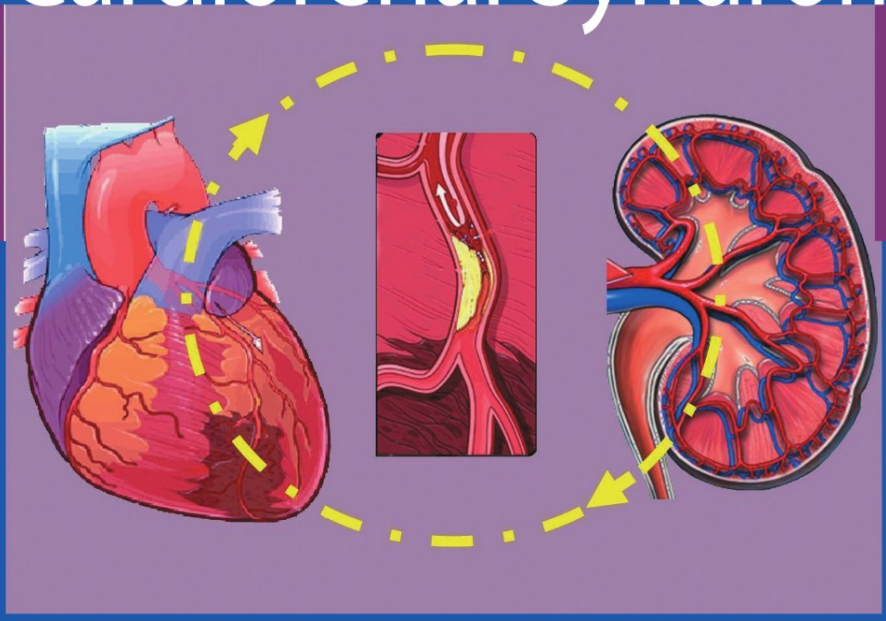
Adel E. Berbari
Giuseppe Mancia
Editors

Cardiorenal Syndrome



Mechanisms, Risk and Treatment

Springer

Cardiorenal Syndrome

Adel E. Berbari · Giuseppe Mancia (Eds.)

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Preface

It has long been known that a close relationship exists between chronic kidney disease (CKD) and cardiovascular disease (CVD), which has led to the adoption of the terminology "cardiorenal syndrome". In recent years, the relationship between CKD and CVD has been shown to be even closer because of the demonstration that renal function acts as a sensor of global (or total) CVD risk. It is thus now well documented that from the initial to the advanced stages of renal disease, the cardiovascular system is involved. Primary disorders of CKD are associated with an enhanced progression of CVD, even when renal function is only mildly impaired. A significant number of patients with CKD die of CVD complications before they progress to end-stage renal failure. This excessive CVD risk is attributed to a high burden of both conventional and kidney (uremia)-related factors as well as to a wide spectrum of clinicopathologic entities. Conversely, primary CV disorders can initiate and perpetuate functional renal impairment and progressive CKD. Overall, the presence of renal dysfunction is an ominous sign of poor outcome in patients who develop ischaemic syndromes or undergo any type of surgical intervention.

Although a large number of clinical studies and reviews has addressed the cardiorenal syndrome, the editors deemed it appropriate to provide readers with a book that comprehensively addresses all the complex interactive aspects of the cardiorenal relationship, i.e. from pathophysiology to epidemiology, diagnosis and treatment. We believe that understanding the mechanisms linking CKD and CVD is essential also to have more clear perspectives on the future therapeutic approaches to this deadly association.

We express our deep gratitude and warm appreciation to the experts who kindly contributed to the various chapters of this book.

