
Anemia*	24/57	42%	16,17
Fetal Distress	22/115	19%	16,17,23,25
IUGR	20/115	17%	16,17,23,25
Cesarean Delivery	73/101	72%	17,18,23,25
Preterm Delivery			
<37 wks	108/192	56%	16,17,18,23,24,25
<34 wks	36/155	23%	16,17,18,24,25
Perinatal Mortality			
Major Malformations	4/131	3.1%	16,17,18,23,25
IUGR, Preterm	3/131	2.3%	16,17,18,23,25
Total	7/131	5.3%	16,17,18,23,25

IUGR = intrauterine growth retardation
*Anemia = hematocrit <28% or haemoglobin <10 mg/dl

and peritoneal dialysis in pregnancy [21,22]. Complications include preeclampsia, placental abruption and stillbirth. The latter two are related to large shifts in extravascular volume and may be less common with peritoneal dialysis [22]. Because of the high complication rate, pregnancy is probably contraindicated if the serum creatinine is above 2 mg/dl or creatinine clearance below 50 ml/min.

3. COMPLICATIONS OF PREGNANCY

Table 37-4 summarizes several maternal and perinatal complications frequently seen in women with diabetic nephropathy.

Preeclampsia is perhaps the most frequent and alarming complication. The condition is suspected when there is an increase in blood pressure and proteinuria in the third trimester. With preexisting renal disease, it may not be possible to clinically distinguish »true« preeclampsia from a »simple« worsening of hypertension and proteinuria. The distinction is important because the former is best treated by delivery whereas the latter is treated with bed rest and antihypertensive agents. Edema and hyperuricemia are common in patients with renal disease and therefore are not useful in the differential diagnosis. Occasionally, thrombocytopenia or elevated transaminases are found and these support a diagnosis of preeclampsia. As a practical matter, it is generally necessary to observe the patient at hospital bed rest, with or without antihypertensive therapy. Hypoalbuminemia commonly results

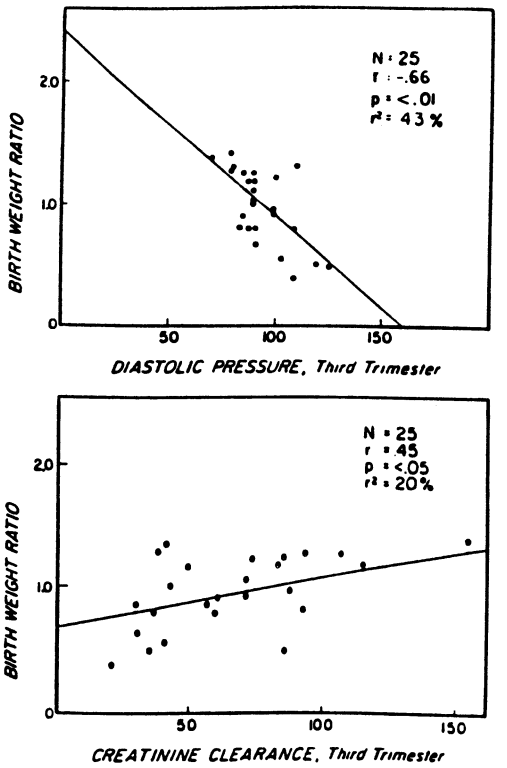

Figure 37-2. Relationship of infant birth weight adjusted for gestational age to mean maternal diastolic blood pressure and mean creatinine clearance in the third trimester in 25 women with diabetic nephropathy and singleton pregnancies. Birth weight ratio = birth weight/50th centile of birth weight for gestational age. From Kitzmiller et al. [16], with permission.

from excessive proteinuria and leads to generalized edema. The edema can be treated with diuretics. It is controversial whether albumin infusions are beneficial or whether they simply »add fuel to the fire«, that is, promote glomerular hyperfiltration and worsening proteinuria. The decision to deliver the infant must balance the gestational age, the severity of the maternal condition, and indicators of fetal well-being. Preeclampsis is the single most common reason for preterm delivery in mothers with nephropathy [24,26].

Anemia results from both decreased erythropoietin production by damaged glomeruli and the physiologic hemodilution of pregnancy. The degree of anemia is related to the severity of nephropathy as reflected in lower creatinine clearance and

is not usually associated with abnormal iron studies [16]. Exogenous erythropoietin can be considered for anemia unresponsive to iron and folate replacement [27].

Fetal growth retardation is related to maternal hypertension (figure 37-2). Serial sonography is indicated to evaluate fetal growth. In addition, fetal heart rate surveillance should be employed because growth retardation is frequently associated with evidence of fetal distress. For women with nephropathy, we begin weekly nonstress testing at 26 weeks' gestation and twice-weekly testing at 34 weeks, earlier if there is growth retardation. Vaginal delivery is acceptable if there is no evidence of fetal distress and no obstetric contraindication. However, in the recent series in table 37-4, there was a remarkable 72% cesarean rate, the reasons for which are not entirely elucidated.

Perinatal mortality in the pooled series was remarkably low. Four of the seven deaths in table 37-4 were due to major malformations and the other three were stillbirths associated with severe fetal growth retardation. Perinatal and neonatal care have improved substantially in recent years. There were no neonatal deaths despite the observation that more than half the deliveries were preterm and nearly one-fourth were before 34 weeks' gestation.

4. EFFECT OF PREGNANCY ON THE NATURAL HISTORY OF DIABETIC NEPHROPATHY

For years, there has been a hypothetical concern that the physiologic hyperfiltration of pregnancy might damage the glomeruli and accelerate the progression of nephropathy to end-stage renal disease. In part, this was the basis for counselling women with nephropathy to avoid pregnancy. However, the few data available that directly address this hypothesis do not support it. Two studies assessed renal function after pregnancy in women with nephropathy [16,28]. Both found that creatinine clearance declined an average of about 10 ml/min per year, no different than the average rate in pooled series of men and women with diabetic nephropathy without pregnancy [29].

With or without pregnancy, nephropathy generally progresses to end-stage renal disease in about a decade [30]. The speed of progression to end-stage disease is little or no different whether a pregnancy is terminated in the first trimester or carried into the third trimester [16]. With end-stage disease, the 7-year survival averages less than 20% [31], although most deaths are caused by ischemic heart disease rather than nephropathy directly. Mølsted-Pedersen noted that 9 of 41 mothers with nephropathy (22%) were dead within eight years of delivery [32]. It has been argued that this grim prognosis alone is reason to counsel these women to avoid pregnancy [33]. However, we believe that this choice is properly left to the patient and her

partner, provided that they have had frank counselling about the nature history of the disease.

5. PREGNANCY AFTER RENAL TRANSPLANTATION

Ogburn et al. compiled the experience of nine women who had pregnancy after renal transplantation for diabetic nephropathy [34]. All were managed with prednisone and azathioprine. No transplant rejections occurred during pregnancy. Complications were frequent, including preeclampsia in six, fetal distress in six, and preterm delivery in all. One mother died; she was reported to be noncompliant, had significant peripheral vascular disease and foot ulcers, and died at 21 weeks' gestation with pulmonary edema of unclear etiology.

There has been hypothetical concern that pregnancy may adversely affect renal graft survival. However, two recent studies with long-term follow-up found no difference in graft survival or function between women who became pregnant and matched controls who did not [35,36].

6. UNANSWERED QUESTIONS

Recent trials involving women with a variety of risk factors for preeclampsia or intrauterine growth retardation have suggested that these complications may be prevented with low-dose aspirin starting in the mid-to-late second trimester [37]. The theoretical rationale for this treatment is that aspirin may reverse the unfavourable thromboxane/prostacyclin ratio associated with preeclampsia [38]. However, these trials have not specifically studied women with diabetes or diabetic nephropathy and it is not clear whether the preeclampsia associated with nephropathy is related to an abnormal thromboxane/prostacyclin ratio. Further, one recent study found an increased rate of placental abruption with aspirin therapy [39]. The National Institutes of Health (USA) Maternal-Fetal Medicine Units Network is currently conducting a placebo-controlled trial of aspirin for pregnant diabetic women. Until the results of this trial are available, we are not recommending low-dose aspirin therapy to women with nephropathy.

Many diabetic women without nephropathy develop significant proteinuria during pregnancy, without associated hypertension or altered creatinine clearance. Because most of these women were not studied before pregnancy, it is not clear how many of them had incipient nephropathy or microalbuminuria prior to pregnancy. Long-term follow-up studies are clearly needed to understand whether the apparent »benign« proteinuria of pregnancy is a marker for increased risk of overt nephropathy in later life.

The appearance of significant proteinuria during pregnancy may be an indication for antihypertensive treatment, regardless of blood pressure. We currently use

diltiazem for this indication after the first trimester. The efficacy of this treatment needs to be evaluated prospectively.

The interaction of pregnancy with incipient nephropathy needs to be studied prospectively. It is plausible, for example, that the physiologic hyperfiltration of pregnancy might accelerate the progression from incipient to overt disease. Two series found that diabetic women with small degrees of proteinuria in early pregnancy were at increased risk for preeclampsia [40]. Long-term, controlled follow-up studies are needed to assess the rate of progression from incipient to overt nephropathy after pregnancy.

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38. URINARY TRACT INFECTION AND DIABETES: DIAGNOSIS AND TREATMENT

RENÉ VEJLSGAARD

From autopsy studies, it has been shown that infections of the urinary tract are 3-4 times more common in diabetic patients than in non-diabetic patients. This claim has been questioned in the controlled clinical studies of recent years in which quantitative bacterial culture from urine has been used in evaluating the results. Usually, these studies have not disclosed significant differences, but they have shown much variation in material, methods, and results. A review on these problems has been given by Vejlsgaard [1].

In an unselected out-patient material - 269 diabetic patients and a strictly comparable group of 260 non-diabetic patients - the following results were found:

1. Of the diabetic patients, 9.3% had bacteriuria with more than 10^5 colonyforming units (CFU) per ml urine, as compared with 4.5% of non-diabetics. The difference was not significant, but close to the 5% level.
2. When the sexes were considered separately, 0.7% of the men had more than 10^5 CFU/ml urine. In the non-diabetic group, 2.1% had a bacteriuria with more than 10^5 CFU/ml urine.

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3. In the case of the women, 18.8% had more than 10^5 CFU/ml urine. In contrast, 7.9% of the non-diabetics had more than 10^5 CFU/ml urine. This difference was significant.
4. Bacteriuria appeared to have no relation to increasing age.
5. Of the patients with bacteriuria, 33% were asymptomatic.
6. It was confirmed that catheterization was performed more frequently in diabetic patients than in non-diabetic patients, but there did not appear to be any relationship between previous instrumental manipulations of the urinary tract and significant bacteriuria.
7. A statistical relationship has been demonstrated between significant bacteriuria, anemia and hypersedimentation.
8. No correlation was found between significant bacteriuria and parity, arterial hypertension, or the degree of glycosuria.

The conclusion is that the classic claim of an increased incidence of urinary infection in diabetes, as judged by significant bacteriuria, holds for women suffering from diabetes, but the pathogenesis is obscure. A few of these observations have been confirmed later [2].

In a further study [3] it has also been shown that:

9. Urinary infections cannot with certainty be correlated with increasing duration of diabetes.
10. The incidence of urinary infections increases significantly as retinopathy becomes severer.
11. Urinary infections cannot be correlated with diabetic nephropathy or with diabetic neuropathy. This could be explained by the inadequate criteria employed for these diseases in the investigation mentioned.
12. The incidence of urinary infections increases with increasing heart disease, coronary sclerosis and peripheral vascular disease.
13. The severity of diabetes as evaluated by insulin requirements, appears to have no bearing on the incidence of urinary infections.
14. It appears from Vejlsgaard's studies that urinary infections cannot be correlated with diabetes mellitus per se, but his study suggests that diabetic vascular disease is a contributory factor in the development of urinary infections in diabetic patients.

Since the pioneering work of Kass [4] improved the diagnosis of urinary tract infections, it has also been demonstrated that infections in pregnant women are much more common than in non-pregnant women.

There are few and contradictory investigations available on the occurrence of significant bacteriuria in pregnant diabetics. Only a single study has dealt with it in diabetic pregnant women compared with comparable controls [5,6]. In this study, the occurrence of significant bacteriuria ($> 10^5$ CFU/ml urine) has been investigated in 132 pregnant diabetics, who were followed throughout pregnancy and matched to three well-defined control groups of, respectively, 132 non-pregnant diabetics, 132 pregnant non-diabetics, and 132 non-pregnant non-diabetics. The matching criteria have been age, duration of diabetes, parity and gestational age at the time of the investigation. The results were as follows:

1. Significant bacteriuria occurred significantly more frequently in pregnant diabetics than in pregnant non-diabetics (18.2% vs 4.5%).
2. Significant bacteriuria did not occur more frequently in pregnant diabetics than in non-pregnant diabetics (18.2% vs 11.4%).
3. *Escherichia coli* was the most frequently isolated bacterial species in all groups.
4. The occurrence of urinary infection could not be correlated to increasing age.
5. On the other hand there was a significantly increasing incidence of urinary infections in patients with duration of diabetes.
6. A statistically significant correlation was found between the presence of diabetic angiopathy, expressed as the occurrence of diabetic retinopathy, and the incidence of urinary infection. No attempt was made to correlate the incidence of significant bacteriuria to other forms of angiopathy, as the material was too small and the criteria inadequate.
7. Urinary infections occurred with significantly greater incidence in White's groups D and F than in A, B, and C.
8. Of the cases with demonstrated urinary infection 62.5% were asymptomatic and ran an asymptomatic course throughout pregnancy.
9. Approximately 25% of the patients with dysuria and pollakisuria did not have significant bacteriuria.

1. DIAGNOSIS

Although recent analyses of cost effectiveness have supported the approach done by many clinicians who do not obtain urine cultures, but only to rely on clinical signs and urine microscopy and/or dipsticks for nitrite and leucocyte esterase activity, it is mandatory to examine quantitative bacterial culture in diabetic patients because of the high incidence of asymptomatic infections. This is useful in preventing morbidity related to angiopathy. Pregnant diabetics especially should be screened for bacteriuria because failure to identify and treat an infected pregnant woman places her at increased risk of acute pyelonephritis and enhances the likehood of premature birth.

Besides affording a diagnosis, isolation of the infecting pathogen and performance of antimicrobial susceptibility testing ensures the provision of specific therapy. A midstream urine specimen must be obtained for culture. If it is not possible to inoculate the urine onto relevant media within 30 min, it must be refrigerated, until it can be cultured. If this is not possible, a »dip slide« method can be used to both transport and screen for significant bacteriuria, which may be defined as the presence in two consecutive urine samples of $>10^5$ CFU/ml of a single bacterial strain. This laboratory definition of a common clinical infection provides a uniquely powerful, epidemiological tool. Using this, we may in most cases determinate who has an infection may require treatment.

2. ANTIMICROBIAL TREATMENT

Discussion of the correct antimicrobial treatment for a patient with urinary tract infection presupposes the acknowledgement that infection of the urinary tract is not a homogeneous disease. For example a very good cure rate (80% - 90%) is common in the dysuria frequency syndrome associated with significant bacteriuria. In contrast the response is particularly bad in patients confined to the bed with diabetes, infected with resistant organisms and having indwelling catheters.

3. DYSURIA FREQUENCY SYNDROME

It should be stressed that it now becomes apparent that less than 50% of these would have a positive culture with normal bacteria, and that they should also be examined for *Neisseria gonorrhoea*, *Chlamydia trachomatis*, and *Candida albicans*. They should receive treatment to guard against these strains. Still other factors (soap, vitamin C, etc.) are a main cause of the urethral syndrome.

4. LOWER URINARY TRACT INFECTION

These infections are usually easily eradicated, unless there is some local defect, and the bacteriuria can be eradicated by any antibiotic that achieves high urinary levels and is active against the infecting organism. The choice will often be a sulphonamide with a short half-life, administered for 6 days (1 gram twice daily). Actually there are now attempts to treat patients with a single, large dose of antibiotic. Sulphonamides (e. g. amoxicillin) have been used to treat young (even pregnant) women with their first acute episode of urinary tract infection with an acceptable cure rate.

This kind of treatment has not been attempted in diabetics. Studies are needed in this very important therapeutic practice.

5. UPPER URINARY TRACT INFECTION

This means most often acute pyelonephritis. Here the concentration of antibiotics in tissue may be more important than the concentration in urine. Ampicillin seems to fulfil this criterion. It seems that at least 2 weeks treatment is necessary for a good cure rate. Administration of 0.5 g ampicillin three times a day for 2 weeks could be recommended.

6. CHRONIC URINARY TRACT INFECTIONS

These are common in diabetics and often due to abnormalities of bladder emptying etc. These infections should always be treated according to the organisms isolated and their susceptibility. Prophylaxis with antibiotics have been used in such cases. Long term, low dosage profylaxis given nightly or after sexual intercourse prevents symptomatic recurrences. Low-dosage prophylactic treatment has also been shown to prevent clinical episodes of infection in children with recurrent, symptomatic infections, and it may prevent kidney damage in children in whom infections are associated with vesicoureteral reflux.

Drugs as nitrofurantoin (1 mg/kg) and trimetoprim (100 mg/kg) have been used. There have been no reports published about the use of such drugs in treating diabetics, but it could be recommended.

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39. ACUTE RENAL FAILURE IN DIABETICS

ANA GRENFELL

Acute renal failure in the patient with diabetes is uncommon [1] and has the same aetiology as in the non-diabetic. However, certain situations such as hypovolaemia and sepsis which may lead to acute renal failure occur more frequently in the diabetic patient. In addition the high prevalence of chronic renal disease make the diabetic particularly susceptible to the development of acute renal failure.

This chapter reviews those conditions most commonly leading to acute renal failure in the diabetic patient (table 39-1), together with their management and prevention. The specific problems of acute renal failure and dialysis in the diabetic will also be considered.

SEVERE HYPERGLYCAEMIA

Hyperglycaemic hyperosmolar nonketotic coma

Hyperglycaemic hyperosmolar nonketotic coma accounts for 10%-33% of »diabetic comas« and typically occurs in elderly or middle-aged patients who either are not known to have diabetes or have non-insulin dependent diabetes. On admission the

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Table 39-1. Common causes of acute renal failure in diabetics

1.	Severe hyperglycaemia
	a. Hyperglycaemic hyperosmolar »coma«
	b. Diabetic ketoacidosis
2.	Septicaemia
3.	Radiocontrast media
4.	Drugs
5.	Renal papillary necrosis
6.	Glomerulonephritis

blood glucose is usually very high, the majority are severely dehydrated and up to 30% may be hypotensive [2-4].

Acute renal failure may complicate this picture either as a result of the initial severe dehydration and hypovolaemia or as a consequence of inappropriate or inadequate treatment [3,5]. More rarely it may result from rhabdomyolysis which occurs in hyperosmolar states relatively commonly [6,7].

The management of hyperglycaemic hyperosmolar nonketotic coma may itself lead to cardiovascular collapse and acute renal failure. Appropriate fluid replacement is vital. These patients are severely dehydrated and yet their increased age, the likelihood of cardiac disease, and impaired renal function make fluid replacement hazardous.

Initially rapid fluid replacement is essential to restore blood pressure, tissue perfusion and urine output so as to avoid cardiovascular collapse and acute renal failure. Later caution is required as over treatment may lead to pulmonary and cerebral oedema [8]. The aim should be to restore about half the calculated fluid deficit in the first 12 hours. Frequent careful reassessment of fluid balance is necessary for successful management. Monitoring of central venous pressure and even pulmonary arterial wedge pressure provides a useful if not essential guide to fluid replacement.

The type of fluid infused remains controversial. Hypotonic saline (0.45%) is recommended by some in all cases [5], whereas others recommend isotonic saline (0.9%) [3,5,9], while yet others recommend colloid [10]. There is a case for initiating treatment with isotonic saline [5,9]. Even though the patient may be severely hypertonic, hypovolaemic shock is the immediate threat to life. Hypotonic saline will not restore intravascular volume rapidly enough since most of the fluid

infused will pass into the intracellular space exacerbating hypovolaemia and increasing the risk of pulmonary and cerebral oedema [8].

The restoration of renal perfusion and urine flow allows glucose to be excreted, and the blood glucose will fall even without insulin [11]. The associated fall in osmolality more than corrects for any increase in serum sodium that is commonly seen in the early course of treatment even if 0.45 % saline is used. The rise in serum sodium reflects the movement of fluid from the extracellular to the intracellular space and is important in preventing too rapid a fall in plasma osmolality and therefore circulating volume. Several authors have reported the development of hypotension, shock and oliguria occurring after the onset of treatment [3,8,12].

If oliguria persists despite adequate replacement of the salt and water deficit and restoration of blood pressure, a trial of a loop diuretic (frusemide 1-3 mg/min i.v.) together with a low dose dopamine infusion (0.5-3.0 μg/kg/min) should be undertaken. The persistence of oliguria despite these measures calls for great care in further fluid administration with reassessment of fluid balance and the need for dialysis.

Rhabdomyolysis, although a rare cause of acute renal failure in hyperglycaemic nonketotic coma, may be a more common complication of hyperosmolar states than has been appreciated [7]. It is often asymptomatic and myoglobin is rarely found in the urine [6,7]. Serum creatinine phosphokinase is the best test and is markedly elevated. Early diagnosis and appropriate management will reduce morbidity and mortality. Treatment with continuous haemofiltration or haemodiafiltration is the best form of dialysis therapy when renal failure is complicated by hyperosmolarity and hypernatraemia.

To summarise, hyperglycaemic hyperosmolar nonketotic coma may lead to acute renal failure either as a result of the initial severe dehydration and hypovolaemia or as a result of inappropriate therapy or more rarely as a result of rhabdomyolysis. Prevention depends on early diagnosis, early initiation of treatment and careful attention to fluid and insulin therapy.

Diabetic ketoacidosis

Acute renal failure is a rare complication of diabetic ketoacidosis [13]. Although fluid deficits of 5-7 litres are not uncommon, the development of ketosis causes patients to present earlier than those in hyperglycaemic hyperosmolar »coma« and thus dehydration is less severe and hypotension less common. The presence of underlying renal disease may be necessary for the development of acute renal failure in these circumstances although acute tubular necrosis (ATN) has been reported in renal biopsies from uncomplicated cases of ketoacidosis [14]. Rhabdomyolysis may also occur as in hyperosmolar non-ketotic coma and lead to acute renal failure.

The management of diabetic ketoacidosis is usually straight forward and has been reviewed by several authors [9,15,16]. The prevention of acute renal failure lies in the prompt initiation of treatment and the adequate replacement of fluid deficits. Similar arguments prevail for the use of isotonic saline as in hyperglycaemic hyperosmolar nonketotic »coma«. If acute renal failure should develop, dialysis should be initiated early since hyperglycaemia, hyperkalaemia and acidosis are difficult to manage in the oliguric patient.

SEPTICAEMIA

Sepsis greatly increases the risk of developing acute renal failure [1,17,18]. Not only can it result in acute renal failure but is also an important determinant of survival, being the major cause of death in patients with acute renal failure from any cause [19].

The pathophysiology is poorly understood but acute renal failure develops against a background of systemic hypotension. Bacterial endotoxin causes release of numerous host mediators including tumour necrosis factor, interleukins and platelet-activating factor which have a direct effect on target tissues as well as activating secondary events to cause a complex interaction of various vasoactive systems. This results in endothelial damage, severe hypotension, intense renal vasoconstriction, and disseminated intravascular coagulation resulting in acute renal failure [20,21]. Diabetic patients are particularly prone to septicaemia especially in association with urinary tract infections. This may lead to acute on chronic renal failure in patients with underlying renal disease such as renal papillary necrosis or diabetic nephropathy. In the absence of these conditions pyelonephritis is a rare cause of acute renal failure.

RADIOCONTRAST-INDUCED RENAL FAILURE

Impairment of renal function following exposure to radiographic contrast media is an uncommon but important cause of acute renal failure, and may account for over 10% of hospital-acquired cases [22]. Diabetic patients in particular are likely to require contrast for angiographic investigations due to their high prevalence of vascular disease. (A more detailed account of this entity appears in Chapter 40).

Even the newest low osmolarity contrast agents are associated with a risk of renal dysfunction [23], although there is disagreement as to whether this is similar to [24] or less than with the high osmolarity agents [25]. The reported incidence varies greatly ranging from 2-5% in low risk patients to 9-16% in high risk patients [24,26,27]. More recent studies suggest that contrast nephrotoxicity may be less common than previously reported [27]. This may reflect methodological differences but also a greater awareness of the problem resulting in a reluctance to order

radiocontrast studies in high risk patients as well as more attention to pre-salination. Renal damage however, may occur despite attention to these details, but most studies confirm that the occurrence of adverse renal effects with contrast agents greatly depends upon the patients underlying condition.

High risk patients include those with pre-existing renal impairment, diabetes, myeloma, dehydration, or congestive cardiac failure; conditions which often co-exist [27,28]. Renal impairment is the most important with over 60% of reported cases occurring in patients with renal insufficiency [24,26-30]. Diabetes mellitus is another important group and probably reflects underlying diabetic nephropathy with sclerosis of the renal vasculature. In some series over 50% of cases have been those with diabetes and renal impairment [28,31,32]. Diabetic patients without renal impairment appear to be at low risk [26,27], although it seems that at any given level of renal impairment the diabetic patient is more likely to experience contrast induced renal failure than the non-diabetic [26,32]. Other risk factors for the development of contrast nephropathy in uraemic diabetic patients appear to include the quantity of dye used and low arterial pressure [33].

The mechanism of renal damage remains uncertain but may involve direct tubular toxicity, ischaemia due to the intense vasoconstriction that follows the initial transient vasodilatation, endothelial damage or intratubular obstruction [27]. Animal models suggest the haemodynamic model may be the most important [34,35] but all may contribute [27]. Irreversible acute renal failure with a more insidious onset may occur less commonly after arteriography as a result of cholesterol emboli resulting from vascular trauma due to catherisation [36].

Typically contrast-induced acute renal failure is mild, reversible and of short duration. Serum creatinine levels start to rise within 24 hours, peak at 3-5 days and return to normal within 7-10 days [33]. Oliguria is relatively common, and when marked is a poor prognostic sign as it is often associated with an irreversible decline in renal function. Short term dialysis may be required and a small percentage of patients go on to require chronic dialysis.

The prevention of contrast-induced renal failure can be achieved by careful selection of patients, avoiding all but the really necessary investigations involving contrast agents in diabetics with renal impairment. As low a dose as possible (<30 ml) of a low osmolarity contrast agent should be used. Dehydration before the investigation should be avoided as this seems to increase the risk and severity of acute renal failure. Animal experiments suggest that radiocontrast injury may be prevented by reducing the demand for oxygen for active tubule transport as well as by improving medullary blood flow [35,37]. Both these can be achieved by pre-hydration with saline and the used of frusemide or perhaps mannitol, measures that have been shown to reduce the incidence of contrast nephropathy in both animals

and man [38,39]. Concomitant use of other potentially nephrotoxic agents such as non-steroidal anti-inflammatory agents or aminoglycoside antibiotics should be avoided.

DRUGS

Drugs are an important cause of acute renal failure. Three main groups probably contribute to the majority of cases and are of particular relevance to diabetic patients.

Angiotensin converting enzyme inhibitors

The greatly increased use of angiotensin converting enzyme inhibitors (ACE-inhibitors) in the treatment of hypertension and cardiac failure has meant that these drugs have become increasingly important as a cause of acute renal failure [1,40]. The suggestion that ACE-inhibitors may have a specific role in the prevention of diabetic nephropathy has led to their widespread use in such patients who commonly have co-existent atherosclerotic renovascular disease and are therefore particularly susceptible to the development of acute renal failure.

Angiotensin converting enzyme inhibitors act to inhibit the conversion of angiotensin I to angiotensin II (A II). Their potential to cause renal failure reflects the role of A II in limiting falls in systemic blood pressure as well as the effect of A II to increase glomerular efferent arteriolar tone and so preserve glomerular filtration rate (GFR) at low renal perfusion pressure. The importance of the former is shown by the dramatic fall in blood pressure that may occur when ACE-inhibitors are prescribed to patients with low cardiac output or reduced circulatory volume. The importance of the latter is shown by the severe but usually reversible fall in GFR when ACE-inhibitors are used in patients with renovascular disease [41]. Acute renal failure may however occur in the absence of renal artery stenosis especially in the presence of volume depletion, cardiac failure, chronic renal insufficiency, diabetes mellitus and combined therapy with non-steroidal anti-inflammatory drugs [42].

Non-steroidal anti-inflammatory drugs (NSAIDs)

The increasing use of these drugs has meant that they now account for up to one third of all drug induced cases of acute renal failure. The renal production of prostoglandins is important in the maintenance of renal circulatory homeostasis under conditions of circulatory compromise such as cardiac failure or dehydration. Under these circumstances inhibition of prostoglandin synthesis by NSAIDs results in a fall in GFR and will exacerbate existing pre-renal failure and/or predispose the kidney to ischaemic damage [43].

Acute renal failure may also develop with the use of NSAIDs as a result of acute interstitial nephritis [43,44]. This idiosyncratic immunological response may be caused by a variety of drugs the commonest being NSAIDs and antibiotics.

Antibiotics

These are among the most common drugs to cause acute renal failure. The aminoglycosides are probably the most important [22,46] and exert a direct toxic effect on the renal tubules. Toxicity is dose related and more common in the elderly, those patients who are salt and water depleted and in those with pre-existent renal disease [45,46]. Gram negative sepsis or more specifically renal hypoperfusion and ischaemia predispose to aminoglycoside induced acute renal failure. The fact that diabetic patients are particularly prone to sepsis and commonly have a background of chronic renal disease means that such agents must be used with attention to dosage in relation to GFR and frequent monitoring of drug levels. Particular care needs to be exercised in the sick patient who may be taking other nephrotoxic drugs.

RENAL PAPILLARY NECROSIS

Renal papillary necrosis occurs in association with certain conditions, the most important being diabetes mellitus, pyelonephritis, urinary tract obstruction, sickle-cell anaemia and analgesic abuse [47]. Some of these conditions commonly coexist in patients with diabetes [48] who may also have vesicoureteric reflux secondary to poor bladder emptying due to autonomic neuropathy [47]. The frequency of renal papillary necrosis is not known as it is often asymptomatic but diabetes has been reported in about 30% of cases [47,49]. The prevalence in patients with insulin-dependent diabetes has been reported from autopsy studies as about 5%. This however, may be an underestimate as suggested by an in vivo study using intravenous urography which reported a prevalence of renal papillary necrosis of nearly 24% in long standing insulin-dependent diabetic patients [50]. Focal or diffuse necrosis of the renal medulla occurs, usually involving the papillae, secondary to a compromise of the renal medullary circulation.

Clinically it may present as an overwhelming illness with acute renal failure, severe septicaemia and death, or as an asymptomatic finding. More commonly it has a chronic course over months to years with superimposed acute symptoms. Oliguria complicating pyelonephritis in a diabetic patient may be due to obstruction by necrotic papillae.

Intravenous pyelography is the most reliable method of making the diagnosis [51]. However, ultrasound may indicate obstruction and loss of renal medullary tissue and should be performed first.

Treatment in the majority of cases is straightforward with antibiotics for infection and the maintenance of urine flow. However, in cases with a fulminant course and the development of acute renal failure, intensive care is required with dialysis and the treatment of septicaemia.

NON-DIABETIC RENAL DISEASE

Non-diabetic renal disease other than that due to diabetic glomerulosclerosis may occur in diabetic patients and may present as acute renal failure [52-54]. Chronic renal disease due to non-diabetic causes occurs in about 3% of insulin-dependent diabetic patients with proteinuria [55] but is much more common in patients with non-insulin dependent diabetes [56,57]. A higher percentage is reported in renal biopsy series as patients with unusual clinical features tend to be biopsied preferentially [52,53]. Glomerular disease presenting as acute renal failure is known as rapidly progressive glomerulonephritis and includes such causes as the microscopic vasculitides, Wegener's granulomatosis, microscopic polyarteritis, autoimmune disease such as systemic lupus erythematosis and post infectious causes such as haemolytic uraemic syndrome and post-streptococcal glomerulonephritis.

The correct diagnosis of the underlying lesion is important and the possibility of non-diabetic renal disease should not be forgotten. Unusual clinical features that suggest such a diagnosis include rapid deterioration of renal function, the absence of retinopathy (especially in Type 1 patients), the sudden development of the nephrotic syndrome, and the development of renal failure in a patient with Type 1 diabetes of short duration (< 5 years). If acute glomerulonephritis is suspected or the diagnosis is in question a renal biopsy should be performed as this will aid the diagnosis and indicate the prognosis for renal recovery and so provide a guide to appropriate therapy.

Acute renal failure may require dialysis but more specific treatments with steroids, immunosuppressive agents, plasmaphoresis, anticoagulants etc may result in considerable improvement and so remove the need for dialysis.

MANAGEMENT OF THE DIABETIC WITH ACUTE RENAL FAILURE

The management of the diabetic with acute renal failure is in essence the same as for the non-diabetic, but may pose additional problems related to the diabetic state. These relate to the problems of blood glucose control, and dialysis of the uraemic diabetic.

Metabolic control

Although uraemia is commonly associated with carbohydrate intolerance, hypoglycaemia and reduced insulin requirements are common in diabetic patients with

chronic renal failure [58,59]. Anorexia and vomiting reduce carbohydrate intake. Renal metabolism of insulin is decreased by about 50-70% and urinary excretion of insulin is reduced as GFR decreases resulting in higher plasma insulin levels [60]. Insulin requirements in diabetic patients who develop acute renal failure are usually reduced [61,62] and hypoglycaemia may be a problem. However, septic catabolic patient may require more insulin due to increased insulin resistance.

Potassium

Hyperkalaemia is a common problem in acute renal failure especially in hypercatabolic patients. In diabetic patients the situation may be complex. In both ketoacidosis and hyperosmolar »coma« total body potassium is depleted and needs to be replaced. If acute renal failure develops, however, potassium supplementation should be stopped. In addition the use of glucose an insulin infusions in the diabetic will cause potassium levels to fall.

Haemodialysis

The results of chronic haemodialysis in diabetic patients have until recently been poor, in part due to technical problems and in part due to the progression of diabetic complications. In recent years results have improved considerably and the experience so gained is pertinent to the management of diabetics with acute renal failure.

Vascular access in diabetic patients may be a problem due to widespread arteriosclerosis and vascular calcification especially in those with diabetic nephropathy. Ischaemic pain and gangrene may occur in the digits of the limb containing a fistula, graft or shunt. It is therefore important to avoid cannulation of peripheral vessels and use the internal jugular or subclavian route for acute dialysis so preserving peripheral vessels for future access in those who do not recover renal function.

Rapid fluid shifts associated with haemodialysis are not well tolerated by diabetic patients and severe hypotension may develop especially in those with autonomic neuropathy. Continuous haemofiltration or haemodiafiltration may be more suitable.

The progression of retinopathy has always been of concern when treating diabetic patients with haemodialysis. In the past deterioration of vision due to vitreous haemorrhage was relatively common and attributed to the use of heparin. Advances in the treatment of diabetic retinopathy and better management of hypertension and fluid overload have considerably reduced the problem despite the continued use of anticoagulants.

Peritoneal dialysis

The use of peritoneal dialysis to treat chronic renal failure in the diabetic patient has increased considerably and is now first line treatment in many centres. It may be used successfully to treat acute renal failure but technical problems are common and the fact that the majority of patients are hypercatabolic makes peritoneal dialysis unsuitable in most cases except as a temporary measure when haemodialysis or haemodiafiltration are not immediately available.

CONCLUSIONS

Acute renal failure in the diabetic occurs as a result of certain specific conditions. The most common are severe hyperglycaemia, septicaemia, the use of radio-contrast media and certain drugs. The management of the diabetic patient with acute renal failure is essentially the same as for non-diabetic patients but may be complicated by the problems of metabolic control, vascular access, and vascular instability. The overall mortality from acute renal failure in these settings may be as high as 50% [1,18,19]. Prevention is important as the development of acute renal failure adds considerably to morbidity and mortality and is often avoidable.

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40. CONTRAST MEDIA-INDUCED NEPHROPATHY IN DIABETIC RENAL DISEASE

INDRA D. DANIELS, ELI A. FRIEDMAN

Diabetes mellitus has been incriminated as a risk factor for radiocontrast-induced nephropathy (CIN) since the 1960's [39]. Two decades later, the precise risk to the diabetic kidney is still debated with incidence rates ranging from less than 1% to over 30% [31,50,52], especially when complicated by chronic renal failure (CRF). Almost 100% of diabetics with a serum creatinine level (SCr) greater than 400 μmol/l (4.5 mg/dl) can develop CIN after contrast exposure [22,52]. Dialysis is needed in 25-50% of all patients who develop CIN [23,29,49] but in 40-50% of diabetics [16,54], a few permanently [54]. Few studies are confined to diabetic patients and most do not report on diabetic subtypes yet differences in outlook between older and younger diabetics and various subtypes of diabetes almost certainly exist - perhaps Type II diabetic patients are less likely to develop CIN than type 1 patients [22,46]. Methodologic differences between studies and variability in contrast dosages exist. Diagnostic increases in SCr vary between 20% [26] and 50% [12,19,37] over baseline, whereas absolute increases may be as little as 26 μmol/l (0.3 mg/dl) [26] or as liberal as 177 μmol/l (2.0 mg/dl) [8,9]. A rise in SCr of at

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least 50% [12,19,38] or 88 μmol/l (1 mg/dl) [14,19,22,51,52,54] within 48 hours of contrast administration seems acceptable. Furthermore, the applicability of »low osmolality« or »nonionic« radiocontrast materials to the diabetic kidney is unclear. These issues will be addressed in this chapter.

INCIDENCE OF CONTRAST NEPHROPATHY FOLLOWING EXPOSURE TO HIGH OSMOLALITY CONTRAST MEDIA

Retrospective uncontrolled studies with small patient populations suggested that diabetic patients with SCr of 135-400 μmol/l (1.5-4.5 mg/dl) have 2-3 times the risk of CIN compared with non-diabetics [16,52]. Diabetics with SCr more than 354 μmol/L (4 mg/dl) had a 45-95% incidence of CIN [9,16,22,52,54] of whom 50% required temporary or permanent dialysis [22,52,54].

An early report noted that 8 diabetics who developed oliguric CIN [16] after intravenous pyelography had long-standing diabetes with complications. Two patients of 8 had baseline SCr greater than 530 μmol/L (6 mg/dl) and developed end-stage renal disease. Others noted a 76% incidence of CIN in diabetics with concentrations of 177-442 μmol/l (2.0 - 4.5 mg/dl) and a 95% incidence in patients with CRF [22]. A retrospective review of 377 contrast procedures [52] identified 12 diabetics: 58% developed CIN, but only 1 of 12 patients had a SCr over 400 μmol/l (4.5 mg/dl).

Identical diagnostic criteria revealed that 12 of 13 Type II diabetics developed CIN after cardiac catheterization [54]. All 12 patients had CRF; 3 of the 12 patients (25%) had received more than one contrast injection. The patient with preserved renal function received the lowest volume of contrast material.

A retrospective analysis of twenty-eight possible risk factors in 266 patients exposed to contrast material showed that CRF increased the risk of CIN by 6.6 times, while diabetes tripled the risk - however, only 11 diabetic subjects were included [11]. Diabetes was not a risk factor for CIN in almost 400 patients undergoing peripheral angiography, although prior CRF was [21].

The relative contribution of CRF and diabetes could not be dissected from retrospective reports involving few patients. A recent retrospective study of 394 patients undergoing femoral arteriography revealed a significant increase in the incidence of CIN in diabetic non-azotemic patients (16%) compared with non-diabetic non-azotemic patients (2%) [26]. However, diabetes was a significant risk factor among non-azotemics by only one of five criteria. Case-control analysis of 60 diabetic and 304 non-diabetic patients with variable renal function who underwent major arteriography [19] noted a 13% incidence of CIN among diabetics compared with 6% among non-diabetics. All patients who developed CIN had baseline SCr over 124 μmol/l (1.4 mg/dl) and CRF outweighed all other risk factors, including diabetes. Diabetes was a risk factor only in patients with normal renal function, but

so were contrast volume and age. A prospective study of 183 patients aged 70 years or older undergoing cardiac catheterization was undertaken [41]. Of these, 30 diabetic patients had a relative risk of 2.9 of CIN, but the combination of diabetes with CRF conferred a greater risk than either of the two factors alone.

Prospective studies indicate that diabetics without CRF have a similar incidence of CIN as non-diabetics with normal renal function [12,14,25,31,37,51] (table 40-1). Some are limited by inadequate patient numbers [44] or relatively few diabetic subjects [12,25,51], so their conclusions may be flawed. Notably, in 378 patients undergoing non-renal angiography, 108 patients of whom were diabetic, diabetes did not alter incidence of CIN in patients with normal renal function [14]. Another prospective analysis of CIN in diabetic patients [37], reported only a 9% incidence in diabetics with renal insufficiency and concluded that diabetic patients with SCr below 150 μmol/l (1.7 mg/dl) have little risk of CIN and that the incidence of CIN in diabetics with CRF is lower than previously reported. Recent studies comparing nephrotoxicity of various contrast agents (figure 40-1) suggest that diabetes per se is not a significant risk factor for CIN [34,46,50]. A large prospective evaluation of diabetic and non-diabetic patients exposed to contrast media needs to be undertaken.

In summary, there are additive risk factors for CIN including diabetes and CRF and there are insufficient data to conclude that diabetes is an independent risk factor or to conclude the magnitude of risk if indeed present.

NON-IONIC VERSUS IONIC RADIOCONTRAST AGENTS

Contrast media discussed thus far have been ionic monomers (figure 40-1) but low osmolar contrast agents (LOCA) (figure 40-1) are now available [1] and are *perceived* to be safer than high-osmolality agents (HOCA); they also cost 10-20 times the price of HOCA [3,17]!

Clinical trials comparing HOCA and LOCA have methodologic limitations such as small sample size, lack of control for other factors, and variable or short follow-up periods [48]. Neither type of agent protects against CIN in patients with normal renal function [48] although effects in patients with CRF or diabetes need to be elucidated.

A prospective trial [29] comparing 59 azotemic, insulin-dependent diabetics exposed to LOCA with a contemporaneous cohort of 24 patients who received no contrast showed that 50% of LOCA-treated patients had at least a 25% increase in serum creatinine. and 9 of 59 patients needed dialysis. Another report of 60 azotemic patients exposed to LOCA [49] showed that 9 of 60 (15%) patients developed CIN, but analysis of 22 clinical variables indicated that diabetes was not a risk factor.

Table 40-1. Incidence of contrast nephropathy in diabetic subjects exposed to high osmolality contrast agents - Prospective studies

Reference	Number of patients: diabetic/total	Definition of CIN: Increase in serum creatinine μmol/l (mg/dl)	Presence of preexisting renal insufficiency	Incidence in diabetics	Incidence in non-diabetics
Shafi [44]	12/40	25% &/or decrease CCr	Yes	11/12(92%)	17/28(61%)
Kumar [25]	24/100	>44(0.5)	No Yes	0/18(0%) 0/6(0%)	0/57(0%) 1/19(5%)
Teruel [51]	7/124	>88(1.0) or 25%	No Yes	1/6(17%) 1/1(100%)	14/100(14%) 11/20(55%)
D'Elia [14]	108/378	≥88(1.0)	No Yes	1/95(1%) 3/13(23%)	1/199(0.5%) 1/10(10%)
Mason [31]	34/120	25% decrease in CCr	No Yes	6/34(18%) _	23/64(36%) 8/22(36%)
Cramer [12]	11/193	≥50%	No Yes	0/11(0%) _	0/172(0.6%) 0/8(0%)
Parfrey [37]	119/214	>50% & >124(1.4)	No Yes	0/85(0%) 3/34(9%)	_ 4/101(4%)
		>25% & >124(1.4)	No Yes	2/85(2%) 3/34(9%)	_ 6/94(6%)
Moore [34]*	119/929	>33% Total and (0.4)	Total Yes	8/119(7%) 8/43(19%)	18/810(2%) 3/117(3%)

*Randomized clinical trial comparing high-osmolar with low osmolar agents, with similar incidences of contrast nephropathy in both groups.
CCr=Creatinine clearance

Several randomized clinical studies have suggested little or no difference between HOCA and LOCA [15,34,37,43,50]. Table 40-2 summarises results in major studies to date, although these have not focused on high-risk patients or on diabetics. One carefully designed study [43] had low statistical power to demonstrate a difference between HOCA and LOCA if a difference truly exists. Another study [34] showed that the frequency of CIN associated with either agent was low, about 3% even with a sensitive definition. Generally, IDDM was one of several variables associated with nephrotoxicity in both groups, but LOCA was not protective for

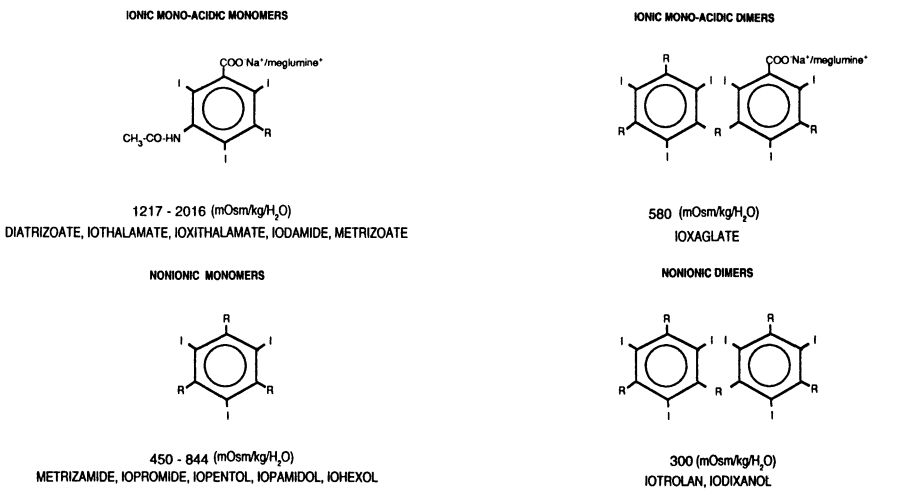

Figure 40-1. Generalized structural formulas for intravenous contrast agents with osmolalities and examples. (Adapted with permission from Spataro [47]).

diabetics, and the combination of diabetes and CRF markedly increased risk. Another study of patients (including 25 diabetics) with CRF [23] suggested that HOCA were more likely than LOCA to cause a mild CIN, although there were few cases of clinically significant CIN. In fact, another group [50] showed a statistically smaller rise in serum creatinine after *HOCA* injection but no difference in clinical nephrotoxicity.

Coincidentally, more diabetics were given LOCA in another trial [3] and multivariate analysis confirmed that CRF is predictive of the risk for CIN particularly in diabetics. The authors noted the low power to exclude a 50% reduction in incidence of CIN with LOCA.

There are several possible reasons why trials may not have shown a difference between LOCA and HOCA. A clinical difference may not exist; studies may not be sensitive enough to various risk factors to detect a clinical difference; or a real difference may exist but be so minor that the clinical relevance is minimal or nil. Pooled data from Barretts [3], Taliercio's [50] and Harris' [23] groups account for over 600 patients, and suggest that the relative risk of developing clinically important CIN after HOCA compared with LOCA is 2.27 [3]. On the other hand, a multidisciplinary working group has reported its appraisal of the literature [28]; they conclude that there is no evidence supporting differences in nephrotoxicity between HOCA and LOCA. At this time, there appears to be no clinically important

Table 40-2. Incidence of contrast nephropathy in diabetic patients given high-osmolality versus low-osmolality contrast agents

Reference	Number of patients: diabetics/ total	Definition CIN: Increase creat μmol/l (mg/dl)	Baseline creatinine μmol/l (mg/dl)	Incidence with HOCA	Incidence with LOCA
*Gomes [20]	99/364	50% and/or 88(1.0)	>121 (1.37)	20/202(10%)#	8/145(6%)#
Schwab [43]	90/443	≥44(0.5)	35-539 (0.5-6.1)	17% overall#	15% overall#
Moore [34]	218/929	>33% and 40(0.4)	130-310 (1.5-3.5)	IDDM: 7/58(-12.9%) NIDDM: 5/46(10.2%)	IDDM: 8/61-(12.7%) NIDDM: 6/53(11.1%)
Harris [23]	25/101	≥25%	120-210 (1.4-2.4)	3/9(33%)	0/16(0%)
Taliercio [50]	47/307	>50%	≥1.5	6/152(4%)#	3/155(2%)#
Barrett [3]	36/249	≥25%	<200(1.4) >200(1.4)	0/8(0%) 3/4(75%)	2/17(12%) 1/7(14%)

*All are randomized prospective studies except for Gomes' which is retrospective using historical controls.
All patients underwent coronary angiography.
#Statistics not provided for diabetic subgroup.

role for LOCA agents in prevention of contrast nephropathy, irrespective of patients' underlying renal function.

AGENTS USED IN MAGNETIC RESONANCE IMAGING

Concern has arisen over the possibility of nephrotoxic injury from paramagnetic contrast media used in magnetic resonance imaging (MRI). Gadolinium DOTA (Gadolinium 1,4,7,10 tetraazacyclo-dodecane tetraacetic acid) has been safely injected into over 3500 patients [4] but these results cannot be extrapolated to high-risk patients or to diabetics. Twenty patients with CRF who were randomized to receive MRI with or without contrast injection sustained no significant change in renal function at 48 hours after contrast exposure [4]. Another group followed 21 patients with CRF for five days after Gd-DOTA injection and reported no nephrotoxicity [36].

Metaanalysis of clinical trials using Gadolinium-DTPA (Gadolinium diethylene-triamine pentaacetic acid) has shown good renal tolerance [36] in 1200 patients with variable renal function at 24 hours post-procedure. Diabetes was not commented upon although 42 patients with baseline SCr >124 μmol/l (1.4 mg/dl) were included. Gadopentate dimeglumine has not exhibited nephrotoxicity in a trial involving over 1000 patients [43] but again, diabetes was not addressed. AMI 25, a new agent which has affinity for the reticuloendothelial system, has no demonstrable nephrotoxicity in animal studies, even at ten times the expected clinical dose for humans [6]. No histologic abnormalities occurred in 11 rat kidneys perfused with AMI 25, while 4 of 7 kidneys perfused with diatrizoate had findings consistent with acute tubular necrosis in a blinded histologic analysis [6].

One needs to remember that the volume of contrast injected in procedures using iodinated contrast media is 5-10 times higher than that used in MRI imaging.It is unclear how these agents would affect the diabetic nephron, as no such animal or human study is yet available.

PATHOPHYSIOLOGY

The reader is referred elsewhere [13,53] for detailed discussion of pathophysiology of CIN but suffice it to say that renal ischemia, intratubular precipitation of urinary proteins and direct toxic effects on renal tubular cells may be important and osmolarity is probably the underlying precipitant. Diabetics conceivably have various reasons to be prone to CIN: tubular hypermetabolism, diabetic microangiopathy affecting the kidney, abnormal erythrocyte rheology, factors promoting stasis in the microcirculation, and hyperglycemia itself.

The medullary thick ascending limb of Henle operates on the verge of hypoxia and is a target for ischemic injury during renal hypoperfusion, which may occur in CIN [5,24]. Increased activity of the sodium-potassium ATP-ase pump is potentially present in diabetics with CRF and may contribute to baseline medullary ischemia. Some suggest that decreased functioning renal mass in diabetic nephropathy leads to an augmented workload per remaining nephron (referred to as tubular hypermetabolism), intensifying regional hypoxia. However, a loss of renal mass in the diabetic patient cannot necessarily be implicated - diabetics may die of uremia without loss of renal mass, cortical thickness or a substantial amount of nephrons, and uninephrectomy does not potentiate CIN in diabetic rats [45].

Arteriosclerosis of afferent and efferent glomerular arterioles in diabetic kidneys and thickening of capillary basement membranes possibly contribute to baseline cell ischemia. Hyaline deposition in the afferent arteriole may interact with basement membrane changes to increase vascular resistance. Diabetic microangiopathy affecting the kidney and peculiar to the diabetic state occurs [32,33] and is

distinguishable from atherosclerosis occurring in diabetics. Arteriolar changes are similar to those in hypertension although patchier, and involve mainly small arterioles which lack an internal elastic lamina, while hypertension affects somewhat larger arterioles.