Beirut-Milan, June 2010

Adel E. Berbari
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Section I
Chronic Kidney Disease and Cardiovascular Disease Interrelationships

Links between Chronic Kidney Disease and Cardiovascular Disease: A Bidirectional Relationship

1

A.E. Berbari

Abstract A strong relationship between chronic kidney disease (CKD) and accelerated cardiovascular disease, defined as the cardiorenal syndrome, is well documented, whether the initial event is in the kidney or in the heart. In the kidney context, mechanisms that link CKD and cardiovascular disease (CVD) involve both conventional and CKD (uremia)-related CVD risk factors. Several pathophysiologic processes responsible for the accelerated CVD spectrum in the CKD population include accelerated calcific occlusive atheromatous disease, diffuse nonocclusive medial-wall calcification, endothelial dysfunction, and uremic cardiomyopathy. In the heart context, disturbed CV dynamics and activation of neurohormonal and inflammatory factors are involved in the initiation of renal functional impairment and progressive kidney disease.

The aim of this chapter is to present an overview of various aspects of cardiorenal association and to pinpoint features that are specific to each clinical entity, whether the initial insult is renal or cardiac. A detailed discussion of the various aspects of cardiorenal association are well covered in the following chapters.

Keywords: Cardiorenal syndrome • Conventional and CKD-related risk factors • Calcific intimal atherosclerosis • Arteriosclerosis • Myocardial dysfunction

1.1 Introduction

Several epidemiologic observations and clinical studies have documented a strong relationship between chronic kidney disease (CKD) and accelerated cardiovascular disease (CVD) morbidity and mortality [1]. This relationship exists whether the initial event is renal parenchymal disease or cardiac disease. Whereas death rates from coronary artery disease fell by 40% in the last decade as a result of control of CVD risk factors

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and therapeutic interventions, no such trend has occurred in patients with CKD or end-stage renal disease (ESRD) [2]. A significant number of patients with CKD die of cardiovascular complications before they progress to end-stage renal failure (ESRF) [3]. On the other hand, renal dysfunction in patients with primary cardiac disease portends a significantly enhanced risk of morbidity and mortality from CVD [4, 5].

An aging population and increasing incidence of hypertension, diabetes mellitus, obesity, and other comorbid factors are associated with an increasing incidence of cardiorenal disorders [1].

1.2 Definition

Cardiorenal syndrome, a term increasingly used to describe the interaction between CKD and CVD, can be defined as a clinicopathologic disorder in which a primary insult in the kidney or in the heart initiates a series of secondary functional and morphologic responses in the other organ [6]. Some authors prefer to use different terms to denote whether the primary insult that initiates the secondary responses is in the kidney (renocardiac syndrome) or in the heart (cardiorenal syndrome) [7]. In this chapter, the term cardiorenal syndrome is retained to describe the cardiorenal association whether the initial insult is in the kidney or in the heart.

1.3 Chronic Kidney Disease as a Promoter of Cardiovascular Disease

CKD is associated with accelerated progression of CVD, even when renal function is mildly impaired. The higher risk for CVD has been reported all along the continuum of CKD – from increased urinary albumin excretion to ESRD. About 50% of CKD patients die of cardiovascular complications before they progress to ESRD [8]. Mortality from CVD is 10–20 times higher in predialysis patients and in those undergoing dialysis replacement treatment compared with age- and sex-matched healthy individuals with no evidence of CKD [9]. Furthermore, CKD patients who develop acute ischemic events or undergo percutaneous coronary interventions or coronary bypass surgery have a much poorer outcome than their counterparts with a normal renal function [4, 5].

1.3.1 Epidemiology

CKD is emerging as a global health problem. It is a major risk for accelerated CVD and progression to ESRF. The prevalence of CKD is surprisingly high in the general

population. In the USA, The Third National and Nutrition Survey Examination (NHANES III) reported a prevalence of 11% in the adult population [10, 11]. Rates appear to be similar in Europe but higher in other populations, such as in Asia and Australia. Furthermore, in patients with comorbid conditions such as hypertension, diabetes mellitus, and heart disease, the incidence of renal dysfunction is higher than in the general population [11].

An accurate estimation of renal function is fundamental for detecting CKD. The diagnosis of renal dysfunction is based on one or more of the following criteria: (1) elevated serum creatinine level; (2) decreased glomerular filtration rate (GFR); (3) increased urinary albumin excretion [11, 12].