Abnormal red blood cell rheology is demonstrable in diabetics with accumulation of glycosylated end products in erythrocytes which impair deformability decrease in renal microcirculatory blood flow [7]. Glycosylated hemoglobin is increased to more than twice its normal value in diabetics accounting for ten per cent of total erythrocyte hemoglobin, and has an increased affinity for oxygen. Unless blood flow is increased, tissue oxygen tension is lowered, further supporting ischemic conditions. Elevation of 2,3-diphosphoglycerate (2,3-DPG), an intraerythrocyte metabolic product, does occur and opposes the impairment of oxygen release due to increased glycosylated hemoglobin. It may inhibit platelet aggregation and is known to be higher in diabetics with vascular complications, but may not be sufficiently protective.

Hyperviscosity of blood may promote stasis in capillary and postcapillary venules resulting in hypoxia and formation of microthrombi [32], particularly upon contrast exposure [42]. Abnormal platelet aggregation perhaps contributes to macro- and microangiopathy [32] and may even result from contrast exposure. Hyperglycemia per se may predispose to CIN [45].

PREVENTION

Intravenous fluid, diuretics, prophylactic dialysis and pharmacologic manoeuvres appear unhelpful in preventing CIN [15]. Biguanides should be discontinued 48 hours before contrast administration, because of the risk of worse lactic acidosis should CIN occur. Cigarroa and co-workers [10] suggest calculation of the amount of radiocontrast material that can be given safely to diabetics with CRF:

$$\frac{\textit{5 ml of contrast/kg of body weight (maximum 300 ml)}}{\textit{serum creatinine (mg/dl)}}$$

Angiography should be performed in stages if necessary rather than exceeding the contrast »limit« [10], allowing an interval of at least 4 days between contrast studies [15,38]. Abandonment of HOCA with indiscriminate LOCA use is certainly not feasible because of the high cost of LOCA and because of lack of evidence of proven advantage.

In summary, diabetes mellitus per se does not confer significant risk of CIN unless complicated by preexisting renal insufficiency, whereupon the two factors become additive. Diabetes appears to be a covariate rather than an independent risk factor. There are no valid reasons to advocate use of new, expensive, low osmolality contrast media rather than conventional, ionic, high osmolar agents in the diabetic

population if the sole rationale is to avoid contrast nephropathy. Agents used in MRI appear to spare the kidneys, perhaps as a result of use of diminutive volumes, and MRI can be considered in selected diabetics with advanced renal insufficiency or with multiple comorbid conditions, pending data that address this population. Radiologists and clinicians must continuously reappraise the need for radiocontrast studies in diabetics and use alternative imaging procedures when possible.

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41. RENAL PAPILLARY NECROSIS IN DIABETIC PATIENTS

GARABED EKNOYAN

Cases of probable renal papillary necrosis (RPN) may have been described for centuries, but it was not until 1877 that RPN was actually identified as a distinct clinicopathological entity in a man who had prostatic hypertrophy, hydronephrosis and bilateral papillary necrosis [1,2]. Shortly thereafter, the first case of RPN in a diabetic was reported in a 60-year old diabetic woman who presented with gangrene of the left foot and at post-mortem had RPN [3]. The propensity of diabetic patients to papillary necrosis was first emphasized in 1937 [4,5]. From the outset a strong association was made between coexistent urinary tract infection in diabetics with RPN, and most of the initial reports considered RPN as a fulminant terminal complication of severe acute pyelonephritis in diabetic patients [6-9]. Subsequent reports described a more indolent chronic form of RPN in diabetics, generally in those with recurrent episodes of urinary tract infection, but not necessarily with coexistent pyelonephritis [10-12].

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STRUCTURAL BASIS AND PATHOGENETIC MECHANISMS OF PAPILLARY NECROSIS IN DIABETICS

The basic lesion of RPN is a tubulo-interstitial nephropathy that affects the inner medulla, in which the blood flow is severely compromised resulting in the focal or diffuse ischemic necrosis of the more distal segments of one or more of the renal pyramids [12]. The fact that the necrosis is anatomically restricted to the papillary tips and the distal segments of the renal pyramids is, most likely, a reflection on local factors unique to this region.

The first of these factors is the specialized vasculature of this region [15,16]. At the base of the renal pyramids, the vascular bundles formed by the vasa rectae are at their widest and their lavish intercommunication forms a rich vascular plexus, which provides the structural basis of the renal countercurrent exchange system [15]. During the course of their descent to the inner zone of the medulla there is a decrease in vessel size and intercommunications such that at the tip of the papilla there are only terminal vessels, with sparse intercommunications, that remain. Most of this medullary blood flow serves a countercurrent multiplier rather than nutrient function. Nutrient blood supply is provided by regional small terminal vessels whose size and frequency gradually diminishes from the outer medulla to the papillary tip. This diminution in blood supply is coupled by a 3-to-4-fold increase in the interstitial space of the inner zone of the medulla as compared to that of the cortex and outer medulla [15-17]. The net effect is that the relatively poor nutrient blood supply to the parenchyma of the papillary tip, compared to the remainder of the kidney, is rather tenuous and the loss of even a few capillaries can result in foci of ischemic necrosis. This, most likely, accounts for the susceptibility of the papilla to necrosis in diseases which affect the renal vasculature and the major role of ischemia in the development of papillary necrosis [12,17,18]. Since the ultimate lesion of diabetes is a microangiopathy, and over half the diabetic patients who develop RPN are over 50 years of age and are hypertensive with widespread arteriosclerosis, either of which can result in obliterative vascular lesions, the central role of ischemia in the development of RPN in diabetics becomes all the more evident. In fact, on careful scrutiny, small focal ischemic lesions can be seen in the papilla of most elderly diabetics (figure 41-1). These sterile infarcted areas strongly suggest that ischemia of the pyramids is important in the development of RPN [8-18].

A second consideration as to why the necrotic lesions are restricted to the papillary tip is the ability of the medulla to establish a hypertonic environment. One detrimental effect of this otherwise essential function is the high concentration of toxic metabolites which can accumulate in the inner zone of the renal medulla [19]. While this mechanism is primarily relevant to the issue of analgesic-induced RPN, diabetics are not immune to analgesic abuse. In fact, 3 of 15 (20%) diabetics with

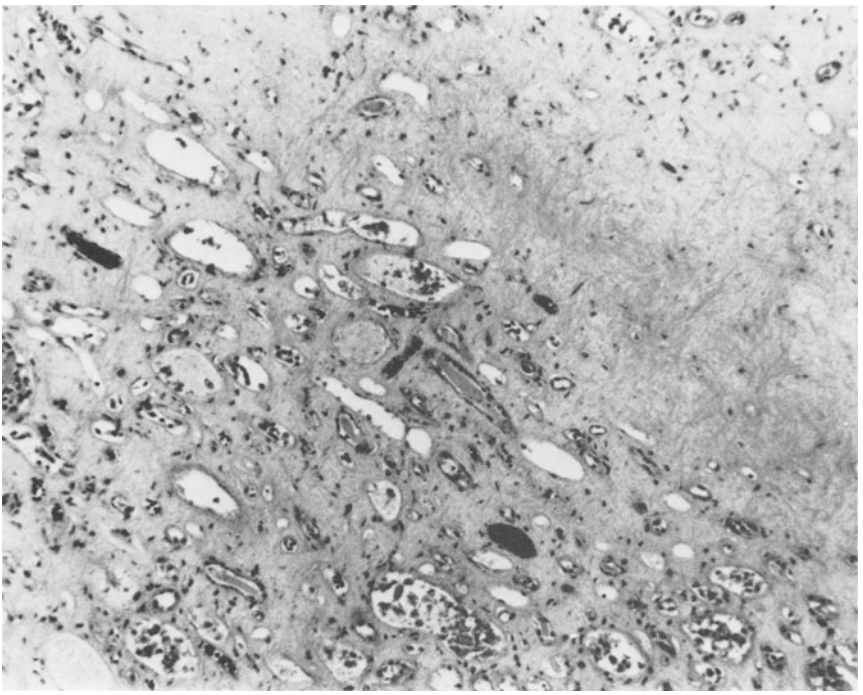

Figure 41-1. Focus of necrosis from the papilla of an asymptomatic 62-year old man with adult onset diabetes mellitus. H&E X 230.

RPN reported in one series were also analgesic abusers [12]. In experimental diabetes mellitus, the papillary production of prostaglandin E_2, $F_{2\alpha}$ and thromboxane has been shown to be significantly decreased at 8 weeks after streptozotocin-induced diabetes (20). The effect of analgesics to further reduce prostaglandins can only aggravate this underlying metabolic defect. Nonsteroidal anti-inflammatory drugs, with their greater potential to inhibit cyclo-oxygenase, exert an even greater detrimental effect in reducing medullary blood flow. Thus, diabetic individuals who abuse analgesics or nonsteroidal anti-inflammatory drugs may be at particularly greater risk of developing RPN.

Another detrimental effect of the medullary hypertonicity is its probable role in compromising the ability to combat infection, thereby rendering the hypertonic medulla more susceptible to bacterial colonization [21]. In diabetics with RPN associated with acute pyelonephritis, the earliest identified lesions consist of scattered

foci of infection located in the renal pyramids, at a level of about two-thirds of the way from the tip of the papilla to the junction of the pyramid with the cortex [7]. As these lesions progress, the foci of infection coalesce resulting in complete necrosis of the terminal two-thirds of the pyramid or papillary tip [7]. It is these earlier observations that led to the conclusion that infection is a principal cause of RPN, and the early suggestion that RPN is basically a form of acute or chronic pyelonephritis whose natural course is altered by the coexistent diabetic state [7,8]. There is no question about the fact that, with few exceptions, patients with RPN will have an infection of the urinary tract. However, urinary tract infection is not a uniform and invariable finding in all cases [12]. Additionally, and perhaps as importantly, infection itself may be a secondary complication to the ischemic necrosis of the papilla. The differentiation between the primacy of the role of ischemia or infection, when both are coexistent, may be impossible. Suffice it to say that infection is common and often contributes to RPN, but its presence is not essential to the development of RPN in diabetic patients [1,12]. The fact remains that diabetics with an acute infection of the kidney are specially susceptible to develop RPN [7,8].

In summary, the pathogenesis of RPN in diabetics is multifactorial. Ischemia appears to be at the core of the process. Varying degrees of vascular changes are almost always present. The high incidence of glomerulosclerosis in patients with RPN attests to the importance of longstanding diabetes-induced vascular changes to the development of papillary necrosis [1]. The fact that despite the prevalence of the vascular ischemic changes in diabetic patients, only a few of them develop RPN attests to the importance of additional factors for the papillary necrosis to progress. The superimposition of infection clearly plays a role in most, but not all, of those who develop RPN. Analgesic abuse is another contributory factor in those who progress to papillary necrosis [12]. In cases where the necrotic papilla sloughs and causes obstruction, the development of obstructive uropathy assumes an added and important role that causes progression of the lesion to the remaining papillae of the affected kidney. In the final analysis, the pathogenetic process may be considered to result from the combination of several detrimental factors operating in concert to cause RPN. In such a scheme whereas each of the factors (ischemia, infection, analgesic toxicity, obstruction) alone can cause foci of necrosis, the coexistence of more than one of them in any diabetic subject increases the risk and extent of the papillary necrosis that can occur.

INCIDENCE AND CLINICAL CHARACTERISTICS

Diabetes mellitus is the most common clinical condition associated with RPN in the United States of America, accounting for some 50 to 60% of the cases of RPN

reported in the major series [12-14]. This is in contrast to the 4 to 12% incidence of diabetes as a cause of RPN reported from Australia and the Scandinavian countries, where analgesic abuse accounts for the majority of cases of RPN [12,22]. The propensity of diabetics to RPN can be appreciated from its finding in 4.4% (range 2.7 to 7.2%) of diabetics who come to autopsy, as compared to that of 0.16 to 0.6% in non-diabetics [1,7-14]. The actual prevalence of RPN in diabetics may be higher than that reported in autopsy series. In a prospective series of 76 patients with longstanding diabetes, intravenous urography revealed radiographic evidence of RPN in 18 patients or 23.7% of the cases. The risk was greater in women and in those with a history of recurrent urinary tract infection [15].

RPN usually, but not invariably, involves both kidneys [6,7]. A review of the cases of RPN in diabetic patients reported in the literature, revealed bilateral RPN in 65% and only unilateral RPN in 35% of the cases [1]. In cases in whom one kidney was involved at the time of initial examination, RPN developed in the other kidney in the ensuing years [12].

The lesion is more frequent in elderly women. The average female-to-male ratio is about 3:1 [1], with a reported range of 1.5:1 to as high as 5.5:1 [7,9,10,12]. The majority of diabetic patients (about 75%) who have RPN are over 50 years old, although RPN does occur in younger diabetics [1,12]. Diabetes of several years duration is usually present prior to the diagnosis of RPN in most cases. In 42% of reported cases of RPN, the diabetes was of longer than 10 years duration [1]. However, RPN has been noted in newly diagnosed diabetics, particularly in those cases that are associated with either severe recurrent urinary infection or prior analgesic abuse [1,12].

CLINICAL MANIFESTATIONS

The clinical symptomatology of the diabetic patient who develops RPN will be determined by the course of the evolving necrotic lesions and the severity of the infection that might accompany it. In brief, the clinical manifestations of symptomatic RPN are those of either nephrolithiasis or pyelonephritis. In the majority of the cases, however, the lesions will remain silent and will be detected only at the post-mortem or radiographic study [12,23].

In general, the necrotic foci that develop are well demarcated (figure 41-1). Once they extend to involve the whole papillary tip, the necrotic parts form a sequestrum which may slough and is excreted into the urine, may be absorbed locally leaving a sinus tract or cavity at its site, or may remain in situ where it becomes calcified and becomes the nidus for calculus formation (figure 41-2). The passage of a sloughed papillae results in lumbar pain and ureteral colic which are clinically indistinguishable from that caused by the passage of a calculus. The

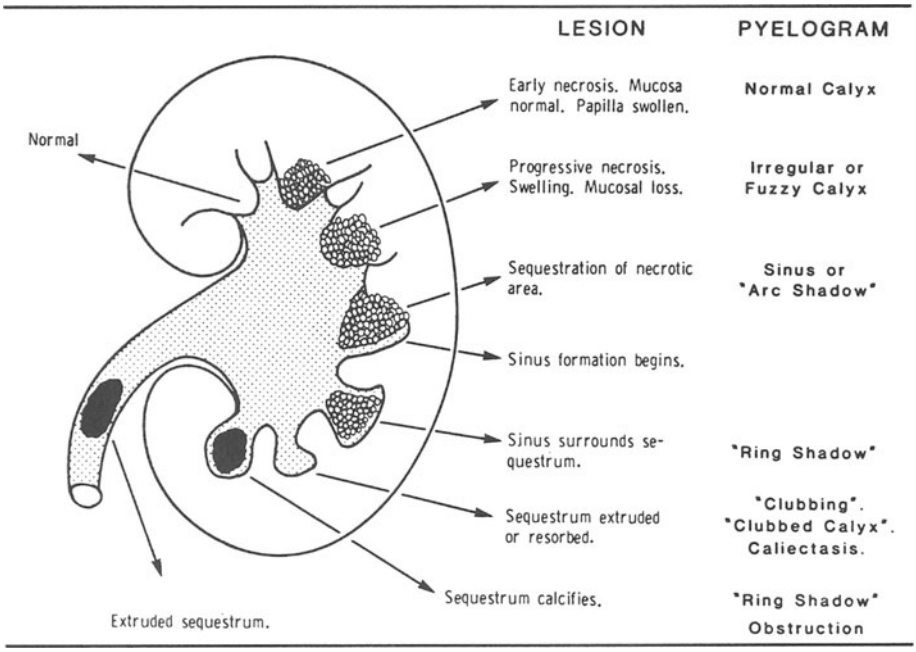

Figure 41-2. The morphologic features and radiographic appearance of the kidney during the various stages of development of papillary necrosis.

sloughing of the necrotic papillary sequestrum and its passage may be associated with haematuria. The haematuria may be massive and cases of exsanguinating haemorrhage requiring surgical intervention have been reported [24].

Alternatively, the necrotic tissue and stagnated urine in the cavities may become a nidus for infection. In its chronic form the course of the infection of these patients may be one of smouldering chronic urinary tract infection which may remain asymptomatic or have recurrent episodes of acute infection [7,12]. In its acute form, the patients with an infection will present with severe prostration and overwhelming sepsis which may pursue a devastating fulminant course with associated rapidly progressive renal failure and the ultimate demise of the patient due to septicemia [7,9,12].

The level of renal insufficiency that develops will depend on the number of papillae involved. While some loss of renal function is expected to occur as a result of any renal parenchymal necrosis, renal failure does not always occur. Thus, even when the lesions are bilateral but affect only one or two papillae on each side, sufficient unaffected renal lobules remain to maintain adequate renal function. Even

when most of the papillae in each kidney are affected, the localization of the necrotic lesion to the papillary tip results in the loss of only the nephrons of the juxtamedullary regions whose loops descend all the way to the papillary tip; whereas the cortical nephrons which terminate in the outer zone of the medulla are spared, thereby leaving a multitude of unaffected functioning nephrons which are sufficient to maintain normal homeostasis. With the loss of several papillae, renal failure will ultimately occur solely on the basis of papillary necrosis, independent of coexistent glomerular changes.

Proteinuria, although a common (80%) abnormality on urinalysis, is usually only modest (<2 mg/day) in quantity [12]. The magnitude of the proteinuria may help differentiate those diabetics with renal insufficiency due to glomerulosclerosis, who will generally have massive proteinuria, from those that develop renal failure secondary to severe RPN, who will have only modest proteinuria.

TREATMENT

In the absence of coexistent contributory factors that can be avoided (such as analgesic abuse) or surgically corrected (such as obstruction due to prostatic hypertrophy), the therapy of RPN should be directed toward the associated complications [1]. Control and eradication of any systemic or urinary tract infection is absolutely essential. The presence of pyuria does not necessarily imply urinary tract infection. Pyuria will be present in the majority of cases of RPN even in the absence of infection [12]. The urine should be cultured and any infection of the urinary tract considered of renal origin and treated with a long course of specific antibiotic therapy, tailored to eradicate the infection depending on the culture results obtained.

Prompt relief of any urinary tract obstruction should be undertaken. Vigorous medical treatment of any infection and conservative management by catheter drainage is essential prior to resorting to any radical surgical procedures. Even in the presence of pyonephrosis, nephrectomy should be deferred. Drainage, by percutaneous nephrostomy or retrograde catheterization, may prove adequate to control such cases. Nephrectomy may become necessary only if the infection cannot be controlled. It should be remembered that in the final analysis RPN is a bilateral lesion, which if not present from the outset, will ultimately affect the other kidney because of the systemic nature of the vascular lesions.

Analgesic use is common amongst diabetics, particularly as their disease progresses and they develop pain due to joint and muscle involvement. Diabetics should be instructed to avoid analgesics in general and non-steroidal anti-inflammatory agents in particular. The inhibitory effect of these agents on prostaglandin

synthesis can further impair the already compromised blood supply of the medulla [25].

Control of hypertension, often a complicating if not coexistent feature of diabetics with RPN, is important. Antihypertensive agents which compromise renal blood flow are best avoided while those which improve renal blood flow are preferred.

Finally, tight control of blood sugar in diabetics has been shown to be effective in reducing the magnitude of proteinuria and that of the deterioration of glomerular filtration rate. In experimental diabetes, insulin treatment increases the papillary production of prostaglandin $F_{2\alpha}$ [20]. Whether it can also reduce the progression and incidence of papillary necrosis remains to be determined.

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42. PROBLEMS RELATED TO THE START OF RENAL REPLACEMENT THERAPY IN DIABETIC PATIENTS

GUDRUN NYBERG

The natural course of diabetic nephropathy is characterised by rapidly declining renal function. If this is unrecognized until the patient has symptoms of terminal renal failure, the nephrologist and the patient face a multitude of problems. The degree of renal failure must be estimated, disturbancies in the acid-base and calcium-phosphate balance corrected, the general state of the patient as regards other diabetic complications evaluated and the appropriate form of renal replacement therapy chosen and instituted. The patient needs thorough and repeated information and comfort.

With antihypertensive therapy the course is quite different, allowing for careful evaluation, planning and information to the patient. Although there is less stress in this situation, the problems are the same.

1. INFORMATION TO THE PATIENT

Some information on dialysis and renal transplantation should be given to all patients with impaired renal function. To those with GFR less than 25 ml/min detailed

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information must be given by a nephrologist. It is unlikely that progression could be stopped by intervention at this point but it may be so slow that renal replacement therapy can be postponed for several years. It is wise not to guess the future course and certainly not based on short term changes in serum creatinine.

2. CONSERVATIVE UREMIA TREATMENT

The patient with renal failure not yet requiring dialysis will benefit from symptomatic treatment of certain disturbances. Serum bicarbonate is often reduced and should be substituted orally. Serum potassium may increase, especially with ACE-inhibition, and should be corrected by diet and/or an ion-binding resin. Increased serum phosphate and deficient vitamin D activation cause hypocalcaemia with secondary or tertiary hyperparathyroidism. Phosphate binders, calcium carbonate and active vitamin D are then indicated. Secondary anemia is frequent and should be treated with erythropoetin to maintain hemoglobin values around 110 g/l. Oedema can usually be entirely prevented by increasing doses of furosemide (up to 2 g per day) sometimes with additional metolazon. Restriction of dietary protein can reduce urea levels and nausea but must be strictly supervised to avoid malnutrition. Beware of insidious weight loss.

3. EVALUATION OF NON RENAL DIABETIC COMPLICATIONS

Cardiovascular disease

The increased morbidity and mortality in cardiovascular diseases observed among patients with diabetic nephropathy remains unexplained (Chapter 7). With improved control of hypertension and hyperglycaemia cardiovascular mortality has been reduced. The most immediate gain is probably caused by the use of diuretic drugs and antihypertensive therapy reducing cardiac work load. Diabetic patients evaluated for kidney transplantation in 1991-1993 had significantly lower left ventricular mass than those evaluated in 1977-1980 and the mass showed a strong correlation with mean arterial pressure [1]. Macroangiopathy remains a profound problem. All candidates for transplantation must be evaluated as regards coronary disease. A careful history and an exercise test are required, and if they rise the suspicion of coronary insufficiency an angiogram should be performed - with due precautions (Chapter 39). Coronary angiography may also be of benefit as a routine because intervention confers an improved prognosis even to asymptomatic cases [2].

Gastrointestinal symptoms

Diabetic autonomic neuropathy may cause impaired gastric emptying and abnormal intestinal motility. The uremic state aggravates nausea. Sporadic vomiting is frequent already at GFR levels around 25 ml/min and becomes increasingly common and

often combined with anorexia as renal insufficiency progresses. This is potentially dangerous due to the risks of hyperglycaemia, ketosis and metabolic acidosis. Moreover, if prolonged, it will add to the physical weakness inherent to the uremic state. Mental depression may contribute to a vicious circle resulting in inactivity, wasting of muscles, malnutrition, apathy, and a severely debiliated state. Some of these patients succumb during chronic dialysis. Those accepted for kidney transplantation carry greatly increased risks of complications. More time is required for rehabilitation even of successfully transplanted cases. The condition should be prevented if possible. Most patients will benefit from discussions with a clinical nutritionist, from physiotherapy, and from assistance of a social worker or a psychologist. An important precaution is to give renal replacement therapy in good time.

Foot problems secondary to macrovascular or microvascular disease and to neuropathy are frequent and may be worsened in advanced renal failure due to oedema or uremic neuropathy.

Urinary voiding is often deficient. The condition may result in an atonic bladder contributing to renal failure and constituting a problem also after successful renal transplantation. It must be screened for even in patients without any complaints. Determination of residual urine, e.g. by ultrasound is a minimum. In our experience, deterioration can be prevented by careful instructions to the patients on how to void [3]. If not, patients can learn surprisingly easy to empty their bladder using a catheter at bedtime or even regularly during the day.

4. GLYCAEMIC CONTROL

In uremia, clearance of insulin is also reduced and the effect of short acting insulin prolonged. The patient may experience periods when insulin seems inefficient alterating with periods with repeated hypoglycemic episodes in spite of much reduced insulin dosage. This is probably an effect of a slow change of the size of the insulin pool. The risk of coma is also increased by the fact that it may develop with few, late or different warning symptoms. However, most patients can handle the situation with better instructions, closer monitoring of blood glucose, and more regular meals and exercise. When insulin clearance improves following kidney transplantation and uremic neuropathy is reversed glycaemic control usually becomes easier. For patients starting CAPD insulin administration in the dialysis fluid may facilitate and improve metabolic control. Learning this in advance is reassuring to the patient with problems.

5. CHOICE AND PLANNING OF RENAL REPLACEMENT THERAPY

There are no studies comparing the various forms of renal replacement therapy given to the same category of patients. In general, renal transplantation is considered the best form of renal replacement therapy, because when successful, it provides a glomerular filtration rate which is much superior to what can be achieved by dialysis. Transplantation, however, confers an increased mortality risk for the first months post transplant and more so in diabetic patients with cardiovascular disease or a debiliated general condition. This must be explained to the patient who may then prefer dialysis. If a simultaneous pancreas and kidney transplantation is available, the risk of prolonged hospitalisation and the lack of proven effect on late complications must be pointed out [4].

The various forms of dialysis should be discussed with the patient, if not his condition or the facilities available leave only one option. If hemodialysis is preferred, vascular access, i.e. an arteriovenous fistula, should be attempted early because this is hazardous in diabetic patients.

6. TIMING OF RENAL REPLACEMENT THERAPY

If a predialytic transplantation can be arranged the profoundly uremic phase may be avoided. This can more easily be accomplished if there is a living kidney donor. Identification of potential donors, information to these and some screening testing may be done when the patient's GFR is around 20 ml/min. The donor investigation then proceeds as the patient's renal function deteriorates. Some uremic complaints should be present before the patient is exposed to the risks of transplantation. GFR around 10 ml/min is probably optimal. The corresponding serum creatinine value may range from 150 to 600 μmol/l depending on the patient's diet and amount of muscle tissue. Endogenous creatinine clearance overestimates renal function. GFR should be measured with filtration markers such as inulin or ^{51}CrEDTA, the sampling of plasma extended to 24 hours or the marker recovered in time-collected urine [5].

Dialysis should be started at lower serum creatinine values in diabetic patients than in the average renal patient, due to their poorer muscle mass, but also at a higher true GFR level considering their increased tendency for nausea and physical weakness.

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43. EVOLUTION WORLDWIDE OF THE TREATMENT OF PATIENTS WITH ADVANCED DIABETIC NEPHROPATHY BY RENAL REPLACEMENT THERAPY

ANTHONY E.G. RAINE

INTRODUCTION

Of all the complications of diabetes mellitus, diabetic nephropathy is one of the most feared. The need for renal replacement therapy (RRT) itself imposes many burdens. Moreover, despite the now widespread availability of such treatment, the survival of patients with end stage renal disease remains disturbingly low [1], largely due to an excess of cardiovascular disease [2]. These problems have become increasingly clear over the past decade, as greater numbers of diabetic patients have entered dialysis and transplant programmes. In the past, access to RRT of patients with end stage diabetic nephropathy was restricted in Europe, particularly in those countries where limitations in resources for provision of RRT historically existed [3]. The dramatic and sustained growth in the availability and provision of this life saving treatment has led to worldwide increases in acceptance of diabetic patients for RRT; for example, it has grown from less than 2% of treated patients in Europe in 1974 [4] to over 10% in the mid-1980's [5]. However, the proportion of RRT patients with diabetic nephropathy is much higher in other countries, notably the United

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States, where according to the United Stages Renal Data System (USRDS) approximately one third of all RRT patients have diabetic nephropathy, and the annual incidence of end stage renal failure in diabetic patients alone is over 40 per million population [6], compared with 3.6 per million in Europe in 1985 [5].

Discrepancies such as these raise several questions. It is unclear to what extent these international differences in provision of RRT are due to a higher underlying prevalence of diabetic nephropathy in some countries than others, or whether they are due to a more liberal treatment pattern. The evolution of end stage diabetic nephropathy will be influenced also by the relative proportions of type I and type II diabetic patients in a population, and any racial variations in diabetes prevalence. Lastly, the specific modes of therapy employed are also relevant, both because they have influenced the availability of treatment, and because they may themselves affect subsequent survival. The aim of this chapter is to review the current patterns in different countries of acceptance of diabetic patients with RRT, and to explore the factors underlying differences in these patterns.

EVOLUTION OF ACCEPTANCE OF DIABETIC PATIENTS FOR RRT IN EUROPE

The most complete longitudinal data available on the changing pattern of provision of RRT comes from the Registry of the European Dialysis and Transplant Association (EDTA), which has gathered annual information since 1965 on all patients receiving RRT in Europe. The total number of patients reported to the Registry as alive on treatment in 1991 was 168927, of whom 33032 commenced therapy during 1991 [7]. The contribution of diabetic nephropathy to this total may be assessed from information given by the reporting physicians. Since 1983 type I and type II diabetes have been coded separately as primary renal diseases, but before that date no distinction was made.

EDTA Registry data have shown that since 1965 there has been a continuing increase in both the number of diabetic patients commencing RRT each year and in particular the proportion of patients accepted for RRT with renal failure due to diabetic nephropathy. Between 1966 and 1973 less than 2% of all patients commencing RRT in Europe were diabetic. This proportion has increased linearly since, reaching nearly 14% in 1990 [8]. To analyse these trends in detail, the number of new diabetic patients accepted for RRT in Europe in the period 1970-1991 in different age cohorts has been examined.

As figure 43-1 shows, the majority of diabetic patients accepted for RRT between 1970 and 1980 were young, 25-44 years of age at the start of treatment, and there has been relatively little increase in this cohort since; 620 young patients were accepted in 1984, and 673 in 1991 for Europe as a whole. In contrast, there

has been a striking and continuing increase in the number of middle aged (45-64 years) diabetic patients commencing therapy. In 1978 equal numbers of patients aged 25-44 years and aged 45-64 years commenced RRT, whereas in 1991 there were three times more middle aged than young patients. The greatest change in treatment pattern, however, is apparent for elderly diabetic patients. Their acceptance rate remained at low levels until 1982, since when it has continued to rise sharply (figure 43-1).

COMPARATIVE ACCEPTANCE RATES OF DIABETIC PATIENTS FOR RENAL REPLACEMENT THERAPY IN EUROPE, NORTH AMERICA AND AUSTRALIA

Less is known of the long term evolution of provision of RRT for diabetic patients with end stage renal disease outside Europe. Nevertheless, current data for Renal Registries indicate major international differences in the treatment of diabetic patients, both within and outside Europe (table 43-1). Within Europe there are differences both in the absolute population prevalence of diabetes mellitus, and in the relative prevalence of type I and type II diabetic patients, type I diabetes being more common in Scandinavian countries and type II in Mediterranean countries [9]. These differences may in part explain the greater proportion of diabetic patients currently commencing RRT in Northern Europe (18%) than in Southern Europe (13%).

Overall, 16% of new RRT patients in Europe have diabetic nephropathy. USRDS data [10,11] show that in the United States the proportion of diabetic patients accepted for RRT is double this, averaging 34%. Although this major difference may in part be explained by differing racial distribution and case mix of type I and type II diabetic patients (see below), it is possible that it is also in part due to a historically more liberal approach to provision of RRT for elderly diabetic patients and those with significant comorbidity. This likelihood is supported by the relatively constant 33-34% proportion of diabetic RRT patients reported to the USRDS in recent years [12] in comparison to the continuing increase apparent in Europe [1,8]. As an illustration of this trend, in the twelve month period up to September 1993, 33% of patients commencing RRT at St Bartholomew's Hospital, London had diabetic nephropathy as their primary renal disease, a proportion identical to that reported in the United States.

According to the Canadian Organ Replacement Registry [13], 24% of patients commencing RRT in 1991 had diabetic nephropathy, a proportion intermediate between European and American experience. In contrast, in Australia diabetes appears to be a less frequent cause of end stage renal failure. Australian and New Zealand Dialysis and Transplant Registry Data (A Disney personal communication)

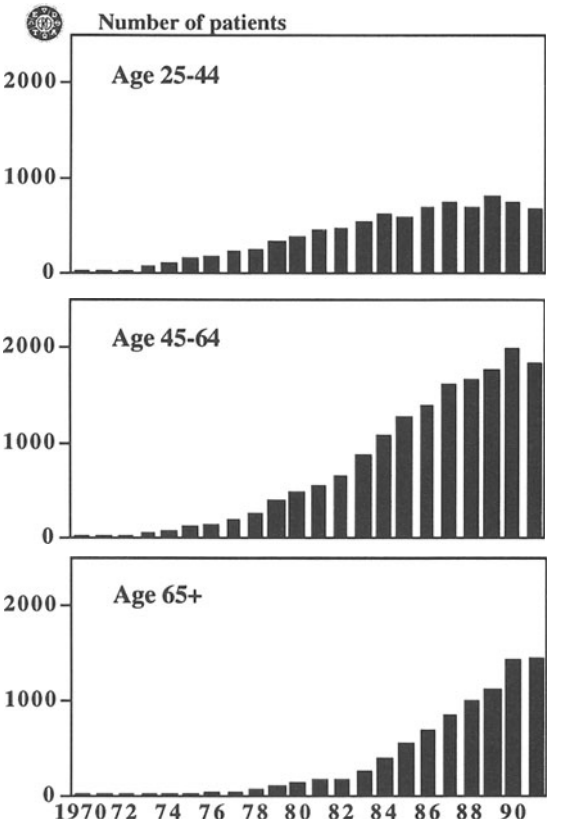

Figure 43-1. The number of new patients with end stage renal failure due to diabetic nephropathy commencing renal replacement therapy in Europe between 1970 and 1991, subdivided into age groups 25-44, 45-64, and 65 years and over. Data from the EDTA Registry.

show that between 1984 and 1992 diabetes accounted for 10-14% of RRT patients, without the pattern of continuing increase apparent in Europe.

DEVELOPMENT OF END STAGE RENAL FAILURE IN TYPE I AND TYPE II DIABETIC PATIENTS

Traditional views have held that end stage renal failure was a relatively rare occurrence in type II diabetic patients [14]. These beliefs have been altered by recent cohort studies, which have shown that the prevalence and rate of development both of significant proteinuria and of renal impairment are very similar in type I and type

Table 43-1. Comparison of acceptance of new diabetic patients for renal replacement therapy in Northern and Southern Europe, the United States and Australia:

	Northern Europe* (% total)	Southern+ Europe (% total)	Total Registry (% total)	United States [10,11] (% total)	Canada [13] (% total)	Australia (% total)
1989	563	741	3771	13597	-	111
	(16)	(12)	(13)	(33)		(12)
1990	556	801	4174	15383	-	138
	(15)	(12)	(14)	(34)		(14)
1991	548	665	4010	-	612	126
	(18)	(13)	(16)		(24)	(13)

* Sweden, Norway, Finland, Denmark, United Kingdom.
+Italy and Spain

II patients [15]. Recent regional surveys have shown a high proportion of type II diabetics on RRT, both in the United States [16] and in Europe [17]. Table 43-2 shows data for the EDTA Registry, giving the numbers of type I and type II diabetic patients commencing RRT in Europe in 1983, 1987 and 1991, and also the total numbers of diabetic patients maintained on RRT in each of these years. There was a small excess of males (53-58%) in each year for both type I and type II diabetic patients. During this time the proportion of new diabetic patients reported as type II increased from 24% in 1983 to 41% in 1991. This increase is explained in part by the increasing acceptance for RRT of elderly diabetics (figure 43-1), the great majority of whom will have type II disease.

However, interpretation of these data is complicated by the likelihood of relative under reporting of type II diabetes. Classification of patients in a Registry database depends entirely on the reporting physician, with the consequent possibility that type II diabetic patients who are insulin-requiring at the time of referral may be misclassified. As an illustration, in a recent survey from Italy 67% of Italian diabetic patients receiving RRT in 1987 were classified as type II by a specific questionnaire, and 33% as type I [18]. In comparison, corresponding EDTA Registry data showed that 35% of Italian patients were type II, and 65% were type I [8]. Data from the

Table 43-2. New type I and type II diabetic patients accepted for treatment and total diabetic patients alive on renal replacement therapy in Europe in 1983, 1987 and 1991; EDTA Registry data.

	Type I		Type II		All diabetics	% total	All RRT patients
	M	F	M	F			
New Patients							
1983	746	554	241	173	1714	8.7	19637
1987	1245	1007	550	444	3246	12.4	26193
1991	1306	1054	885	765	4010	15.5	25853
Alive on Treatment							
1983	1580	1086	875	558	4099	4.0	101819
1987	3669	2728	1519	1059	8975	6.2	145793
1991	4733	3647	2435	1925	12740	8.1	158090

ANZDATA Registry for Australian patients (A Disney, personal communication), showed that in 1987 60% of new diabetic patients were type I, whereas in 1992, 43% were type I and 57% were type II.

These proportions are comparable with those available for the United States, where in one survey twice as many type II as type I patients commenced RRT [19]. Nevertheless, interpretation of these international comparisons is complicated by differences in racial mix. Cowie et al. [19] reported that in Michigan the incidence of end stage renal failure was 2.6 times higher in black than in white diabetic patients, whether type I or type II, after adjustment for the higher prevalence of diabetes amongst blacks. Most black diabetic patients receiving RRT in this study had type II diabetes (77%), while more white patients had type I diabetes (58%). It is likely that variations in racial mix also make a significant contribution to the incidence of diabetic end stage renal disease in other countries, but detailed information to verify this likelihood is not yet available. Clearly, the relative proportions of type I and type II diabetic patients commencing RRT for end stage renal disease will be determined by several factors, including the greater underlying frequency of type II diabetes mellitus in the general population, racial variations in susceptibility to development of nephropathy in both type I and type II disease, the older age at presentation of type II diabetic patients and the higher mortality rate of type II than type I patients during the phase of progressive renal impairment, before

development of end stage renal failure. Large scale population based prospective studies currently in progress should in due course provide answers to many of these issues.

MODE OF TREATMENT OF END STAGE DIABETIC NEPHROPATHY

In Europe most (60%) of the renal failure population are treated by haemodialysis [20], and the same holds true for those patients with diabetic renal failure. At 31 December 1991 66% of all diabetic patients were receiving haemodialysis, 16% were treated by peritoneal dialysis and 18% had a functioning renal graft. The patterns of evolution of these different modes of therapy between 1970 and 1991 for diabetic patients in the EDTA Registry database are shown in figure 43-2.

All modes of treatment have increased progressively, although numerically the group receiving haemodialysis has always been the largest. Between 1976 and 1991 the numbers of patients maintained on haemodialysis have increased 19-fold, those receiving peritoneal dialysis have increased 55-fold and those with a functioning graft have increased 26-fold. Analysis of treatment modality according to age shows that the great majority of elderly patients receive haemodialysis, whereas in young patients renal transplantation is the favoured option. In 1991 41% of diabetic patients aged 25-44 had a functioning graft, compared with 42% receiving haemodialysis and 17% maintained on peritoneal dialysis. For patients aged 65 and over, the corresponding percentages were 1%, 82% and 17% respectively.

Within Europe significant differences exist between countries in relation to the pattern of mode of RRT provision for diabetic patients. In Germany the majority of patients receive haemodialysis, whereas in Scandinavian countries and the United Kingdom renal transplantation is a favoured mode of treatment. Peritoneal dialysis is also preferred in certain countries such as France and, especially, the United Kingdom [8]. In the United States, recent USRDS analyses show that in 1989, 67% of patients were being treated by haemodialysis, 20% had a functioning renal transplant, and 11% were undergoing peritoneal dialysis, 2% being unspecified [12], proportions overall which are similar to those in Europe.

CONCLUSIONS

It is clear that the last 20 years have seen dramatic increases in the numbers of diabetic patients worldwide receiving RRT for diabetic end stage renal disease. In Europe alone the annual incidence of treated end stage diabetic nephropathy has increased from 3.6 per million population in 1985 [5] to 5.8 per million in 1990 [8]. Nevertheless in the United States the annual incidence of diabetic end stage renal failure is over 40 per million population [11]. Current indicators suggest that the disparity in acceptance rates between Europe and the United States is narrowing

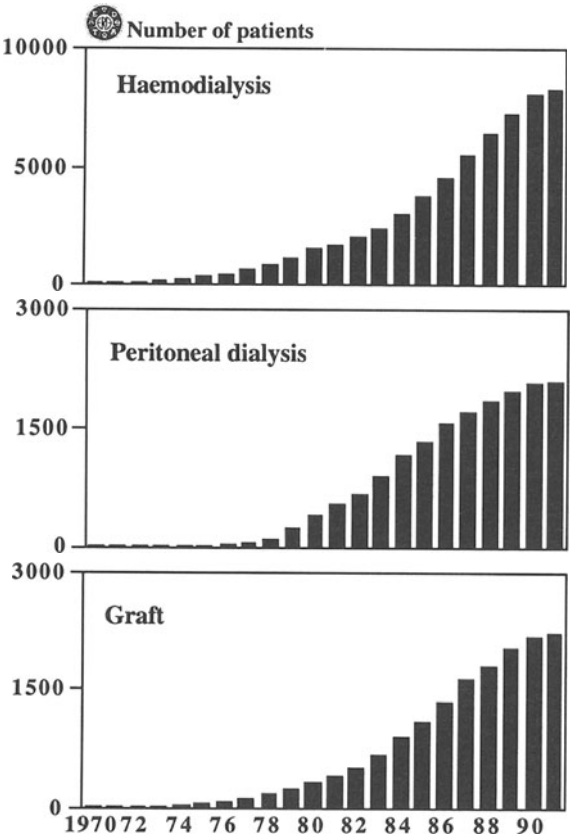

Figure 43-2. Total numbers of patients receiving specific modes of RRT (haemodialysis, peritoneal dialysis, or renal transplantation) in Europe for each year between 1970 and 1991. Data from the EDTA Registry.

rapidly. Even so, a realistic estimate of the comparative prevalences of end stage renal failure from diabetic nephropathy in the two populations may be possible only when the acceptance rate for new patients has plateaued, of which there is no sign at present (figure 43-1). The prevalence of diabetic renal disease in the United States is also greatly affected by the black population, who in 1986-1989 accounted for 31% of all diabetic RRT patients [12] and in whom the risk of end stage diabetic nephropathy is nearly 3-fold that in whites [19].

Future trends in the evolution of provision of RRT for diabetic patients will be determined by several complex and interrelated factors. These include the notable

recent increase in rate of development of diabetes mellitus in Western populations, and the improved medical management of cardiovascular and other complications in elderly diabetic patients, which will result in increased survival, and will therefore, paradoxically, increase the numbers of patients progressing to end stage renal disease. Set against this are the recent observations from large controlled clinical trials that effective control of hyperglycaemia reduces the incidence of diabetic nephropathy [21], and that use of converting enzyme inhibitors in early type I diabetic nephropathy results in a 50% reduction in the combined end points of death and end stage renal disease [22]. These findings give hope that the current epidemic of end stage diabetic nephropathy, with its attendant morbidity and mortality, may decline in the foreseeable future.

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44. HAEMODIALYSIS IN TYPE 1 AND TYPE 2 DIABETIC PATIENTS WITH END STAGE RENAL FAILURE

EBERHARD RITZ, ANTONY RAINE and DANIEL CORDONNIER

INTRODUCTION

In the early days of haemodialysis, efforts to treat and rehabilitate uremic diabetics were largely unsuccessful [1] until dialysis procedures and volume control had become more effective. Although diabetics have a poorer outcome than non-diabetics, survival on dialysis has improved to such an extent that today virtually no restrictions for admission to renal replacement therapy for these patients are justified. Consequently, diabetic nephropathy (assuming that in most cases renal failure is due to diabetic nephropathy) accounts for a large proportion of the dialysis population second only to glomerulonephritis and in some centers (as in Heidelberg) even exceeding glomerulonephritis [3].

1. EPIDEMIOLOGY

As reported in detail elsewhere [4] there has been a constant increase in the absolute number and proportion of diabetics entering renal replacement programs in Europe during the past two decades. However, wide differences exist between countries and

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there is a notable North-South gradient. This may be related to differences in life style and to differences in genetic predisposition, even within countries, such as in France where a high prevalence in the Northern regions bordering Belgium and Germany contrasts with a low prevalence in the Southern region bordering Spain [5]. A striking difference between metropolitan France (6.9%) and overseas territories (Guadeloupe 15%, Tahiti 34%) may reflect racial differences in the propensity to develop diabetes and diabetic nephropathy as has been described for the black population in the USA [6]. The renal risk in type II diabetes has clearly been underappreciated [7]. Misclassification has also occurred in many studies since the use of insulin was equated with type I diabetes [4,5,7]. Cordonnier et al. [5] noted that the relative proportion of type I diabetics decreased by 50% when patients were reexamined by diabetologists and when C-peptide measurements were performed. Similar underreporting has also been recognized in Italy: 35% were classified as type II by the registry, but 57% by a specific questionnaire [8]. In Germany, we also noted major discrepancies between the proportion of type II reported by the EDTA registry and that found in our own study [9]. While virtually all patients with type I diabetes entering renal replacement programs suffer from diabetic nephropathy, a certain proportion of type II diabetics ranging from 20% [7] to 50% [5], was reported to suffer from other standard primary renal diseases. The question whether a considerable proportion of type II diabetics with proteinuria actually suffers from superimposed glomerulonephritis remains controversial [10,11].

2. SURVIVAL AND CAUSES OF DEATH

In a matched case control study we found that actuarial 5 year survival in diabetics is worse than in matched non-diabetic dialysis patients [12] and this difference has not diminished in recent years. According to the 1991 EDTA returns actuarial 5 years survival was 38% in 45-54 year old type I diabetics commencing renal replacement between 1985 and 1990 compared to 70% in age matched non-diabetic patients and 31% in 55-64 year old type II diabetics vs. 58% in age matched non-diabetic patients [4]. The causes of death are mostly cardiovascular [13] as shown in table 44-1. Surprisingly no significant difference in survival was noted between younger type I and older type II diabetics [14]. Survival is roughly similar on haemodialysis and CAPD. While in the European series a slightly better survival on CAPD was found for elderly patients in general and for elderly diabetics specifically [15], the US Renal Data System shows generally better survival on CAPD for the younger patients and slightly worse survival for elderly diabetic patients [16]. If one wishes to improve survival it is imperative to reduce both cardiovascular death and death from infection. Today septicemia mostly originates

Table 44-1. Causes of death (57 months after start of dialysis)

	Type I (n=67)		Type II (n=129)	
Dead	29	(=40%)	80	(=43%)
Myoc.infarction	8/29		12/80	
Sudden death	7/29	62% CV	13/80	(60% CV)
Cardiac other	3/29		17/80	
Stroke	0/29		6/80	
Septicemia	7/29		11/80	
Interruption of treatm.	2/29		8/80	
Other	2/29		13/80	

after ref. 13

from foot gangrene and rarely from infected vascular access [13]. The predictors of cardiac death will be discussed in the following paragraphs.

3. PREDICTORS OF SURVIVAL

It is clearly important to identify the high risk patient in order to target appropriate preventive measures. Cardiac death is strongly predicted by a history of vascular disease, specifically myocardial infarction or angina pectoris. Interestingly, in our study proliferative retinopathy and polyneuropathy, possibly through causing imbalance of autonomic cardiac innervation, were also predictive [13], in good agreement with the data of Kikkawa [17]. Surprisingly actual blood pressure level and left ventricular hypertrophy (by echocardiography) did not predict cardiac death; in contrast hypotensive episodes during dialysis were predictive in elderly diabetics. The most potent predictors, however, were elevated total cholesterol, LDL cholesterol and LDL/HDL ratio (table 44-2). The implications for patient management are obvious.

4. METABOLIC CONTROL ON RENAL REPLACEMENT THERAPY

Using the euglycemic clamp technique, DeFronzo documented impaired efficiency of insulin in uremic subjects [18] and this was partially improved with institution of maintenance haemodialysis. This observation suggests that putative dialysable

Table 44-2. Lipid values (mg/dl) in patients dying from myocardial infarction (MI) or sudden death (SD)

	Type I			Type II	
	MI (n=8)	SD (n=7)	Survivors (n=38)	MI + SD (n=20)	Survivors (n=46)
Total cholesterol	278* (224-293)	221 (186-321)	228 (148-329)	261 (126-355)	221 (66-372)
LDL cholesterol	197 (156-243)	148 (127-205)	163 (89-322)	187 (91-278)	153 (43-295)
LDL-HDL ratio	6.0* (5.3-8.6)	4.8 (2.9-7)	4.4 (2.4-8.3)	5.4 (3.1-14)	4.9 (1.6-11.9)
Apo-lipoprotein B	132 (127-160)	108 (94-154)	110 (72-173)	131* (71-185)	110 (38-178)
Triceps skinfold thickness mm	16 (15.8-16)	18.6 (13-19.3)	12 (5.5-33)	10.7 (7.5-30)	13 (7-32.5)

*Significant difference between the respective group and survivors ($p < 0.05$)
after ref. 14

inhibitors of insulin action [19] are removed by dialysis. Peptidic inhibitors of non-insulin-mediated glucose uptake have also been identified in the ultrafiltrate of dialysis patients [20]. In clinical practice, the need for insulin decreases upon institution of maintenance haemodialysis, although complexities arise because of the prolongation of insulin half life in anephric patients and the confounding effects of reduced food intake (anorexia of renal failure) and of refeeding (after commencement of haemodialysis) [21,22]. Most nephrologists prefer to dialyse against glucose (200 mg/dl) to achieve better stabilisation of plasma glucose concentrations. This strategy allows patients to stay on their regular insulin schedules and take their regular meals irrespective of dialysis sessions. Diabetic control is occasionally rendered difficult by diabetic gastroparesis and the tendency of gastric motility to deteriorate acutely during dialysis sessions [23].

5. DIABETIC COMPLICATIONS ON RENAL REPLACEMENT THERAPY

In contrast to previous experience [1] de novo amaurosis has become rare in the diabetic on dialysis. In a series of 200 diabetics entering hemodialysis from 1987-1989, no single case experienced loss of vision in an eye whose vision had been normal when entering hemodialysis [13]. With appropriate laser treatment and control of blood pressure, previous concerns about haemorrhagic retinal complications with dialysis anticoagulation are no longer justified. Diabetic polyneuropathy, specifically autonomic polyneuropathy with cystopathy, gastroparesis and intestinal dysmotility have emerged as major problems on dialysis. The observation that polyneuropathy is predictive of cardiac death suggests that imbalanced autonomic innervation of the heart also contributes to arrhythmia and sudden death. This suspicion gains further credence from the observation that 3% of patients dying from myocardial infarction vs. 18% of survivors had been on betablockers, the agents of choice for treating imbalanced autonomic innervation [13]. Detection of cystopathy and latent urinary tract infection is important when patients are prepared for renal transplantation. Ischemic heart disease has emerged as a major threat to the dialysed diabetic. The issue is further compounded by the fact that this complications is often clinically silent. Studies of Weinrauch and subsequently others [24] identified hemodynamically significant coronary stenosis in approximately 30% of prospective diabetic recipients of renal allografts. There is no unanimity, however, whether routine coronary angiography should be performed in asymptomatic diabetics prior to renal transplantation. The Göteborg group [25], despite not employing routine pretransplantation coronarography unless patients had overt cardiac problems, found no excess loss from myocardial infarction in diabetic allograft recipients. Low risk patients can be recognized by relatively simple algorithms [26]. The reocclusion rate after PTCA is disappointing; i.e. 70% after one year [27], but long-term prognosis with bypass surgery appears to be more encouraging. Uncontrolled observations suggest that symptomatic ischemic heart disease is strikingly ameliorated when hemoglobin levels are raised by treatment with recombinant human erythropoietin [28]. Left ventricular hypertrophy and diastolic left ventricular malfunction are early and very common complications [29] and may contribute to circulatory instability during dialysis sessions [30]. Amputation because of neuropathic or ischemic foot lesions is required in approximately 8% of dialysed diabetic patients over three years [9]. Preexisting arterial occlusive disease and a history of smoking are potent predictors [9]. Ischemic foot lesions benefit strikingly from treatment with rhEPO. Interestingly, in transplanted diabetics the rate of amputation tends to be higher, possibly because of the use of steroids and/or cyclosporin [21].