GFR can be measured directly from serum creatinine and urinary creatinine excretion obtained from 24-h urine collection, estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation, or by the Cockroft-Gault formula. The latter is valid for GFR >60 ml/min/1.73m^2, as it tends to overestimate renal function in advanced stages of renal impairment as well as in overweight and obese individuals. Based on the estimated GFR (eGFR) by the MDRD equation, CKD is classified into five (I–V) stages; eGFR <60ml/min/1.73m^2 is the cutoff value for definition of CKD because it represents a reduction by >50% of the normal GFR value of 125 ml/min.1.73m^2 in young men and women. This level of GFR is associated with the onset of laboratory abnormalities characteristic of kidney failure, including increased prevalence and severity of several CVD risk factors. GFR values of 59–30 and 29–15 ml/min/1.73m^2 define CKD stages III and IV, respectively. GFR values <15ml/min/1.75m^2 indicate ESRF (stage V) [11, 12].

An increase in the rate of urinary albumin excretion in timed 24-h urine collection is classified as (1) microalbuminuria 30–300 mg/day and (2) macroalbuminuria >300 mg/day [12]. Only 25% of individuals with GFR <60ml/min/1.73m^2 have macroalbuminuria, and a similar proportion of those with low GFR have macroalbuminuria [13]. Increased urinary albumin excretion has important implications, as it is associated with a worse prognosis for both CVD development and CKD progression [12].

1.3.2 Pathophysiologic Mechanisms

The cause(s) of the excessive risk of CVD in patients with CKD are not completely understood. Most of the Framingham conventional risk factors, such as older age, hypertension, dyslipidemia, glucose intolerance/diabetes mellitus, and left ventricular hypertrophy (LVH), are highly prevalent in CKD [12, 14]. However, these factors do not fully account for the extent of CVD in CKD. Several cross-sectional studies have suggested that other factors that are not included in the Framingham risk profile may play an independent and important role in promoting vascular disease in these patients. Unique risk factors related to ESRD and uremia, such as homocystinemia, oxidative stress, inflammatory markers, anemia, and hemodynamic and metabolic alterations, have been identified and also likely contribute to the excess CVD risk [14].

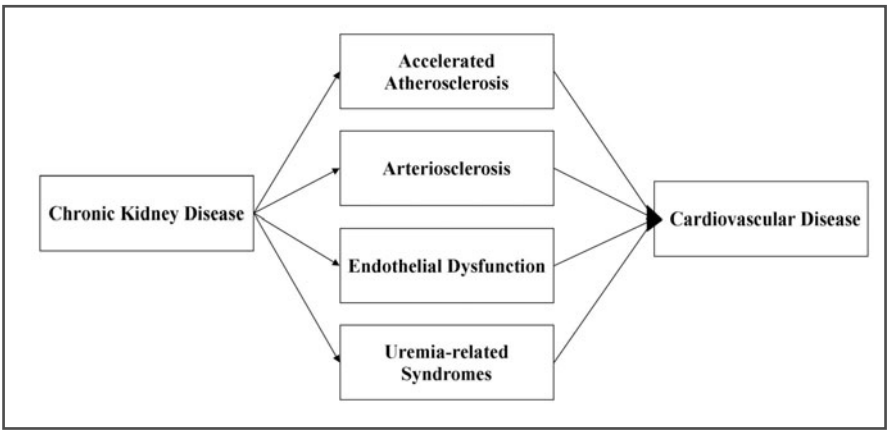

Fig. 1.1 Chronic kidney disease – cardiovascular disease links

Several mechanisms are involved in the pathophysiology of CVD in CKD in interrelated and complex ways. In CKD, several clinicopathologic entities underlie CVD, including endothelial dysfunction, accelerated atherosclerosis, arteriosclerosis, and cardiomyopathy [11] (Fig. 1.1).