It is commonly stated that vascular access is more difficult in diabetics. Venous hypoplasia is very common in elderly female diabetics and in polymorbid patients

veins are often thrombosed from preceding i.v. therapy. Otherwise, however, we have not found that fistula problems are more frequent in diabetics than in non-diabetic patients. It is advisable, however, to create the fistula prophylactically once serum creatinine exceeds approximately 5 mg/dl, since »maturation« of the fistula takes decidedly longer in the diabetic patient.

6. TRANSPLANTATION IN THE DIABETIC PATIENT

There is unanimous agreement that medical rehabilitation for the uremic diabetic is best after transplantation [31]. Recent US data (Port, Ann Harbour, personal communication) show that while the survival benefit from transplantation is marginal for patients with glomerulonephritis, it becomes dramatic for the diabetic. This applies not only to the younger type I but increasingly also to the elderly type II diabetic, if patients with severe vascular disease are excluded [32]. Outcome of transplantation in diabetics is poorer (figure 44-1), but results are continuously improving and an increasing number of patients is asking for transplantation. This is true for both type I (simultaneous pancreas and kidney graft) and for type II (kidney alone). The latter as a matter of fact are not necessarily very old and very handicapped. In the French Uremidiab study [33,34] 40 of the French type II diabetics on dialysis were less than 50 years of age and their own perception of their handicap was not different from that of diabetic patients without nephropathy or non-diabetic dialysed patients. So far cases of transplantations prior to the stage of dialysis dependency have remained anecdotal. Although successful pancreas transplants undoubtedly improve the quality of life, the medical benefit from this procedure remains unproven, although interesting data have accumulated suggesting more favourable evolution with respect to autonomic polyneuropathy.

SUMMARY

The number of diabetic patients entering renal replacement programs has increased in all Western countries. Haemodialysis is the preferred modality of treatment, hemofiltration and CAPD being used only in a minority. The proportion of patients undergoing renal or combined renal and pancreatic transplantation is rising encouragingly. Survival in diabetic compared to non-diabetic patients is worse for all renal replacement modalities. This is mainly due to cardiovascular death. Cardiac death is poorly predicted by the level of blood pressure and blood pressure-related target organ damage, while cholesterol and other lipid parameters are potent predictors. Common clinical problems in the dialysed diabetic include metabolic control, visual disturbance, sequelae of autonomic polyneuropathy, amputation and vascular access.

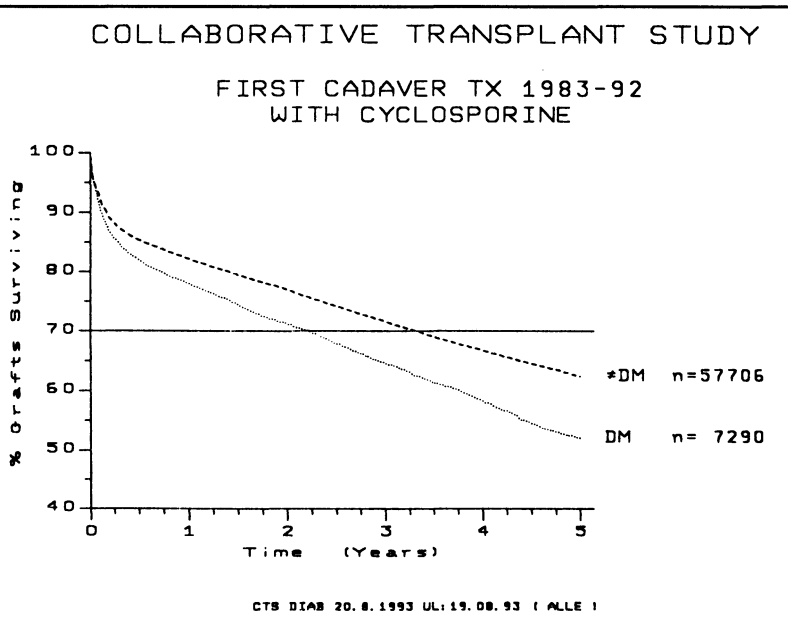

Figure 44-1. Renal graft survival in patients with type I diabetes. (First graft). According to the CTS study (combined transplantation study, courtesy Professor Opelz, Heidelberg).

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45. CONTINUOUS AMBULATORY PERITONEAL DIALYSIS IN UREMIC DIABETICS

ELIAS V. BALASKAS and DIMITRIOS G. OREOPOULOS

Diabetic nephropathy has become the leading cause of end-stage renal disease (ESRD) in such countries as United States, Japan, Scandinavia and much of Western Europe [1]. Haemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD) and renal transplantation are standard therapies for these patients. Despite encouraging results with renal transplantation [2], the majority are treated with dialysis, mainly because of the advanced age of most diabetics and the lack of kidney donors. When transplant is not available or is not medically feasible the choice of dialysis therapy depends on such factors as nephrologist bias, existence of extrarenal disease in the patient, treatment availability and other medical and social factors [1]. CAPD, which offers some advantages in the diabetic, was proposed, from early on, as the preferred dialytic treatment [3]. Now, CAPD is the first choice in dialytic treatment for ESRD in diabetes in Australia, New Zealand, England, Canada and some regions of the United States [1].

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1. INDICATIONS AND CONTRAINDICATIONS

CAPD has both medical and social benefits and most patients with diabetes are eligible for it. This technique enables patients to stay at home and allows flexibility in treatment, giving such social benefits as care at home, long distance travel and uninterrupted employment [4]. The medical benefits of CAPD include [4]: (1) slow and sustained ultrafiltration and a relative absence of rapid fluid and electrolyte changes, (2) ease of blood pressure control, (3) preservation of residual renal function for long periods, (4) easy peritoneal access, (5) good glycaemic control with intraperitoneal (IP) insulin administration, and (6) steady-state biochemical parameters. Moreover, CAPD is ideal for those awaiting transplantation because it requires only a short training period and provides satisfactory support in the immediate posttransplant period [5]. Since this method avoids the rapid fluctuations in extracellular fluid volume and blood pressure, it may be better for patients with significant cardiovascular disease. CAPD becomes imperative for those patients who live a long distance from the dialysis center; among the latter, even if they are not ideal candidates for CAPD, it should be given a trial before recommending change of domicile.

However, patients with previous recurrent peritonitis, severe visual impairment, or any physical disability that limits dexterity (if they do not have a helper at home) are not inappropriate candidates. Elderly patients may have a learning disability and need a helper who is willing to take the responsibility. CAPD, especially if it is accompanied by hypotension may aggravate the symptoms of patients with generalized vascular disease, particularly with involvement of the iliac and femoral vessels. Previous extensive abdominal surgery, low-back pain, history of diverticulitis, polycystic kidney disease, chronic recurrent pancreatitis and chronic obstructive pulmonary disease (COPD) are not necessarily contraindications to CAPD, especially if there are no other contraindications. Finally, severe inflammatory bowel disease, low peritoneal membrane transport, severe active psychotic or depressive disorder and those with intellectual impairment with no helper are contraindications and patients with these disorders should not be assigned to CAPD [1].

2. MODALITY OF TREATMENT

CAPD is a continuous process in which 2 to 3 litres of a commercial dialysate is exchanged 3 to 5 times per day through a subcutaneously tunnelled intraperitoneal catheter. The most widely used of these catheters is the Tenckhoff of which there are many modifications, but the most commonly used of them are the Toronto Western Hospital (TWH) and Swan Neck Missouri (SNM) catheters. Modifications of the Tenckhoff catheter have reduced considerably the incidence of pericatheter

leak, one-way obstruction, and catheter-tip displacement from pelvic cavity [6], however, exit-site infection remains the main problem.

The choice of peritoneal catheter implantation technique (bedside or insertion by peritoneoscopic or surgical technique), which varies from center to center, depends on local surgical practice. Preinsertion patient preparation, insertion technique, subcutaneous tunnel creation, post-operative care, catheter break-in procedure and subsequent catheter and exit-site care in diabetics are similar to those in nondiabetic patients. However, usually CAPD technique is modified to accommodate individual patient handicaps such as visual impairment and extremity amputation. Devices such as Ultraviolet Box, splicer, Oreopoulos-Zellermann connector, Y-transfer set with a UV system, and Injecta-Aid have helped visually or otherwise handicapped diabetics to continue independent lives. [7].

Glucose is an effective osmotic agent in dialysate for generating ultrafiltration during CAPD and an average of 100-150 grams of glucose are absorbed per day. However, glucose may be associated with toxic effects on peritoneum and undesirable metabolic complications, including obesity, hyperinsulinaemia, hypertriglyceridaemia and premature atherosclerosis. Because of these problems many have attempted to substitute (for glucose) other alternative osmotic agents, such as amino acids, xylitol, gelatin, glycerol and polyglucose, but have been foiled by adverse effects, cumulative systemic effects or prohibitive costs [8]. Thus, glucose remains the preferred osmotic agent.

Frequently, diabetic patients with ESRD have many comorbid conditions such as severe vascular disease and eye complications and may be better off if they start dialysis early, at a creatinine clearance of about 10 ml/min, in the hope of preventing or slowing the progression of diabetic complications [9,10]. Furthermore, an increased tubular secretion of creatinine in patients may make creatinine clearance an unreliable index of GFR [11].

3. BLOOD SUGAR CONTROL AND INSULIN ADMINISTRATION DURING CAPD

The aim of the treatment is to achieve at most times a fasting blood sugar below 140 mg/dl, and postmeal levels below 200 mg/dl and a glycosylated haemoglobin of 9% or below. In CAPD patients, blood sugar can be controlled by diet, oral hypoglycaemic agents, IP or subcutaneous (SC) insulin administration, or combination of these. The choice of the route of insulin adminstration depends on such factors as individual patient variations, preferences, and responsiveness [12].

For diabetics on CAPD, insulin can be administered via the IP or SC route and both methods have their own advantages and disadvantages [13]. It seems that the IP route gives better blood glucose control as assessed by mean blood glucose, mean

amplitude of glycaemic excursions and glycosylated haemoglobin [3,4,9,13-15). Several insulin dosage schedules have been described [7,12,13,15,16].

The absorption kinetics of intraperitoneally administered insulin and that secreted physiologically by the islet cells share several physiological similarities. Insulin secreted by the pancreas is transported to the liver via the portal vein and thereafter, 50% of the portal venous insulin is extracted by the liver before reaching the systemic circulation [17]. In the basal state, the ratio of insulin in the portal/-peripheral blood is 3:1 and, in response to administered glucose or amino acids, may reach to 9:1. This high concentration of insulin in the liver, which promotes metabolic modulation of absorbed nutrients, may be important in the normal glucose homeostasis [12]. IP insulin administration allows for continuous delivery of the hormone at a basal rate. Absorption of IP insulin occurs preferentially by diffusion across the visceral peritoneum into the portal circulation and directly across the capsule of the liver [16,18] simulating physiological insulin secretion; this suggests that the metabolism of insulin may be more physiological when the hormone is delivered into the peritoneal space than by systemic injection.

IP insulin absorption continues until the end of the dwell and promotes the control of glycaemia throughout the entire period. Insulin levels in the serum peak 15 to 45 minutes after administration into an empty peritoneal cavity, 90 to 120 minutes when insulin is added to the dialysis solution, but only approximately 50% of the insulin instilled into the peritoneal cavity is absorbed after an 8 hour dwell time [17-22]. The addition of IP insulin has no effect on solute clearances, ultrafiltration volume, or glucose absorption from the dialysate [23] and no one has reported a connection between the IP insulin administration and development of sclerosing peritonitis.

The glucose absorbed from dialysate (80-250 g/day) and the incomplete absorption (<50%) of the insulin delivered intraperitoneally increase the insulin requirements of diabetic patients on CAPD. There are great interindividual variations (18-283 units/day) in IP insulin requirements [23] but usually, the daily IP dose is more than twice the pre-CAPD SC dose [22]. The total daily dose of insulin is divided among all four exchanges but to avoid nocturnal hypoglycaemia, the dose added to the overnight dwell is reduced.. Each exchange with IP insulin should be carried out before meals to achieve peak insulin absorption at the time of food intake and thus minimize postprandial hyperglycaemia. More insulin is added to each additional hypertonic dialysis incorporated into the daily program. In the case of the blind patient who cannot add insulin to the dialysate bags, insulin can be mixed with the dialysis solution up to 24 hours before use without significant insulin absorption onto the plastic bags [24].

One can achieve adequate control of blood glucose with both (IP and SC) methods of insulin administration. SC route may be preferred in patients with frequent episodes of hyper- or hypoglycaemia, excessive IP requirements and inability to add insulin to the dialysate bags [13,14]. However, IP insulin delivery is associated with fewer glycaemic excursions, so that during the day, the difference between low and high glucose values are lower than that seen with SC insulin [25]. Insulin-mediated glucose uptake is closer to normal in CAPD patients treated with IP insulin than in HD patients treated with SC insulin [26]. In a retrospective study, at every time interval for as long as 15 months, blood glucose levels were significantly lower in CAPD patients taking IP insulin compared to both CAPD and HD patients taking SC insulin [27].

It has been reported that IP insulin administration is associated with lipoprotein profiles of lower atherogenic potential, correcting a key step in reverse cholesterol transport in diabetics [28]. Intraperitoneal insulin can suppress hepatic glucose production with a relatively lower degree of hyperinsulinaemia compared to that given by the SC route [29,30]; this is important because increased peripheral insulin levels may be directly related to an increased risk of atherosclerosis [31].

IP insulin delivery avoids SC injections, and some of the causes of glycaemic lability such as degradation in the subcutaneous tissues and variations in absorption; this assures good patient compliance [17,32]. During episodes of peritonitis, IP insulin requirements are increased or decreased, depending upon the relative importance of increased insulin absorption and reduced carbohydrate intake due to anorexia versus increased glucose absorption and the infection-related hyper-catabolism state [12,33].

In CAPD patients, the influence of IP insulin in the progression of target- organ disease is difficult to determine because of the advanced stage of diabetic complications when dialysis is started; however it seems clear that short-term metabolic control with IP insulin is better than that with SC insulin [4]. Subcapsular liver steatonecrosis [36] and malignant omentum syndrome [37] have been reported with IP insulin but more studies are needed to assess these complications.

Despite the reported increased incidence of peritonitis with IP insulin administration in diabetics on CAPD [34], a survey by the National CAPD Registry showed similar peritonitis rates for patients using SC and IP insulin [35].

From these data, it seems that IP insulin administration offers some metabolic and long-term benefits for diabetic patients compared to SC insulin delivery and may be one reason to choose CAPD over HD.

4. BLOOD PRESSURE CONTROL

Although no comparative studies have been done between CAPD and HD diabetic patients regarding blood pressure control, it is generally accepted that this control is better on CAPD; the continuous ultrafiltration and sodium removal, without wide and rapid fluctuations (in fluid removal) produces a stable dry body weight [38]. Thus, the reduction in blood pressure starts with the initiation of CAPD, continues to decrease over the next few months and correlates well with the reduction in the fluid body weight, emphasizing the importance of fluid volume in the pathogenesis of hypertension in ESRD [4,38]. Blood pressure control is satisfactory in at least three quarters of all CAPD patients [39], and often can be achieved without drugs [4,14].

During the course of CAPD, some patients may become sodium depleted due to a combination of dialysate sodium loss and restricted sodium consumption [4]. Total body sodium depletion can lead to hypotension, especially in patients with diabetic autonomic neuropathy and/or with cardiac dysfunction [4].

In diabetic patients, particularly those with significant cardiovascular disease, rapid fluid removal during a HD session can lead to hypotension resulting in ischemic symptoms and complications; the rapid infusion of saline or colloid solution is needed to correct this transient hypotension and maintain blood pressure. On the other hand, the continuous nature of CAPD produces a slow rate of ultrafiltration; one to two litres are removed over a 24-hour period without large and rapid fluctuations of intravascular volume. However, CAPD patients too can develop gangrene if hypotension persists.

All these factors lead us to conclude that CAPD with its effect on salt and water balance and the slower rate of ultrafiltration controls blood pressure in dialysis patients better than does HD, making CAPD the preferred technique in diabetic patients with ESRD, particularly those with severe cardiovascular and cerebrovascular diseases.

5. RESIDUAL RENAL FUNCTION

As is generally accepted, the preservation of residual renal function is important in the management of dialysis patients because of its contribution to the overall solute clearance and fluid removal. Furthermore it can permit liberal fluid and dietary intake and in some cases a reduction in the dose of dialysis. During the last 10 years, many studies have shown that CAPD preserves renal function better sometimes for periods up to 5 years, than does HD [40-42]. This observation may be explained by the rapid changes in extracellular fluid volumes during HD that reduce blood pressure, renal blood flow, glomerular capillary pressure and produce ischemia of remaining nephrons. Another more attractive and important explanation

is that HD has a nephrotoxic effect because of the release of various cytokines, such as interleukin-1 and tumour necrosis factor, and reactive oxygen metabolites during the contact of the blood with HD membranes; these may directly or indirectly damage residual renal tissue [43,44]. On the other hand, at least theoretically, CAPD may be associated with steady glomerular capillary pressure in the remaining functioning glomeruli without any fluctuations to high or low levels; this stability may protect residual renal function [12].

6. VISUAL FUNCTION

Before they start dialysis, during the end stage of renal failure, most diabetic patients already have irreversible retinal lesions usually accompanied with severe hypertension [9,15]. In diabetics on CAPD good blood glucose and hypertension control have been reported to improve visual function [45] whereas others have found that visual acuity deteriorates further [46]. The progression of retinal lesions is similar in CAPD and HD [47] whereas a study of 60 diabetics on CAPD showed improvement (22%), stabilization (57%) and deterioration (21%) [15]. Blood pressure regulation may be of great importance in the stabilization of visual acuity and preservation of vision [47,48]. Contrary to CAPD, HD often leads to rapid fluctuations in intravascular volume while the later technique with heparin administration and hypertension or hypotension during sessions may aggravate retinopathy in these patients [47].

7. PERIPHERAL VASCULAR DISEASE

Severe peripheral vascular disease is a common complication in diabetics with ESRD and leads to ischemic gangrene of the extremities [15]. During the early years it was reported that CAPD might exacerbate peripheral vascular disease - an exacerbation that was associated with persistent hypotension [49]. In all diabetics the prevalence of gangrene of foot or leg ulcer is 10.2%. The results obtained in diabetics on CAPD are conflicting because some studies have reported a high rate of gangrene and amputations [10,15,50] whereas others had a low rate [14]. However, the prevalence of gangrene is similar in CAPD and HD [15,50]. The gangrene and amputation rate can be reduced by preventing hypotension, by avoiding intense ultrafiltration and high doses of antihypertensive drugs, as well as a foot care program.

8. PERIPHERAL AND AUTONOMIC NEUROPATHY

Peripheral neuropathy, which is an almost ubiquitous finding in patients with ESRD induced by diabetes and uremia, tends to progress even after the initiation of both HD and CAPD. It is present in about two-thirds of patients and 25% have no

peroneal nerve conduction [15]. Clinical improvement and stabilization have been reported on CAPD but deterioration has been also observed, and low nerve conduction velocity persists in most cases [51]. Autonomic neuropathy, which is observed in about 10% of patients, can lead to severe postural hypotension. Also, gastroparesis may contribute to malnutrition and micturition disorders after transplantation [15]. During HD with its rapid fluctuations of intravascular volume, diabetic neuropathy may deteriorate.

9. PERITONEAL MEMBRANE FUNCTION

Peritoneal membrane function is assessed in terms of solute and water control. Diabetics maintain a steady biochemical state indicating good peritoneal membrane function [14,15]. In diabetics on CAPD peritoneal ultrafiltration capacity and peritoneal clearances are not different than in nondiabetics [9] and longitudinal studies of peritoneal permeability have shown stable solute transport characteristics for four or more years [52,53]. Ultrafiltration failure is not a frequent cause of technique failure in CAPD diabetics [14,15].

10. PERITONITIS AND PERITONEAL CATHETER-RELATED INFECTIONS

For all CAPD patients, peritonitis is the most common complication and the major cause of hospitalization and »dropout«. Whether diabetic patients are more susceptible to infection than nondiabetics and consequently are at a greater risk of peritonitis is still debated. Many workers have reported no difference in the incidence of peritonitis between diabetics and non-diabetics [3,10,14,46,48] whereas others have found increased peritonitis rates in diabetics [9] and diabetes has identified as a risk factor for the first episode of peritonitis [54]. Isolated bacteria are not different in diabetics and most of these episodes are caused, again, by skin bacteria [14,15]. During peritonitis, due to increased and rapid absorption of glucose, hyperglycaemia is frequent and insulin requirements increase [9,13,15]. However, rarely, inflammation may lead to increased insulin absorption and insulin requirements may decrease [33]. In both diabetics and non-diabetics, peritonitis during CAPD requires the same antibiotic treatment; most episodes are mild and can be treated on an outpatient basis [9,14,15]. Although peritonitis may lead to fatal complications, usually treatment is successful and the mortality rate is low [14,15]. IP insulin administration does not seem to be a risk factor for peritonitis since diabetics not receiving insulin have higher peritonitis rate than those on either IP or SC insulin. Patients using a combination of IP and SC insulin have the lowest rate, according to the National CAPD Registry [55].

Peritoneal catheter-related infections (exit site, tunnel) are reported to be more common in diabetics than in non-diabetics on CAPD [13,56,57]; others have found

no difference in the incidence of exit site/tunnel infection between diabetics (on any insulin administration schedule) and non-diabetics on CAPD [54,55]. Staphylococcus aureus nasal carriage, more common in diabetics than in non diabetics, has been linked to exit site infections [56]. Also, repeated SC insulin injections are said to increase the risk of S. aureus nasal carriage in diabetics [58] and consequently IP insulin administration may reduce this risk [13]. However this was not confirmed by others [14]. All above mentioned findings need confirmation by large studies.

11. MALNUTRITION

Malnutrition, which remains a frequent complication of long-term CAPD, seems to be multifactorial and worsen in diabetics [15]. Gastroenteropathy leading to nausea, vomiting and diarrhoea, persistent urinary loss of protein and higher than non-diabetic protein losses in the dialysate [9,59] produce an increased incidence of mild to moderate malnutrition that is worse in diabetics than in non diabetics [60,61]. Diabetic microangiopathy may produce an increased glomerular permeability with increased protein losses which during peritonitis are excessive. In association with inadequate food intake, this loss may lead to malnutrition [9,14,59-61]. As has been recognized, malnutrition has a negative effect on survival of both HD and CAPD patients [61]. Malnourished diabetic patients on CAPD may benefit from IP administration of amino acids but the results are conflicting [62].

12. HYPERLIPIDAEMIA

The continuous absorption of dialysate glucose in CAPD patients produces an increase in circulating triglycerides, which tends to be proportional to the initial serum triglyceride level [63]. Hypertriglyceridaemia and, to a lesser extent, hypercholesterolaemia are frequent among CAPD patients whereas HDL-cholesterol varies [63,64]. Diabetics with lipid abnormalities on CAPD may be at higher risk of developing atherosclerotic disease [15]. Hypertriglyceridaemia can be managed by dietary restriction, avoidance of lipid-elevating medications, exercise programs and correction of other risk factors, but occasionally more drastic measures are needed such as lipid-lowering drugs or changes in peritoneal dialysis regimens [64]. IP insulin administration has been reported to have a beneficial effect on lipoprotein profile [28].

13. OTHER COMPLICATIONS - HOSPITALIZATION

Other complications such as the mechanical complications of peritoneal catheters, dialysate leaks, hernias, haemorrhoids, sclerosing peritonitis and others, are not influenced by diabetes and occur with the same frequency in diabetics and non-diabetics [9,15].

The frequency of hospitalization and success of rehabilitation depend on selection criteria and the age of the patients. In general, diabetes leads to a significant increase in hospital days among CAPD and HD patients [65]. In earlier studies, the overall hospitalization rate varied between 30 and 40 days/patient-year, about twice the number of days for non-diabetic patients of the same age, probably because of numerous complications and increased morbidity [3,15,51]. However, recent studies have reported lower hospitalization rates with an average of 20 to 23 days/patient-year [9,14] and a smaller difference than before (23 days vs. 17 days for diabetics and non-diabetics respectively) [9]. Diabetics on HD have similar rates of hospitalization [66]. Peritonitis is the main cause and accounts for 30-50% of the hospitalization days [15].

14. CAUSES OF CAPD FAILURE AND DEATH

The main cause of CAPD failure is peritonitis and to a lesser extent, other severe abdominal complications such as sclerosing encapsulating peritonitis, colonic perforation and loss of ultrafiltration. Other reasons for discontinuating dialysis are permanent access problems and malnutrition [15]. A recent study from our center showed that the most frequent cause of CAPD failure was not peritonitis but inability to cope with treatment, probably because we use CAPD as the treatment of first choice but discontinue it if the patient cannot cope with it [14].

The most frequent causes of death are of vascular origin, namely myocardial infarction, cardiac arrest and cerebrovascular accident [14,15], these account for more than 50% to 70% of the deaths. Other causes include infections, malignancies and other infrequent causes. The distribution of these causes is similar in patients on HD and CAPD.

15. PATIENT AND TECHNIQUE SURVIVAL

Survival rates of diabetic patients remain significantly lower than those of non-diabetics on CAPD [9,10,15,48,67-70], although one group has reported similar rates in the two groups [68]. The risk factors that reduce the survival of diabetics are age over 45 years, a previous or current cardiac disease and systolic blood pressure higher than 160 mmHg [48,68]. The high mortality of diabetics on CAPD seems to be related to the comorbid conditions, especially the presence of cardiovascular disease at the start of dialysis; the course of heart disease does not seem to be affected by CAPD. The few diabetics, who have survived for long periods, were younger, free of or with minimal clinical cardiac disease, non-smokers, and with a higher predialysis serum creatinine and lower haematocrit [71]. In our center, seven diabetic patients have been on CAPD for more than five years (range: 65 to 109 months), they were older (5 over the age of 65) and at the

beginning of dialysis had a variety of comorbid conditions (3 or more/patient) [72]; there was no difference in serum creatinine and haematocrit levels between these patients and those who did not survived for long periods. The recent clinical use of such compounds as aminoguanidines to inhibit the formation of advanced glycosylation end products may prevent some diabetic complications, but more studies are needed to confirm these observations [73,74].

After the second year patient survival decreases sharply during the fourth year varies between 30%-57% and during the fifth year, between 28% to 40% [9,14,48,67-70]. Some discrepancies may due to different numbers of patients in the various studies. It is interesting to note that blind diabetics live longer than the sighted ones [68].

The best method to compare survival rates between diabetics on CAPD and on HD is a randomized prospective study containing large numbers of patients to avoid biases in selection common in the EDTA and USRDS registry [69,70] and in other surveys [75,76]. In some regions [77] selection criteria are based on race and sex and regional differences in survival of diabetics seem to exist. Since a prospective study of comparing diabetics on CAPD and HD will never be possible, the next best technique is a retrospective comparison of large numbers of patients dialysed with the two modalities, correcting for risk factors by the Cox proportional hazards model.

Analysis of the USRDS and EDTA data showed that mortality rates tended to be higher for HD than for CAPD in younger diabetic patients while the opposite was the case among older patients [69,70]. The relative risk of death was similar for patients younger than 60 years of age on HD and on CAPD during the 1984 and 1988 periods; for those older than 60 years, the relative risk of death was greater for CAPD patients in 1984 but had improved by 1988. Recent studies from the Michigan Kidney Registry using Cox proportional hazards analysis [78,79] in patients beginning dialysis in 1989 showed that diabetic patients aged 20 to 59 years old had a relative risk of death on CAPD 38% lower than on HD ($P<0.01$). Among diabetics older than 60 years, CAPD patients had a 19% higher risk of death than those on HD, but this difference was not statistically significant ($P=0.08$). The higher mortality rate for older patients on CAPD probably reflects selection bias regarding treatment modality for diabetic patients since older diabetic patients with severe cardiac and peripheral vascular diseases and other comorbid conditions are preferentially chosen for CAPD/CCPD treatment [4]. The lower technique survival rate for CAPD reflects the role of peritonitis as the main complication and the most frequent cause of CAPD failure. The introduction of improved CAPD systems particularly the Y-set system, and the institution of adequacy standards for CAPD may reduce the drop-out rates and lead to improved technique survival rates [4].

16. CAPD IN IDDM (TYPE I) VS NIDDM (TYPE II) DIABETIC PATIENTS

There have been only a few studies of possible differences between insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetic patients on CAPD. Four- and five-year patient and technique survival has been satisfactory and is almost equal between the two groups [80] whereas others have reported decreased 3-year patient and technique survival for NIDDM patients [81]. In our center, [14], we found comparable patient and technique survival rates. In our Type I patients (most of whom were on IP insulin) we achieved a 50% lower rate of peritonitis than in our Type II patients whereas other workers found no difference in the peritonitis rate between patients using IP and those using SC insulin [13,55]. Also, median hospitalization was 7 days in Type I and 9 days in Type II, but the mean of 28 days/patient-year of hospitalization in Type II was about twice that in Type I (14 days/patient-year). A possible explanation of this difference is that the Type II diabetics have a higher average age and a higher incidence of peritonitis [14]. Future prospective studies are needed to demonstrate all possible differences between Type I and Type II diabetic patients.

CONCLUSION

It is apparent that CAPD has certain unique beneficial features both medical and social that lead to better long-term outcomes in diabetic patients. With its potential medical benefits, as enumerated recently by Khanna [4] and its social advantages, CAPD has offered excellent treatment for diabetic patients with ESRD. Consequently there are significant reasons to recommend CAPD as first choice, renal-replacement treatment for the majority of diabetic ESRD patients.

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46. SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION: INDICATION AND RESULTS

INGE BJØRN BREKKE, GUNNAR SØDAL, HALLVARD HOLDAAS, PER FAUCHALD and JAK JERVELL

More than 4.000 pancreas transplantations have so far been performed at some 150 transplant centres world wide [1]. In the majority of cases, the pancreas has been transplanted simultaneously with a kidney transplant to type I diabetics with end stage diabetic nephropathy.

Adding a pancreas to a kidney transplant was initiated in the late 1960's in an attempt to improve the extremely poor results of renal grafting in diabetics by normalizing blood glucose. Since then, new immunosuppressive drugs have drastically improved the outcome of renal transplantation in general, not the least in diabetics. However, pretransplant problems in obtaining acceptable blood glucose control are usually augmented after a renal transplant, partly due to diabetogenic effects of the immunosuppressive medication. Accelerated generalized atherosclerosis is often the consequence, reflected by a high incidence of cardiovascular and cerebrovascular disease and reduced life expectancy.

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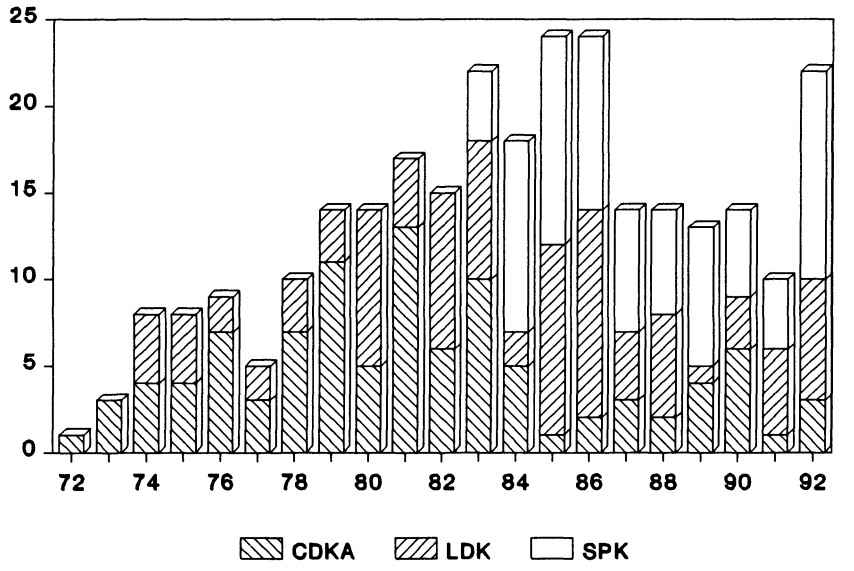

Figure 46-1. Annual number of diabetic transplant recipients.

On the other hand, adding a pancreas transplant to a renal transplant increases potential surgical as well as immunological risks. The number of reoperations and rejection episodes and the duration of hospital stay are increased [2].

The question is: Do the benefits of constant normoglycaemia, and the potential aspects of its long-term influence on diabetic complications, outweigh the increased postoperative risks. If demonstrated that there is no penalty on patient survival or kidney graft function, the answer must be yes.

We have compared the long-term patient and kidney graft survival in our diabetic patients according to type of transplant. The results of this study are reported together with references to studies on effects of pancreas transplantation on late diabetic complications and quality of life. The weakness of our study, as of most of the studies referred to, lies in the patient selection process. However, if 75-85% of the recipients of combined grafts are long-term insulin independent without any penalty on patient survival or renal graft function, arguing for randomized studies is difficult.

Table 46-1. Demographic data on diabetic transplant recipients.

Type of transplant	Sex M/F	Age (yrs)	Duration of diabetes (yrs)	Predialytic %
LDK (n=52)	33/19	38	24	58
CDKA (n=34)	25/9	42	27	32
SPK (n=79)	56/23	39	25	32

1. OUR POLICY FOR URAEMIC DIABETIC PATIENTS

When serum creatinine reaches a level of approximately 300 μmol/litre the patient undergoes a full pretransplant investigation. A living related donor kidney (LDK) transplantation is advocated if a suitable and well motivated donor is available. The transplantation may then be performed as an elective procedure, preferably predialytic, at a time when the patient is in optimal shape.

Since the initiation of our pancreas transplant programme in 1983, those who do not have a living related kidney donor are placed on the waiting list for simultaneous pancreas and kidney (SPK) transplantation, or for a kidney alone from a cadaveric donor (CDKA). In the first years the only excluding factor for acceptance for the combined transplantation was age above 50-55 years. Our present policy is to also exclude from the combined transplantation patients with established or imminent gangrene or uncorrectable symptomatic coronary heart disease. Thus, uraemic diabetic patients are allocated to three different transplant modalities (figure 46-1). Near 50% of the diabetic patients who received a renal transplant in these years also received a pancreas. Only 5% of the total uraemic diabetic population are considered unsuitable for renal transplantation.

1.1 Demographics

Patient age, gender, duration of diabetes, and percentage of predialytic transplantation are shown in table 46-1. The mean age of patients receiving a CDKA was higher than in patients of the two other groups and several in the CDKA group were excluded from the SPK transplantation because of age over 50 or for some other reason. The most striking difference between the LD group and the SPK group is that almost 60% of those who received LD kidneys were predialytic at the time of transplantation, compared to only 32% in the SPK group.

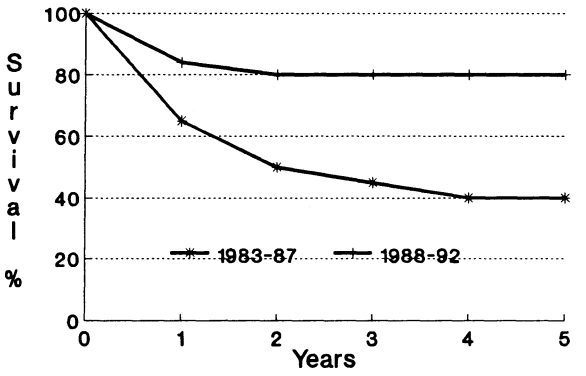

Figure 46-2. Survival of duct-occluded (1983-87) and duct-drained (1988-92) pancreatic transplants.

2. TRANSPLANT PROCEDURES

2.1 Surgical techniques

After having transplanted 53 duct occluded segmental grafts (39 simultaneously with a kidney) during the 5-year period, June 1983-March 1988, we changed to pancreaticoduodenal grafting with bladder drainage. The surgical techniques are described in details elsewhere [3,4].

2.2 Immunosuppression

Rejection episodes are more frequent in SPK than in renal transplants alone [2,5]. Therefore, in most centres, a monoclonal or polyclonal antibody is added to the triple (steroids, cyclosporin, azathioprene) medication during the first 7-14 days after transplantation. We have routinely used triple immunosuppressive medication, and only selected recipients of combined grafts received quadruple induction therapy.

3. RESULTS

The results of pancreas transplantation have improved considerably during the last decade [6], dependant first of all on improvements in immunosuppressive medication and surgical techniques. In our centre, we have experienced a significant improvement in long-term pancreas graft survival (insulin independence) after changing from duct-occluded segmental to pancreaticoduodenal grafting (figure 46-2). At two years the actuarial pancreas graft survival rates with the two techniques were 55% and 80% respectively.

3.1 Patient survival

Improved long-term survival of SPK-graft recipients compared with diabetic recipients of renal transplant alone has been reported [2,7,8]. However, randomized

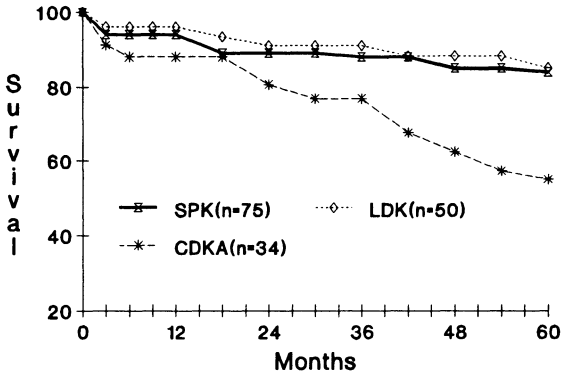

Figure 46-3. Patient survival according to type of transplant.

studies have not been published and it remains unclear to what degree the results are related to patient selection. In our own updated series,there is no difference in 5-year survival between recipients of LDK and recipients of SPK. The actuarial 5-year survival rates of 85%-87% are similar to our result in non-diabetic renal graft recipients, and significant higher than in diabetic recipients of CDKA (56%) (figure 46-3). It should be noted that all SPK recipients are included in this study, whether they have a functioning pancreas transplant or not. Thus, the result in this group reflects pros and cons of the whole procedure, more than favourable effects of normalized carbohydrate metabolism.

3.2 Kidney graft survival

No difference in long-term (5 years) kidney graft survival was observed comparing the LD (68%) and the SPK groups (63%), both groups having survival rates significantly higher than those of the CDKA group (52%) (figure 46-4).

3.3 Metabolic control

All patients with a functioning pancreatic graft were normoglycaemic at all intervals examined. HbA_1 and intravenous glucose tolerance tests showed values within normal range in most of the recipients of segmental grafts [9] and in all recipients of pancreaticoduodenal grafts.

3.4 Quality of life

A functioning pancreas transplant means independence of insulin injections and dietary restrictions as well as absence of hypoglycaemic episodes. The impact of this on quality of life will vary from one individual to the other. However, studies

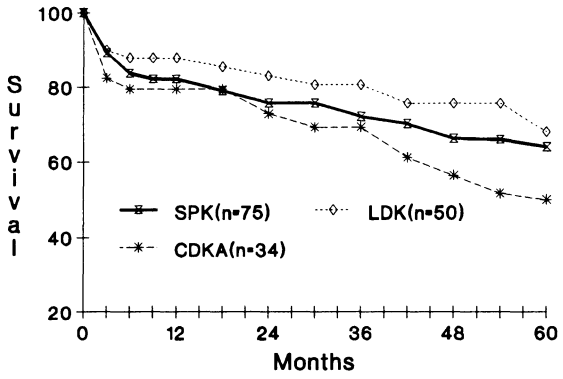

Figure 46-4. Kidney graft survival according to type of transplant.

comparing various groups of diabetic individuals on renal replacement therapy have shown a higher degree of satisfaction with health and life in general in recipients of SPK transplants than in all other groups [7,10-13].

The general experience is that almost all patients who have lost their pancreas transplants are very eager to have another try.

Independence of insulin is of particular benefit for the blind diabetic, who usually is dependent on assistance for insulin injections and blood glucose measurements. The functioning pancreas transplant may enable the patient to master daily life, with a minimum of assistance from others.

3.5 Effect on diabetic complications

Several studies have shown that improved or normalized glucose control may prevent, or even reverse diabetic ***nephropathy*** [14-16]. For the diabetic renal graft recipient this has so far not been of major clinical importance as diabetic nephropathy seems to be a rather rare cause of renal graft loss.

At the time of transplantation, most patients have advanced proliferative ***retinopathy*** which, as a rule, is unaffected by established euglycaemia [17].

Improvements of peripheral ***neuropathy*** and prevention of further progression of autonomic neuropathy has been reported by several authors [18].

4. CONCLUSION

This study shows that patient and kidney graft survival are significantly improved in a selected group of diabetic uraemic patients receiving SPK transplants compared with diabetic recipients of CDKA. No difference in outcome was found comparing recipients of SPK and LDK. The results suggest that patient selection plays an

important role in the outcome of kidney transplantation in diabetics. However, it is also demonstrated that the increased postoperative morbidity experienced in recipients of SPK does not have any adverse impact on either patient or kidney graft survival.

The value of the combined procedure lies in the improvement in quality of life accomplished by constant euglycaemia and independence of insulin injections and dietary restrictions. The prospects of possibly delaying further development of diabetic complications probably also have a beneficial impact on the level of emotional well-being. These aspects makes SPK a favourite therapeutic option for a selected group of diabetic individuals approaching end stage renal disease. Experience from other centers is recently reviewed elsewhere [19].

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47. RENAL TRANSPLANTATION FOR DIABETIC NEPHROPATHY

ELI A. FRIEDMAN

BACKGROUND

Diabetes mellitus, in 1994, is the leading cause of end-stage renal disease (ESRD) in the United States (US), Japan, and most nations in industrialized Europe. All registries in Europe, Asia, and North America show that glomerulonephritis and hypertensive renal disease rank well below diabetes in frequency of diagnosis among new ESRD patients, substantiating Mauer and Chavers contention that »Diabetes is the most important cause of ESRD in the Western world [1]«. The growth of both the total and diabetic population of ESRD patients in the US is depicted in figure 47-1. Data from 1990, the most recent calendar year report of the United States Renal Data System (USRDS), underscore this point. Of 165,363 patients — including 40,174 with diabetes (24.3%) — receiving either dialytic therapy or a kidney transplant in the US in 1990 — 45,153 developed ESRD during 1990 [2]. There were 15,383 (34.0%) diabetics whose renal failure was attributed to diabetes in the new incidence group. Therefore, while the *incidence* of ESRD caused by diabetes is 62 per million out of a total for all diseases of 169 per million, the *prevalence* of

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS. 495

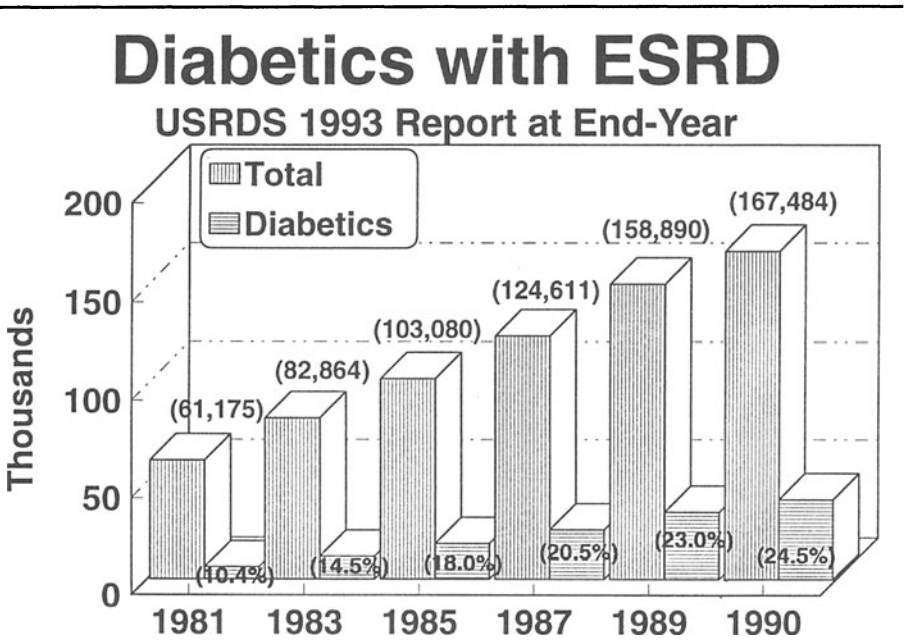


Figure 47-1. Prevalence of ESRD from all causes and ESRD due to diabetic nephropathy in the US on December 31st of each year shown (USRDS for 1993).

diabetics among those undergoing ESRD treatment decreased to a smaller segment of the whole (152 per million out of a total of 618 per million).

An explanation for the progressive sharp reduction of diabetics in the entire ESRD population lies in their higher death rate compared to other causes of ESRD. Because early trials of maintenance haemodialysis in diabetic ESRD patients approached disaster, neither prolonging useful life nor gaining rehabilitation [3], a near unanimity among nephrologists concluded that individuals with diabetic nephropathy should be excluded from ESRD therapy. Indeed, this excess morbidity and mortality, in uraemic diabetics previously discouraged their acceptance for renal transplantation in the belief that their rehabilitation was unobtainable. Even today, a negative view toward proffering renal transplants to diabetics persists as evidenced by a 1993 report from the Groote Schuur Hospital which concludes: »Despite very strict selection criteria, the results of renal transplantation in diabetic patients remains poor. Better treatment strategies are needed to justify acceptance of these patients for transplantation [4]«.

Elsewhere in the world, a more favourable assessment of the utility of renal transplantation in the diabetic ESRD patient is the opinion of groups with a large experience. As summarized by the center with the largest contribution to pioneering treatment for the uraemic diabetic: »Kidney transplant results in diabetic recipients have exceeded the expectations of 20 years ago, both at our institution and others. We currently advocate a kidney transplant for all uraemic diabetic patients [5]«. Central to the improved prognosis for diabetic kidney transplant recipients is recognition that careful regulation of hypertension and hyperglycaemia reduces stress in the peri- and post-transplant period.

Caution is appropriate when extrapolating results in treating the uraemic diabetic from one institution to another. Variables which affect outcome and are not always identified are listed in table 47-1. Comparing treatment of diabetic ESRD patients in Norway and the US illustrates this caveat. Firstly, about 10% of American diabetics are thought to have insulin-dependent diabetes mellitus (IDDM) while as many as 50% of Norwegian diabetics have IDDM. As detailed elsewhere in this text, distinguishing IDDM from non-insulin-dependent diabetes mellitus (NIDDM) separates two disorders with markedly different clinical courses. To illustrate, we surveyed the race and gender of 232 of 1450 (16%) diabetic patients undergoing maintenance haemodialysis at 14 centers in Brooklyn and found the largest patient subset consisted of 87 black woman, who comprised 37.5% of the total study population [6]. NIDDM was clearly diagnosed in 139 or 59.9% of surveyed diabetic patients on haemodialysis, but diabetes type could not be determined in 24 (10.3%) of patients.

Secondly, what is applicable for younger IDDM patients may be inappropriate for older persons with NIDDM. However, an extensive overlap in signs and symptoms often blurs distinction between diabetes types. Nagai found that of 551 patients diagnosed as diabetic before the age of 30 years, 337 (61.2%) had NIDDM [7]. In Japanese diabetics, diabetic retinopathy and nephropathy are as frequent in young onset NIDDM as in IDDM. Defining the faulty limits of present diabetes classification systems, Abourizk and Dunn remarked that: »Clinicians treating diabetic patients encounter numerous insulin-taking diabetic subject who clinically are neither IDDM nor NIDDM«. Further to the point, these workers reviewed 348 consecutive diabetic patients of mean age 53 years, evaluated in Hartford, and concluded that diabetes type could not be established in 35% of whites, 57% of blacks, and 59% of Hispanics. Until a new classification of diabetes is in hand, recommendations pertaining to kidney transplantation in diabetics *by diabetes type* must be interpreted with awareness of the above difficulty. For example, a combined pancreas-kidney transplant is applicable in IDDM but not NIDDM.

Table 47-1. Variables in comparing diabetic kidney transplant recipients

Diabetes type
Mean age
Race
Socioeconomic status
Co-morbid conditions
Skill of surgeon and group
Immunosuppressive regimen
Available support services (podiatry, ophthalmology, cardiology, nephrology, psychiatry)

IDDM VERSUS NIDDM

As a generalization, the majority (70 to 95% depending upon race) of diabetics in Europe and the U.S. have NIDDM: some population subsets such as 100% full blooded **native American** have no IDDM despite a high prevalence of NIDDM. In both IDDM and NIDDM, ESRD is the end-point of nodular and diffuse intercapillary glomerular sclerosis, following, in sequence, hyperfiltration, microalbuminuria, fixed proteinuria and azotemia [8,9,10].

After 20-30 years of IDDM, about 30-40% of patients manifest irreversibly failed kidneys [11]. Over the past forty years, a decreasing proportion of diabetics with IDDM have developed ESRD, reflecting the impact of enhanced blood pressure and blood glucose control. While previously, renal failure was thought relatively rare in NIDDM [12], recent reports of a single population followed longitudinally indicate an approximally equal risk of nephropathy in both major diabetes types. For example, in Rochester, in the US, Humphrey et al. found equivalent rate of renal failure over 30 years in cohorts of 1,832 NIDDM and 136 IDDM patients [13]. Complementing this study, a report from Heidelberg, Germany reached the same conclusion, noting that after 20 years of diabetes, a serum creatinine level >1.4 mg/dl was present in 59% of IDDM and 63% of NIDDM subjects [14]. The message to be extracted from these and other studies is that ESRD is not an unusual conclusion of diabetic nephropathy in NIDDM and may have an incidence approaching that in IDDM. Whatever the incidence of ESRD in NIDDM, in the US, Europe, and Japan, the large majority of new diabetic ESRD cases occur in NIDDM.

URAEMIA THERAPY

Planning long-term management for the uraemic diabetic patient requires matching life style, availability of desired regimen, and social support systems. Understandably, a small proportion of uraemic diabetic patients opt for passive suicide by

declining further dialysis or a kidney transplant [15]. After exclusion of a reversible, profound depression, those individuals wishing to terminate ESRD care — a blind, double lower limb amputee with intractable heart failure, for example — should be guided to a hospice or provided with emotional support at home to minimize agonal discomfort.

Interventional options in therapy must be presented in clearly understood terms in order to enlist the patient as an active member of the renal team. As listed in table 47-2, diabetic patients can have their lives sustained by peritoneal or haemodialysis, performed at a facility or in the patient's home. The decision to perform self-dialysis at home demands unusually strong patient motivation, appropriate space, and an empathetic partner. Survival and rehabilitation of those few (0.7%) diabetics who elect home haemodialysis is superior to facility haemodialysis. Approximately 60% of diabetic individuals with ESRD in the US are treated with facility haemodialysis (figure 47-2). Peritoneal dialysis, utilized to treat about 10% of diabetic ESRD patients permits survival equivalent to that of maintenance haemodialysis. Kidney transplantation is currently applied to fewer than one in five uraemic diabetics (19%) in the US.

KIDNEY TRANSPLANTATION

The combination of diabetes and uraemia presents a major challenge in surgical management [16]. Nevertheless, multiple reports document the consensus belief that long-term survival of the uraemic diabetic patient with a well functioning renal transplant is greater than that afforded by other renal replacement therapy [17]. By 1985, at centers performing a large number kidney transplants, patient and graft survival in renal transplantation in diabetic patients improved to be about equal to non-diabetic patients. Analysis of U.C.L.A. compiled national statistics in the US notes that in 1991, diabetic persons comprised 23% of first renal transplant recipients. In the diabetic recipient cohort, renal allograft survival was not different from other causes of ESRD, excepting the superior functional survival in IgA nephropathy. At its best, one year post-renal transplant, of 995 diabetic recipients in a study of combined pancreas and kidney transplants was a remarkable 84% [18].

Anticipation of delayed wound healing and worry over complicating sepsis are not reasons to exclude diabetics from kidney transplantation. Nor is it true — as previously thought — that diabetics are significantly more likely to develop major complications following transplant surgery than are non-diabetic patients. Nevertheless, adjustments to the treatment plan must be made prior to, during, and after the transplantation procedure to accommodate for the unique problems imposed by diabetes and its vascular complications [19].

Table 47-2. Choices for ESRD management in diabetic nephropathy

HAEMODIALYSIS
Home haemodialysis
Facility haemodialysis
PERITONEAL DIALYSIS
Intermittent (IPD)
Continuous ambulatory (CAPD)
Continuous cyclic (machine) (CCPD)
KIDNEY TRANSPLANTATION
Living donor kidney
Cadaver donor kidney
KIDNEY and PANCREAS TRANSPLANTATION
HAEMOFILTRATION (Europe)

PATHOGENESIS OF RECURRENT DIABETIC MICROVASCULOPATHY

Kidneys in diabetic individuals are under stress induced by haemodynamic and metabolic perturbations. Debate is intense over the relative importance of intraglomerular hypertension [20] versus hyperglycaemia as key causes of glomerulosclerosis. Lacking a reliable indicator of renal morphologic damage, however, precise timing of the transition from diabetes as a purely metabolic disease to that of a multisystem vasculopathy is often a clinical guess. The relative importance of capillary hypertension, hyperglycaemia, hyperlipidaemia, glycation, advanced glycated end-product formation, sorbitol synthesis, nitric oxide formation and genetic predetermination to the pathogenesis of intercapillary glomerulosclerosis is unknown.

No single mechanism explains a large body of seemingly incompatible experimental data. The *hyperglycaemia school* infers from the results of kidney transplantation that ambient glucose concentration is the main risk factor for glomerular damage. Support for this thesis is drawn from several observations: 1. Recurrent intercapillary glomerulosclerosis and renal failure can develop in kidneys obtained from non-diabetic donors that are transplanted into diabetic recipients [21]. 2. Kidney graft recipients who become diabetic only after administration of corticosteroid drugs (steroid diabetics) may develop typical diabetic glomerulopathy — nodular and diffuse intercapillary glomerulosclerosis. 3. In isolated case reports (not confirmed elsewhere), early diabetic glomerulopathy may be reversed by

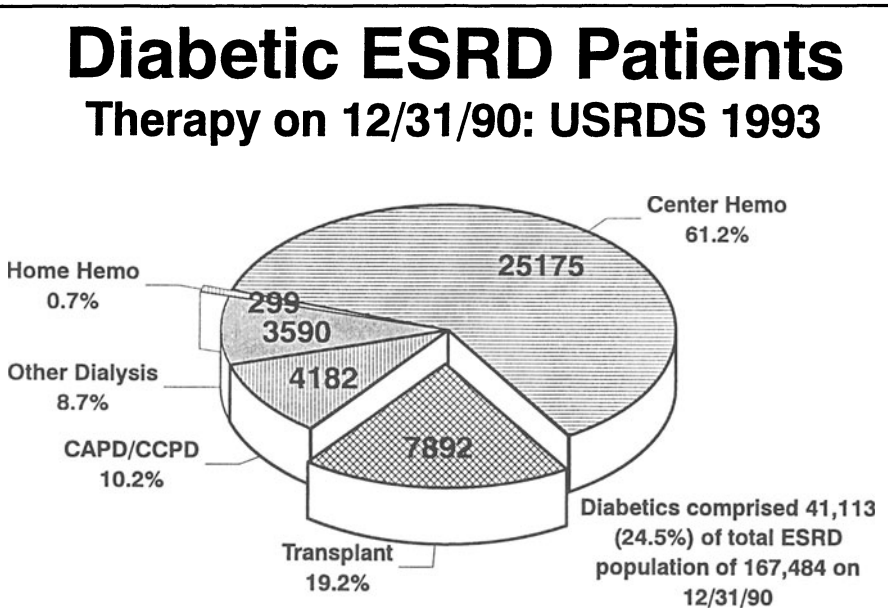


Figure 47-2. Distribution of diabetic patients according to modality chosen for ESRD therapy in the US on December 31st, 1990 (USRDS for 1993).

establishment of a euglycemic environment, as shown by disappearance of glomerulosclerosis in two cadaveric donor kidneys obtained from a diabetic donor after transplantation into nondiabetic recipients [22]. Further to the point, if nephromegaly is accepted as an early morphologic change in diabetic nephropathy, then the reduction in renal size induced by sustained euglycaemia in IDDM is evidence that correction of euglycaemia reverses morphologic injury [23].

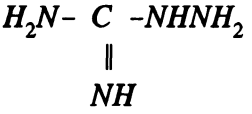
ADVANCED GLYCOSYLATION END-PRODUCTS (AGES)

Brownlee recently reviewed the importance of glycosylation of proteins to the progression of diabetic microangiopathy through the mechanism of formation of advanced glycosylation end-products (AGEs) [24]. Renal failure is associated with both a high serum level of AGEs and accelerated vasculopathy in diabetes. Vlassara et al., injected AGEs to nondiabetic rats and rabbits and showed that physiologic and morphologic changes typical of diabetes resulted [25]. Diabetic uraemic patients accumulate advanced glycosylated end-products in »toxic« amounts that are not decreased to normal by haemodialysis or peritoneal dialysis, but fall sharply, to within the normal range, within days of restoration of renal function by renal

transplantation [26]. *It is this persistent high level of AGEs in dialysis patients which we postulate is responsible to the greater mortality in diabetics of dialytic therapy as compared with a functioning renal transplant.*

AMINOGUANIDINE

Aminoguanidine hydrochloride (Synonyms: guanylhydrazine hydrochloride hydrazinecarboximidamide hydrochloride) is a nucleophilic hydrazine derivative. It has an empirical formula of CH6N4.HCl, a molecular weight of 110.5 and a chemical structure as depicted:



Aminoguanidine administered to streptozotocin-induced diabetic rats pharmacologically inhibits formation of AGEs. In a 9 month trial from the onset of experimental diabetes, aminoguanidine prevented the widening of the glomerular basement membrane that is typical of diabetes [27].

Experimental diabetic retinopathy is also prevented in rats by treatment with aminoguanidine which blocks retinal capillary closure, the principal pathophysiologic abnormality underlying diabetic retinopathy [28]. Similarly, experimental diabetic neuropathy in the rat also is minimized by treatment with aminoguanidine as judged by motor nerve conduction velocity and the accumulation of AGEs in nerves [29].

The rationale for preventing AGE formation as a means of impeding development of diabetic complications has been reviewed [30,31]. An especially appealing aspect of this approach to preventing diabetic complications is the elimination of the necessity for the patient to attain euglycaemia [32]. Aminoguanidine treatment significantly prevents NO activation and limits tissue accumulation of AGEs. Corbett et al. speculate that aminoguanidine inhibits interleukin-1 beta-induced nitrite formation (an oxidation product of NO) [33].

In a derivative study [34], aminoguanidine but not methylguanidine, inhibited AGE formation from L-lysine and G6P while both guanidine compounds were equally effective in normalizing albumin permeation in induced-diabetic rats. A role for a relative or absolute increase in NO production in the pathogenesis of early diabetic vascular dysfunction was also inferred as was the possibility that inhibition of diabetic vascular functional changes by aminoguanidine may reflect inhibition of NO synthase activity rather than, or in addition to, prevention of AGE formation. An alternative role assigned to aminoguanidine is that of a glucose competitor for the same protein-to-protein bond [35] that becomes the link for the formation and

Table 47-3. Co-morbid risks in diabetic patients evaluated for uraemia

1)	Cystopathy. Cystometrogram, urine culture, residual volume.
2)	Heart disease. Electrocardiogram, exercise stress test, coronary angiography.
3)	Gastrointestinal disease. Gastroparesis, obstipation, diarrhoea. Abdominal radiography.
4)	Respiratory disease. Vital capacity.
5)	Preservation of vision. Visual acuity, fluorescein angiography.
6)	Bone consequences of uraemia. Metabolic radiographic bone survey, plasma aluminum level, bone can.
7)	Limb preservation. Podiatric assessment, Doppler flow studies of limb perfusion.
8)	Dental assessment.
9)	Social worker and nurse educator's assessment of potential for self-care.

accumulation of irreversible and highly reactive advanced glycation end-products (AGE) over long-lived fundamental molecules such as the constituents of arterial wall collagen, GBM, nerve myelin, DNA and others. The precise mechanism by which aminoguanidine prevents renal, eye, nerve, and other microvascular complications in animal models of diabetes is under active investigation by Brownlee and associates [36], and others in diverse specialties [37]. Extensive international, multicenter trials of the efficacy of aminoguanidine in the prevention of diabetic nephropathy and the delay of death of diabetic haemodialysis patients are in progress.

Co-Morbidity

Co-morbidity, extrarenal coincident disease, distinguishes diabetic ESRD from nondiabetic ESRD patients (table 47-3). By means of a scoring system (table 47-4) the severity of co-morbid illness in two patients or groups of patients can be expressed quantitatively and compared. We have found the co-morbid index to be a useful tool in the pre-transplant assessment of diabetics on dialysis.

CARDIOVASCULAR DISEASE

Stress on the cardiovascular system may follow the intentional volume expansion during surgery. Pre-transplant cardiovascular evaluation in the diabetic patient is a vital facilitating step prior to kidney transplantation. Should severe coronary artery disease be discovered, revascularization of the myocardium by coronary artery bypass or angioplasty becomes a stipulated requirement to reconsideration of kidney transplantation [38]. Khauli et al. first reported the use of coronary angiography for detecting the presence and severity of coronary artery disease and left ventricular

Table 47-4. Variables in morbidity in diabetic kidney transplant recipients the co-morbidity index

1)	Persistent angina or myocardial infarction.
2)	Other cardiovascular problems, hypertension, congestive heart failure, cardiomyopathy.
3)	Respiratory disease.
4)	Autonomic neuropathy (gastroparesis, obstipation, diarrhoea, cystopathy, orthostatic hypotension).
5)	Neurologic problems, cerebrovascular accident or stroke residual.
6)	Musculoskeletal disorders, including all varieties of renal bone disease.
7)	Infections including AIDS but excluding vascular access-site or peritonitis.
8)	Hepatitis, hepatic insufficiency, enzymatic pancreatic insufficiency.
9)	Hematologic problems other than anaemia.
10)	Spinal abnormalities, lower back problems, or arthritis.
11)	Vision impairment (minor to severe - decreased acuity to blindness).
12)	Limb amputation (minor to severe - finger to lower extremity).
13)	Mental or emotional illness (neurosis, depression, psychosis).

To obtain a numerical Co-Morbidity Index for an individual patient, rate each variable from 0 to 3 (0 = absent, 1 = mild - of minor import to patient's life, 2 = moderate, 3 = severe). By proportional hazard analysis, the relative significance of each variable can be isolated from the other 12.

dysfunction in 48 diabetic patients scheduled for a kidney transplant [39]. The benefit of pre-transplant myocardial revascularization was inferred by the uniform successful outcome in 23 diabetic patients, none of whom died. The remarkably good two-year patient and graft survival for living donor and cadaver donor recipients given »standard« immunosuppression with azathioprine and prednisone was 81% and 68%, and 61% and 32%, respectively.

We concur with Khauli et al. who »discourage transplantation« in patients who have »the simultaneous presence of >70 per cent arterial stenosis and left ventricular dysfunction«. A reasonable policy was proffered by Philipson et al. who studied 60 diabetic patients being considered for a kidney transplant and advised that »patients with diabetes and end-stage renal disease who are at highest risk for cardiovascular events can be identified, and these patients probably should not undergo renal transplantation [40]«. The basis for this position was an analysis of treatment outcome in which only seven patients had a negative thallium stress test, four of whom received a kidney transplant, without subsequent »cardiovascular events«. By contrast, of 53 diabetic patients with either a positive or nondiagnostic stress thallium tests, cardiac catheterization was employed to identify 26 patients

with mild or no coronary disease or left ventricular dysfunction; 16 patients in this group received kidney transplants without cardiovascular incident. In a subset of ten patients with moderate heart disease, of whom 8 received renal transplants, two died of heart disease, while of thirteen patients with severe coronary artery disease or left ventricular malfunction, eight died before receiving a transplant, three from cardiovascular disease. What may be the most important finding by Khauli et al. is that 38% of diabetic ESRD patients had coronary artery disease.

Risk of cardiac death in the uraemic diabetic is so great [41] that pre-kidney transplant evaluation — including a thorough history and physical examination — should include an electrocardiogram, echocardiogram, thallium stress test, and, if needed, coronary artery catheterization and Holter monitoring [42]. Kidney transplantation should not performed in diabetics who evince arrhythmias on minimal exercise, EKG changes on stress, and/or an ischemic myocardium with occluded coronary vessels. An additional benefit of thorough pre-transplant cardiac evaluation is the guidance gained to assist in regulation of volume expansion during the operative procedure.

SCREENING FOR CARDIOVASCULAR DISEASE

All diabetics with ESRD who have experience symptomatic peripheral vascular disease require evaluation pre-operatively with noninvasive Doppler flow studies, and in some instances, angiography to avoid placement of the renal allograft in an area of compromised arterial flow. Specifically, arteries supplying a lower extremity with marginal peripheral flow must not be used to revascularize an organ allograft, because the extremity may be placed in jeopardy of amputation [43]. Diabetic ESRD patients frequently have nearly occlusive arthrosclerotic narrowing of the internal iliac artery forcing use of the external iliac artery for the arterial anastomosis to the allograft. In this circumstance, a local proximal endarterectomy of the external iliac artery can be performed.

MORTALITY

Death in diabetic renal transplant recipients, as in diabetics on dialytic therapy is most often attributed to cardiac disease or a myocardial infarction (MI) as shown in figure 47-3. Despite careful evaluation of the coronary and peripheral vascular systems prior to renal transplantation, there is a high incidence of extremity amputation and cardiovascular death in diabetic renal allograft recipients followed for three or more years [44], due to progression of diabetic macro and microvasculopathy [45]. Age is a correlate of survival in all ESRD patients. Consistent with this generalization, diabetic renal transplant recipients over 40 years of age have a higher mortality rate than that of younger diabetic renal transplant recipients, mainly

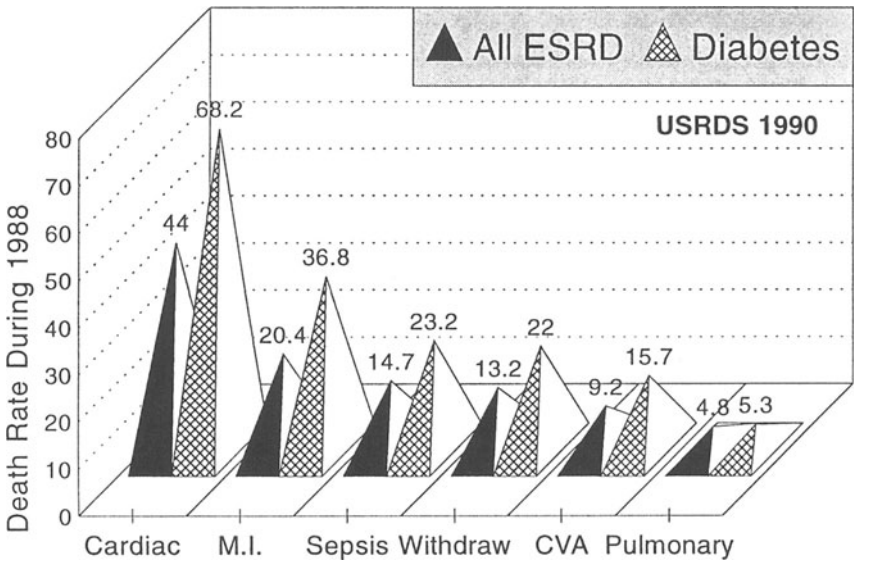


Figure 47-3. Death rate for diabetic ESRD patients compared with death rate for all ESRD patients in the US. Note the higher rate in diabetics for heart disease, myocardial infarction, sepsis, and withdrawal (passive suicide) (USRDS for 1990).

due to a higher rate of cardiovascular death [46]. When comparing different modalities applied to ESRD in diabetes, it should be kept in mind that the increased risk of cardiovascular death post-transplant in older diabetic patients is also present should the same patient be managed by dialytic therapy. Restated, arteriosclerotic heart disease is the leading cause of death in diabetics treated by dialytic therapy or kidney transplantation. The latest USRDS long-term survival results for ESRD due to diabetes are shown in figure 47-4, which underscores the clear advantage of renal transplantation both from cadaver donor and living related donor kidneys.

POST-TRANSPLANT MANAGEMENT

Diabetic recipients of renal transplants spend more days during more frequent hospitalizations than do non-diabetic patients [47]. Post-transplant hospitalizations are prompted mainly by suspicion of allograft failure, infections, or cardiac disease. Perturbations in plasma glucose levels due to changing doses of corticosteroids usually can be managed at home. When wide swings in glucose concentration, including alternating hypo and extreme hyperglycaemia (hyperosmolar non-ketonic coma), become life threatening, hospital admission is wise.

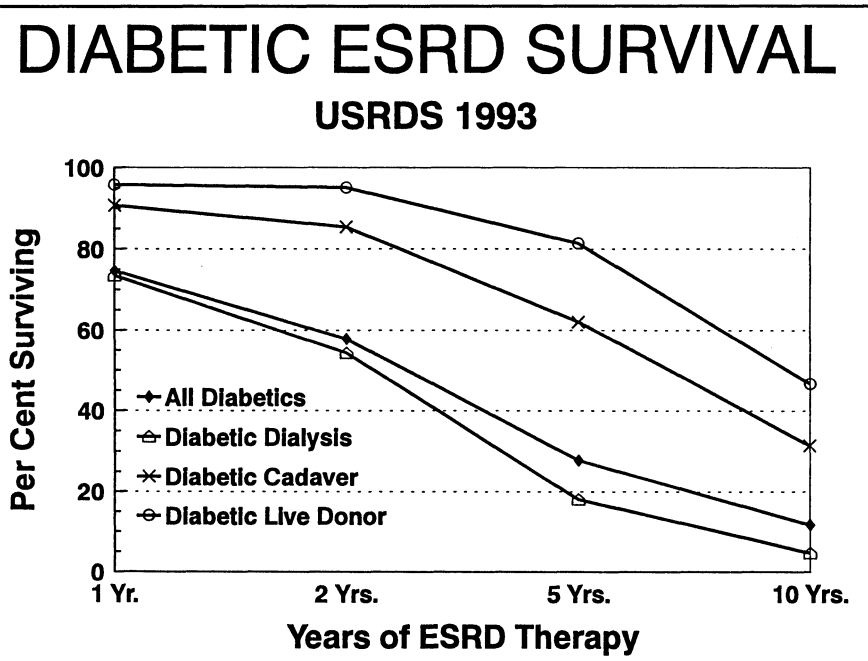


Figure 47-4. Comparative survival by life table analysis over 10 years for diabetic and nondiabetic renal transplant recipients of living-related and cadaver donor kidneys compared with survival on dialytic therapy. Outcome was not statistically different between peritoneal and maintenance haemodialysis, therefore, data are pooled for these two modalities. (USRDA for 1993).

Restoration of normal renal function in a diabetic who developed ESRD because of diabetic nephropathy does not reverse concomitant advanced extrarenal micro- and macrovasculopathy. What distinguishes the diabetic from the nondiabetic renal transplant recipient are the multiple organ system perturbations associated with long standing diabetes. Starting with the immediate post-transplant period, management of the diabetic renal transplant recipient is often complex. For example, distinguishing between acute allograft rejection, acute tubular necrosis, and cyclosporin drug nephrotoxicity in an oliguric newly transplanted patient may be impossible. In many instances, determining a single pathogenetic mechanism after interpretation of renal scans, sonograms, biopsies, and tests of glomerular and tubular function is still largely an art based on experience.

AUTONOMIC NEUROPATHY

Throughout transplant surgery, and the day or two before oral feeding is resumed, metabolic control of plasma glucose concentration is best effected by frequent — hourly when needed — measurements of glucose and an intravenous infusion of 1-4 units per hour of regular insulin. Bethanechol, which may be given in combination with metoclopramide or cisapride, also improves gastric motility. Constipation, sometimes evolving into obstipation, is a frequent problem following transplantation; Effective stimulants to resume spontaneous defecation are early ambulation, stool softening agents, and suspension of cascara. Autonomic neuropathy may, at the other extreme, induce explosive and continuous liquid diarrhoea enervating and dehydrating the post-operative diabetic patient. In our experience, loperamide given hourly in doses as high as 4 mg/hr almost always halts diarrhoea. Another troublesome manifestation of diabetic autonomic neuropathy is diabetic cystopathy, a functional urinary bladder outflow obstruction. Encouragement to the patient adapting to a regimen of frequent voiding and self-application of manual external pressure above the pubic symphysis (Credé Maneuver) plus administration of oral bethanechol usually permits resumption of spontaneous voiding. Repeated self-catheterization of the bladder may be the only means to avoid an indwelling catheter when an atonic bladder is unresponsive to the above protocol.

IMPOTENCE

Caused by arterial insufficiency and diabetic neuropathy, erectile impotence is common in diabetic dialysis patients and, in a minority of patients, may improve after a successful kidney transplant. Unless due to psychiatric cause, impotence in diabetes has a poor prognosis. Resort to a penile prostheses, or pre-coital intrapenile injections of prostaglandins may be appropriate for rehabilitation when impotence persists.

LIFE QUALITY

Diabetic renal transplant recipients rate their quality of life as equivalent to that of the general population in the US. Rehabilitation of the diabetic transplant recipient often hinges on a team approach to management which minimizes the time devoted to multiple visits to different specialists. Typically, the diabetic transplant recipient is expected to make repeated visits to ophthalmologist, podiatrist, endocrinologist, nephrologist and internist. Success of the renal transplant team depends upon collaboration with an ophthalmologist skilled in laser surgery and a podiatrist experienced in preventative management of diabetic feet. Progressive vasculopathy, even in those given a renal transplant before initiation of a dialysis regimen, does

Table 47-5. SUNNY, Health Science Center at Brooklyn. Kidney transplants in diabetes. 175 transplants in 158 recipients 1/1/78 to 12/31/91.

Patient survival	1 Yr	2 Yrs	5 Yrs	10 Yrs
All	81.4%	76.7%	62.8%	54.2%
Men	84.3%	77.4%	62.6%	58.9%
Women	76.5%	74.9%	63.6%	47.4%
Blacks	72.4%	72.4%	54.4%	46.0%
Whites	83.4%	78.1%	64.3%	51.9%
Live donor	84.6%	82.7%	63.0%	53.4%
Cadaver donor	79.5%	73.4%	62.2%	54.8%
Graft survival	68.5%	63.1%	46.6%	37.1%

not prevent worsening many diabetic patients become increasingly disabled due to progressive extrarenal disease processes.

RECURRENT NEPHROPATHY

Recurrent diabetic glomerulopathy, along with allograft rejection, cyclosporin toxicity and single kidney hyperfiltration pose threats to renal allograft integrity. First detectable as GBM thickening with mesangial expansion after two years [48] and later as characteristic glomerulosclerosis in recipients with IDDM [49], after five or more years [50], recurrent diabetic nephropathy may present as a nephrotic syndrome followed by progressive azotemia and finally and sadly as recurrent ESRD. Life table analysis of the experience with 175 renal transplants in 158 diabetic recipients is shown in table 47-5. Approximately half of those given a living related kidney survived their first post-transplant decade. After kidney transplantation, survival of diabetic recipients may be longer than a decade [51]. Of 265 ESRD patients with IDDM at the University of Minnesota, who were given a renal transplant between December 1966 and April 1978, 100 were alive with a functioning graft 10 years later, an actual patient and primary graft survival of 40% and 32%, respectively. HLA-identical recipients of living related kidneys attained a remarkable actual 10-year functional graft survival of 62%. 23 recipients died in the second decade after kidney transplantation; death from cardiovascular disease occurred in 10, continuing the pattern observed during the first decade.

CONCLUSIONS

A functioning kidney transplant provides the uraemic diabetic patient a greater probability for survival with good rehabilitation than does either CAPD or maintenance haemodialysis. There are no reports, however, of prospective controlled studies of dialysis versus kidney transplantation in diabetic patients whose therapy was assigned randomly. For the minority (< 10%) of diabetic ESRD patients who have IDDM, serious consideration should be devoted to performance of a combined pancreas and kidney transplant to effect a cure of the diabetes so long as the pancreas functions [52]. No matter which ESRD therapy has been elected, optimal rehabilitation in diabetic ESRD patients requires that effort be devoted to recognition and management of co-morbid conditions. Uraemia therapy, whether CAPD, haemodialysis or a kidney transplant should be individualized to the patient's specific medical and family circumstances. Although physical rehabilitation is greater in kidney transplant recipients than in uraemic diabetic patients treated by CAPD or maintenance haemodialysis, past surveys - mainly of non-diabetic patients - indicate that the patient's subjective ranking of life quality is equivalent in all three modalities.

Introduction over the past three years of recombinant erythropoietin for uraemic anaemia has so greatly improved the medical stability of dialysis patients whose red cell mass is increased that reappraisal of for all conclusions pertaining to survival, morbidity, and rehabilitation in ESRD that were completed before its introduction. So great is the impact of erythropoietin that new baselines for *usual outcome* must be drawn for CAPD and haemodialysis in both diabetic and non-diabetic patients. Some very well dialysed diabetic haemodialysis patients with normal haematocrits might now opt to delay cadaveric transplantation until less toxic drugs, such as FK 506 [53] are introduced for immunosuppression.

Attention to control of hypertension and hyperlipidaemia may slow the course of macrovascular disease, particularly of the coronary arteries, which threatens long-term survival of diabetic kidney recipients. Pre-transplant cardiac evaluation is mandatory to identify and correct silent coronary artery disease that may be severe and life threatening. Continuously improving results have been reported in the treatment of ESRD in diabetes, first by dialytic therapy, then by renal transplantation, and currently, in IDDM, by combined pancreas and kidney transplantation. This inexorable progress reflects multiple small advances in understanding the pathogenesis of an inexorable disease.

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ST VINCENT DECLARATION, 1994:

GUIDELINES FOR THE PREVENTION OF DIABETIC RENAL FAILURE

GIAN CARLO VIBERTI, CARL ERIK MOGENSEN, PHILIPPE PASSA, RUDY BILOUS and RUGERO MANGILI (External adviser: Anthony Raine)

EPIDEMIOLOGY AND PHASES OF DIABETIC NEPHROPATHY

Diabetic nephropathy is a major cause of premature death in diabetic patients, largely from uraemia and cardiovascular disease. Diabetic nephropathy develops in about 30% of people with insulin-dependent diabetes mellitus. The cumulative risk of nephropathy in people with non-insulin-dependent diabetes varies considerably with ethnic origin. It ranges from 25% in individuals of European origin to around 50% in other ethnic groups such as the Afro-Caribbean, Asian Indians, and the Japanese. In the UK geographic areas at high density of these ethnic groups are likely to experience a higher incidence of renal disease. Asian Indians develop non-insulin-dependent diabetes more frequently and at a younger age than Europeans and Afro-Caribbean have a significantly higher frequency of arterial hypertension. All these factors are believed to contribute to their higher risk of kidney failure. Overall non-insulin-dependent diabetes is significantly more common than insulin-dependent diabetes and the number of non-insulin-dependent diabetic patients being accepted into renal replacement therapy (RRT) programmes is now equal, if not greater, than

Mogensen, C.E. (ed.), THE KIDNEY AND HYPERTENSION IN DIABETES MELLITUS.

that of insulin-dependent diabetics. In Europe diabetes is the only increasing cause of end-stage renal failure and diabetic patients represent around 13% of all patients receiving RRT. This percentage rises to approximately 30% in the United States of America. The cost of renal replacement therapy for end-stage diabetic renal failure in the United States was around $2 thousand million in 1991.

Diabetic renal disease is a multi-stage condition that requires several years to become clinically overt. At the onset of the disease, there are usually changes in renal function, such as glomerular hyperfiltration, increased renal blood flow and hypertrophy of the kidney. At an early stage, most of these changes can be reversed, but they persist in many patients and may have prognostic significance for the later development of clinical nephropathy. These early changes seem to occur both in insulin- and non-insulin-dependent diabetic patients.

The first sign of diabetic nephropathy is a persistent increase (that is, at least two out of three consecutive sterile timed urine specimens) in the albumin excretion rate to 20-200 μg/min (30-300 mg/day). This phenomenon is called microalbuminuria and may be detected after one year of diabetes in insulin-dependent diabetic patients of post-pubertal age and at diagnosis in non-insulin-dependent diabetes. Microalbuminuria indicates incipient nephropathy. Blood pressure is often raised in incipient nephropathy although hypertension, according to WHO criteria (blood pressure > 140/90 mmHg), may not be present. Lipid abnormalities already accompany microalbuminuria including elevation of low density lipoprotein cholesterol, total triglycerides and apoliprotein B and reduction in high-density lipoprotein (subclass 2) cholesterol. The glomerular filtration rate may begin an accelerated decline when albumin excretion approaches 200 μg/min (300 mg/day). Microalbuminuria in both types of diabetes is predictive of persistent proteinuria and early death from cardiovascular disease. Moreover, microalbuminuria is associated with a higher prevalence of retinopathy, particularly in IDDM, peripheral vascular disease and neuropathy. Microalbuminuria which develops in the first few months of a diabetic pregnancy may signal an increased risk of pre-eclampsia.

The development of persistent proteinuria, by definition an albumin excretion rate >200 μg/min (300 mg/day), peaks after about 17 years of diabetes in IDDM and usually after a shorter time span in NIDDM of European origin. It marks the onset of clinically overt nephropathy and is a harbinger of renal failure and cardiovascular complications in both types of diabetes. Various degrees of arterial hypertension usually occur with persistent proteinuria, and with time the protein loss may increase to cause nephrotic syndrome with hypoalbuminaemia and peripheral oedema. Lipid disturbances and atherosclerotic complications are prominent in this phase. Some degree of diabetic retinopathy usually accompanies persistent proteinuria and its absence should alert the health professional to the possibility of

non-diabetic causes for the proteinuria. It should be remembered that up to 10% of patients with insulin-dependent diabetes and 30% of those with non-insulin-dependent diabetes and proteinuria have a non-diabetic renal disease. Persistent proteinuria is accompanied by a gradual decline in the glomerular filtration rate. If untreated, this eventually leads to uraemia and death - on average, after 7-10 years.

People with end-stage renal failure require renal dialysis or transplantation. The outcome of renal replacement therapy, however, remains poorer in diabetic than in non-diabetic patients with chronic renal failure. Moreover, the associated vascular, neuropathic and infective complications add to the socio-economic costs of replacement therapy in the patients with diabetes.

SCREENING AND MONITORING PROGRAMME

A screening programme is needed for microalbuminuria and persistent proteinuria to detect the subset of diabetic patients at risk of developing renal failure and early cardiovascular morbidity and mortality. Those patients found to be at risk should be regularly monitored. It should be remembered that heavy exercise, urinary tract infection, acute illness and cardiac failure can also transiently increase urinary albumin excretion. All diabetic patients who are above the age of 12 years, after initial stabilisation of their metabolic control, should have their urine tested for albumin excretion at least once a year. The most accurate method is a timed urine collection, either overnight or for 24 hours. However, this is often impractical and inconvenient for many patients. A reliable screening method is to measure albumin concentration or albumin/creatinine ratio in the first morning urine sample. Semiquantitative side room tests have been developed for albumin concentration in the microalbuminuria range and may be used in the doctor's office or by the patients themselves as first line screening to be confirmed by quantitative assays.

An albumin concentration below 20 mg/litre, an albumin/creatinine ratio below 2.5 mg/mmol for men and 3.5 mg/mmol for women and an albumin excretion rate below 20 μg/min should be considered normal. If a normal concentration or albumin/creatinine ratio is found, a timed urine collection is not needed. If the urinary albumin concentration or the albumin/creatinine ratio is elevated (that is $\geq$20 mg/litre or $\geq$2.5 mg/mmol for men or $\geq$3.5 mg/mmol for women respectively), this abnormal value should be confirmed. If a repeat value is within the normal range, no further action is needed. If the value persists abnormal, ideally a timed urine collection is required to confirm the diagnosis. An albumin excretion rate greater than 20 μg/min (30 mg/day), in two out of three urine samples, tested within 6 to 12 weeks, warrants the diagnosis of incipient or overt nephropathy. When facilities are not available locally, referral to a specialist centre should be considered.

Patients with normal rates of albumin excretion do not need to be monitored more than once a year. All diabetic patients should have their blood pressure (Korotkoff phase I/V) measured under standardised conditions at least once a year.

Patients with elevated rates of albumin excretion should be monitored more often as required by clinical conditions and treatment strategies. The progression of their proteinuria should be checked either by timed urine collection (when facilities are available) or by the use of repeated early morning albumin/creatinine ratios. In these patients regular and more frequent checkups should be carried out to assess blood pressure levels, glycaemic control, serum lipids and serum creatinine. Regular screening for retinopathy, neuropathy, coronary, cerebrovascular and peripheral artery disease should be performed (see diagram).

PREVENTION AND TREATMENT PROGRAMME

Incipient Nephropathy: The Microalbuminuric Stage

There are at present no methods for detecting susceptible individuals before the development of microalbuminuria though levels of albumin excretion rate in the upper area of the normal distribution appear to predict microalbuminuria. Blood glucose control over time is important in determining who will develop nephropathy but individual susceptibility to hyperglycaemia is also very important.

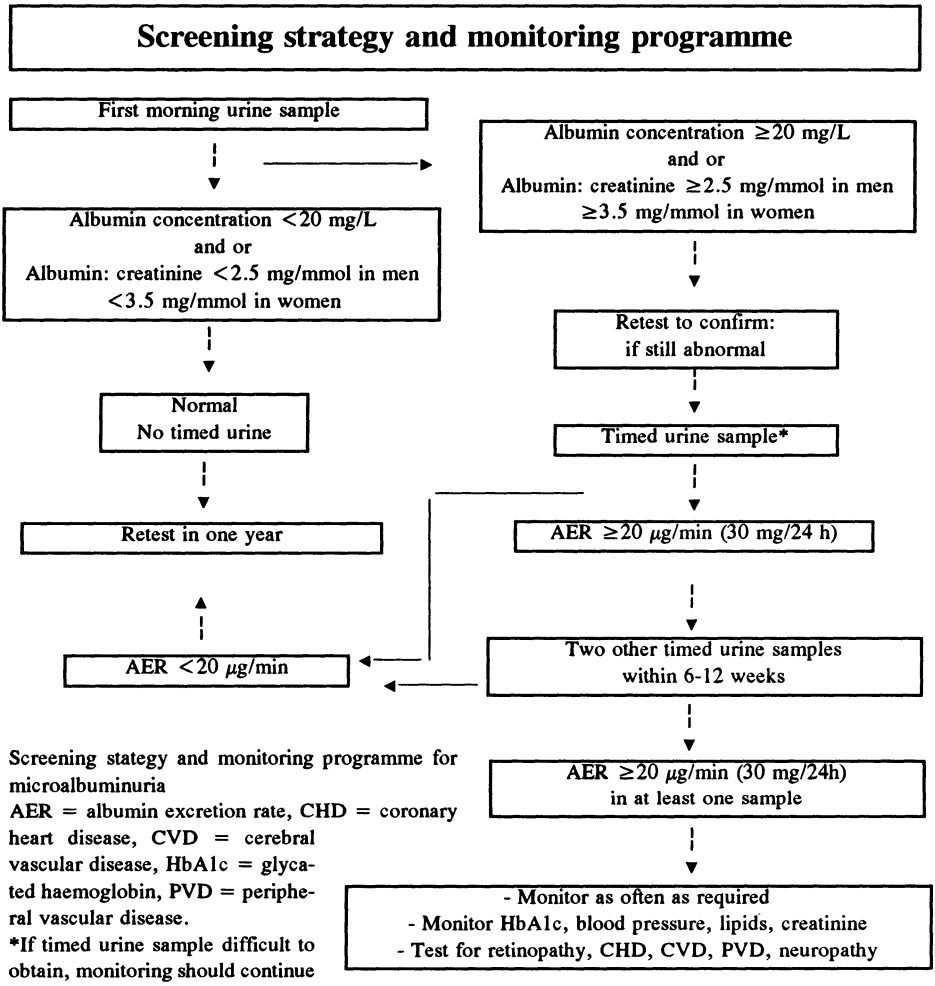
Glycaemic control

In microalbuminuric patients blood glucose control should be improved as much as possible as this may delay the progression to persistent proteinuria. Improved blood glucose control seems to prevent histologic worsening of glomerulopathy. Primary prevention of the development of microalbuminuria is possible with intensified insulin treatment in insulin-dependent diabetic patients. There is a linear relationship between achieved level of glycaemic control and the development of retinopathy. This pattern of relation may apply to renal complications as well. Thus the best possible control should be aimed for in each individual patient. However, due regard must be placed on the potential for increased risk of hypoglycaemia and loss of warning symptoms with intensified insulin regimens.

There are as yet no firm data in non-insulin-dependent diabetic patients but insulin treatment could be considered in those microalbuminuric patients who are poorly controlled on oral agents.

Blood pressure

Raised arterial blood pressure has particular damaging consequences not only for the kidney but also for the heart and retina. In adult subjects hypertension should be



Screening stategy and monitoring programme for microalbuminuria
AER = albumin excretion rate, CHD = coronary heart disease, CVD = cerebral vascular disease, HbA1c = glycated haemoglobin, PVD = peripheral vascular disease.
*If timed urine sample difficult to obtain, monitoring should continue with the use of the Albumin/Creatinine (A/C) ratio. No prospective study has however so far evaluated the validity of A/C ratio as a monitoring index (see Research Programme section).

defined as a blood pressure greater than 140/90 mmHg in patients less than 60 years of age and greater than 160/90 mmHg in patients older than 60 years. If non-pharmacological interventions (such as dietary or life style changes, including salt and alcohol intake restriction, weight reduction and increased exercise) do not suffice, pharmacological agents that do not adversely affect lipid or carbohydrate metabolism should be considered.

Treatment with angiotensin converting enzyme (ACE) inhibitors with or without diuretics has been found to delay progression to overt diabetic nephropathy in normotensive insulin- and non-insulin-dependent patients. However, anti-hypertensive treatment regimens should be tailored to the individual and consideration of concomitant cardiovascular disease may determine the treatment choice.

Serum lipids

Microalbuminuria may be associated with elevated levels of cholesterol and triglycerides in both insulin-dependent and non-insulin-dependent patients. There are no long-term data on the effect of non-pharmacological and pharmacological lipid lowering interventions in these patients. However, dietary restriction, weight reduction and improved metabolic control should be considered in all diabetic patients with incipient nephropathy.

Smoking

Smoking is associated with the development of microalbuminuria and should be vigorously discouraged in all patients.

Protein restriction

There are some preliminary data that a diet rich in protein (particularly of animal origin) may contribute to the development of microalbuminuria in insulin-dependent diabetic patients. Although long-term clinical trials of protein restriction have not been carried out, it is probably reasonable to limit the protein intake in microalbuminuric patients to approximately 0.8-1 g/kg body weight per day and to consider a replacement of some animal protein with vegetable sources. Special consideration however must be made for children and adolescent patients.

Clinical Nephropathy: The Macroalbuminuric Stage

Several factors may influence the rate of progression of overt nephropathy to endstage renal failure and its associated vascular complications. They require early identification and treatment.

Blood pressure

Treatment of hypertension in insulin-dependent diabetic patients with a variety of drugs including cardio-selective beta-blockers, diuretics, hydralazine, and ACE inhibitors have all shown a positive benefit in slowing the rate of decline of renal function. The addition of ACE inhibition to standard anti-hypertensive treatment appears to confer an additional benefit in relation to the doubling of serum creatinine and early mortality in insulin-dependent diabetic patients with nephropathy, an effect partly independent of blood pressure lowering. Few data, however, are available in non-insulin-dependent diabetic patients.

The targets for blood pressure control are the same as those outlined for microalbuminuric patients. Non-pharmacological intervention is usually not sufficient to correct arterial hypertension at this stage of nephropathy. Loop rather than thiazide diuretics should be preferred when there is water retention. If thiazide diuretics are used, low doses should be employed. Initiation of ACE inhibitor therapy should be combined with close monitoring of serum creatinine and potassium because of the possible co-existence of renal artery stenosis, particularly in older non-insulin-dependent diabetic patients and of hyporeninism-hypoaldosteronism in long-standing insulin-dependent diabetic patients. Postural hypotension with supine hypertension may be troublesome in those patients with concomitant autonomic nephropathy.

Protein restriction

A beneficial effect of protein restriction has been shown in insulin-dependent diabetic patients with nephropathy, but a 3 year study in a large group of predominantly non-diabetic patients with renal impairment has failed to show any significant benefit.

Thus a reduction in animal protein intake should be considered in insulin-dependent patients with clinical nephropathy to a level of between 0.6 to 0.7 g/kg body weight/day. The replacement of animal by vegetable protein sources could also be considered as the latter seems to be less damaging to the kidney. All such treatment should be undertaken under expert nutritionist control and great care should be taken to minimise any potential untoward effects of low protein diets.

Serum lipids

Abnormal lipid profiles are prominent in clinical nephropathy and may contribute to the progression of renal failure and the incidence of cardiovascular complications. However, there are no published studies to date indicating any direct benefit from non-pharmacological or pharmacological intervention to reduce circulating serum lipids in these patients. We recommend that dietary and life style modifications

should be adopted as for patients with incipient nephropathy until more definite data are available.

Glycaemic control

There is no convincing evidence that strict blood glucose control helps to slow the progression of established clinical nephropathy. Intensified insulin treatment may expose patients with nephropathy to the risk of hypoglycaemia and there are data suggesting that warning symptoms are blunted in such patients. In non-insulin dependent diabetic patients with impaired renal function biguanides, chlorpropanide and glibenclamide must not be used and insulin therapy should replace oral agents when the GFR is lower than 30 ml/min.

Associated complications

Micro- and macrovascular complications may progress rapidly in clinically proteinuric patients. Monitoring of retinopathy, neuropathy and atherosclerotic complications should be performed and any abnormalities promptly treated. Guidelines for the management of these problems occur elsewhere in this document. Smoking has been found to be associated with a higher prevalence and poor prognosis of proteinuria and every effort should be made to encourage patients to stop.

Nephrological referrals

When a patient's serum creatinine exceeds 200 μmol/l (2.2 mg/dl) joint treatment by diabetes and renal specialists should be considered and preparation for renal replacement therapy should begin as appropriate to local resources and practice.

Endstage Renal Failure: The Uraemic Phase

Diabetes should not exclude patients from renal replacement therapy programmes. The mode of therapy used (dialysis or transplantation) will depend upon clinical judgement and local facilities and resources. Good glycaemic control is important for patient well being prior to and throughout renal replacement therapy.

In specialised centres consideration might be given to combined kidney and pancreas transplantation to maintain euglycaemia and prevent recurrence of glomerulopathy in the transplanted kidney. During the azotaemic phase the measurement of HbA_{1c}, by standard techniques, and therefore its use as a monitoring index for diabetic control, is unreliable because of carbamylation of haemoglobin. Carbamylated haemoglobin comigrates with glycated haemoglobin. Serum fructosamine may be preferable provided gross changes in serum albumin concentration are taken into account.

Recent data have suggested that careful cardiovascular assessment including coronary angiography and correction of significant coronary lesions may confer improved life expectancy, particularly in those patients undergoing transplantation. The investigation and management of vascular disease in the individual patient will depend greatly upon local resources.

PREGNANCY AND PROTEINURIA

The development of micro- or macroalbuminuria during a diabetic pregnancy should alert the physician to the risk of pre-eclampsia. Pregnancy is no longer a contraindication in a diabetic woman with proteinuria and renal failure. However proteinuria may rise and the risk of eclampsia is increased. Worsening of arterial hypertension with acceleration of micro- and macrovascular disease may occur. In some cases, pregnancy may adversely affect the natural progression of diabetic nephropathy. The rates of spontaneous abortion and fetal malformations in women with diabetic nephropathy is reduced to around 9%. Good blood glucose control before and during conception is critical to reducing the frequency of malformations. The preferred forms of treatment for moderate to severe hypertension (mild hypertension may not require any therapy) are methyldopa or an adrenoceptor antagonist, such a labetalol or oxprenolol, or hydralazyne or a calcium-channel blocker. A stepwise approach seems most suitable. Bed rest may be of some value in severe cases. Pregnancy in a diabetic woman with proteinuria should be carefully considered and planned. Management should be in a specialised centre and by collaboration of a team of experts including diabetologist, nephrologist and obstetrician.

COUNSELLING AND EDUCATION

An important role is identified for the diabetes specialist nurse in instructing diabetic patients and in briefing the community and practice nurses about care for renal complications.

Counselling is considered important at all stages from onset of diabetes through the phases of microalbuminuria and established nephropathy to end-stage renal failure and renal replacement therapy. It should serve the purpose of (1) helping understand diabetic kidney disease in its correct prospective; (2) alleviating anxiety concerning early renal damage; (3) explaining the options for prevention and treatment; and (4) introducing the patients to future treatments of renal replacement therapy.

At the stage of renal support treatment close liaison is required between diabetes and renal specialist nurses to ensure that continued care is taken of diabetes control and of the other vascular and neurological complications (e.g. retinopathy, foot disorders) which continue to progress and may be accelerated by the renal failure.

EVALUATION OF THE EFFECTS OF PREVENTIVE STRATEGIES

Construction of a Dataset

Ideally a dataset and data record for kidney disease in diabetes should be constructed. Its purpose would be to provide the information necessary for the management of diabetic renal damage to include surveillance of patients not known to be affected, continuing management of those with nephropathy of any degree and quality assurance and development.

The objectives of the dataset are: (1) to provide an efficient and inexpensive means of monitoring people with diabetes for renal damage; (2) to provide the basis of continuing monitoring of those with evidence of renal damage due to diabetes, in order to ensure adequate decisions are made over continuing care; (3) to provide evidence on progress in meeting the St Vincent Declaration objective for diabetic renal disease; (4) to provide evidence with which providers of care can judge the quality of the care they are providing, and make informed judgements on improving it.

The recommended dataset should include data fields for: serum creatinine, dialysis/transplantation, cause of renal impairment, reagent strip micro/macroalbuminuria, urinary tract infection, urine albumin concentration/AC ratio, albumin excretion rate, systolic blood pressure, diastolic blood pressure, anti-hypertensive therapy, ACE inhibitor treatment, serum cholesterol, serum triglyceride. Datafields for demographic details, diabetes treatment, blood glucose control and other micro- and macrovascular complications appear elsewhere in this document.

Assembling this dataset has to take into consideration (1) that the overall incidence of diabetic nephropathy is low and data will have to be aggregated over quite large populations in order to measure changes; (2) that some of these patients are managed exclusively by renal services; (3) that diabetic renal disease is associated with other pathological changes due to diabetes requiring close coordination with datasets of other working groups of this document for proper care of the patient.

The logistic and financial means for the practical realization and implementation of a dataset and data record for diabetic nephropathy remain to be explored. Some facilities are however already available at present and important initiatives have been taken. The database of the European Dialysis and Transplantation Association (EDTA) Registry is an invaluable source of information to measure annual changes in the number of diabetic patients entering renal replacement therapy (RRT) and their demographic characteristics. The EDTA Registry has recently set up a Diabetic Nephropathy Working Group to study and monitor end-stage renal failure in diabetes and to liaise with complementary initiatives such as the St Vincent Declaration Action Programme. The EDTA Registry provides data only on patients receiving

renal replacement therapy, and gives no information on the true prevalence or incidence of end-stage renal failure. No registry for the recording of proteinuria and serum creatinine in diabetic patients is available. However, this information has been collected in a large series of diabetic patients screened in several European countries by the EURODIAB Study. On a sample basis this study may provide a partial dataset against which to test the efficacy of recommendations for treatment. Multiple factors can affect the prevalence and incidence of proteinuria, elevated serum creatinine and end-stage renal failure and changes in outcome should not be assumed to result necessarily from the recommendations made in this document. Caution is advised in the interpretation of the data.

Health Economic Analysis

A cost/benefit analysis, in patients with insulin-dependent diabetes mellitus, of screening for and anti-hypertensive treatment of early renal disease, as indicated by microalbuminuria, has shown that cost and savings would balance if the annual rate of increase of albuminuria was decreased from 20 to 18% per year. This simulation study suggests that screening and intervention programmes could have life saving effects and lead to considerable economic savings. The costs and cost-effectiveness of measures for treatment of established nephropathy has not been established but a number of analyses are currently underway. For renal support therapies kidney transplantation appears the most cost-effective form of treatment but it should be remembered that renal replacement therapies are not straight alternatives to each other because not all patients are suitable for all modes of therapy.

RESEARCH PROGRAMME

Research in the field of diabetic renal disease needs urgent encouragement and support. Important questions remain unanswered. The following areas are identified as worthy of coordinated effort:

(a) familial, cellular and genetic markers of susceptibility to diabetic nephropathy;
(b) the molecular mechanisms of diabetic kidney disease;
(c) structure and functional relationships in the diabetic kidney;
(d) identification of early predictors of microalbuminuria;
(e) mechanisms of coronary heart disease related to micro- and macroalbuminuria;
(f) the significance of microalbuminuria in children;
(g) the reliability of the use of A/C ratio to monitor the efficacy of treatment;
(h) the natural history of kidney disease in non-insulin dependent diabetic patients in different ethnic groups;

(i) intervention studies in non-insulin-dependent diabetic patients with raised albumin excretion using blood pressure and lipid lowering therapies with clinical outcomes of total mortality and cardiovascular disease morbidity and mortality;
(j) the feasibility and efficacy of low-protein diets and types of anti-hypertensive treatment for diabetic renal failure in different countries and in different ethnic groups;
(k) validation of the positive cost/benefit ratio of screening, monitoring and treatment of microalbuminuria based on clinical data. Identification of the precise costs and cost-effectiveness of secondary and tertiary prevention strategies.

RECOMMENDATIONS

6.1 Close collaboration with the EDTA Diabetic Nephropathy Working Group has been established and should be developed to explore, in representative patients' samples across Europe, specific questions related to risk of development and treatment of established diabetic nephropathy and its cardiovascular complications. Although the establishment of a dataset for diabetic nephropathy may not yet be practical, large studies of representative samples of insulin and non-insulin dependent patients to establish a baseline reference should be encouraged with prolonged follow-up of these patient cohorts.

6.2 All patients who have had insulin-dependent diabetes for more than 1 year and who are above the age of 12 years, and all patients with non-insulin-dependent diabetes from the time of diagnosis, should be screened for albuminuria at least once a year. The urinary albumin excretion rate in timed urine collections should be determined only for patients with an albumin concentration ≥ 20 mg/litre or albumin/creatinine ratio ≥ 2.5 mg/mmol in men and ≥ 3.5 mg/mmol in women. Elevated albumin excretions rates (≥ 20 μg/min) need to be confirmed in two further collections within 6 to 12 weeks. The monitoring of patients with persistently elevated albumin excretion rates should be performed as often as clinically required along with estimates of glycaemic control, blood pressure, serum lipids and serum creatinine and checks for retinopathy, neuropathy and coronary, cerebrovascular and peripheral artery disease. Blood pressure should be measured at least once a year in all diabetic patients.

6.3 Persistent microalbuminuria should be treated by improved blood glucose control and antihypertensive therapy when indicated. Anti-hypertensive treatment, particularly with ACE inhibitors may be prescribed even with arterial pressures $\leq 140/90$ mmHg. Correction of coexisting hyperlipidaemia should be considered. Persistent macroalbuminuria requires vigorous treatment of arterial hypertension and the reduction of animal protein in the diet under the super-

vision of a nutritionist. Hyperlipidaemia needs to be corrected and smoking should be strongly discouraged. Special attention must be paid to the treatment of associated micro- and macrovascular complications. The addition of an ACE inhibitor may afford special benefits. Proteinuria during pregnancy and pregnancy in proteinuric diabetic patients require special attention and management by a joint team of specialists.

6.4 Joint care by diabetes and renal specialists should be initiated when a patient's serum creatinine concentration reaches 200 μmol/litre (2.2 mg/dl) and plans for renal replacement therapy should be made. Specialists should agree on management protocols for end-stage renal failure on a regional, district or institutional basis, and review and update them at regular intervals.

6.5 Counselling and education of diabetic patients and briefing of primary health care providers should be provided throughout all phases of diabetic kidney disease. The role of the diabetes specialist nurse is essential in this context.

6.6 There is an urgent need to establish methods for the reliable testing of the impact of a set of recommendations such as these on health care for any population under study. Methods of analysis should be reviewed and updated, and the need for large-scale clinical trials should not be overlooked. All intervention initiatives should include an evaluation of cost-benefit and cost-effectiveness.

6.7 Funds should be made available centrally (at the European level) and locally (at the national level) for the study of the causes and prevention of diabetic renal disease. The primary prevention of renal damage in diabetes must be regarded as the ultimate goal of this research.

6.8 This document must be regularly reviewed and updated as new information is gathered. It should be a flexible working platform from which new investigation and intervention can be launched.

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