1.3.2.1 Atherosclerosis

Accelerated atherosclerosis and increased CVD events have been extensively documented in CKD. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive vascular lesions. In CKD, the atherosclerotic lesions have a distinct morphology. They are frequently calcified, with a relative increase in media thickness, whereas in the general population, they are fibroatheromatous [11, 15].

In CKD, as in the general population, the accumulation of conventional risk factors initiates the atherosclerotic process. Among these risk factors, dyslipidemia is a major determinant. The dyslipidemic pattern is more atherogenic and is characterized by increased triglycerides, low high-density lipoprotein (HDL) and normal or near-normal total serum cholesterol concentrations [15]. In mild renal dysfunction, this atherogenic dyslipidemic pattern plays a critical role in the pathogenesis of accelerated atherosclerosis. In this context, however, several studies have reported that mild to moderate renal dysfunction is atherogenic when associated with a conventional risk profile but, by itself, is not an independent risk factor for CVD [16]. With worsening renal function, however, the atherogenic dyslipidemic pattern becomes a weaker predictor of acceleration of CVD. In moderate to severe renal impairment, no relationship has been documented between renal function and progression of the atherosclerotic process. For example, no difference in atheroma plaque volume and growth could be demonstrated in patients with GFR >60ml/min/1.73m^2 versus those with GFR <60ml/min/1.73m^2 [17].

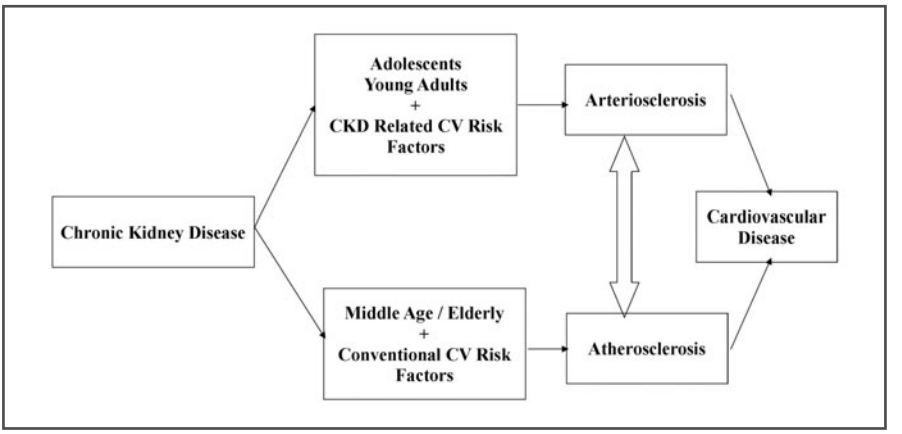

Fig. 1.2 Pathogenesis of atherosclerosis and arteriosclerosis

These data imply the involvement of other factors in CVD progression. Substantially impaired renal function is associated with multiple CKD uremia-specific factors [18]. Although several pathobiologic processes may be involved, disturbances in mineral metabolism play a major role in aggravating vascular disease by calcification of the intimal atheromatous lesions and media of the vascular wall [19]. Occlusive atherosclerotic disease is more frequent in the older CKD population [15]. Clinical presentations include ischemic heart disease (angina, myocardial infarction, and sudden cardiac death), cerebrovascular and peripheral vascular disease, and heart failure [15] (Fig. 1.2).

1.3.2.2 Arteriosclerosis

Arteriosclerosis is also an important component of the CVD spectrum in patients with CKD (Fig. 1.1). It is a diffuse, nonocclusive remodeling process that involves the central elastic arteries (aorta and its major branches) [20]. It is characterized by an increase in luminal diameter, destruction of the elastic lamellae, extensive medial calcification, and an increase in the extracellular matrix [20]. These morphological changes reduce elasticity and compliance and increase stiffness of the arterial wall. Factors that link CKD to increased arterial stiffness have not been completely elucidated. The extensive medial calcification points to a role of altered mineral homeostasis. In ESRD, mineral metabolism is characterized by hyperphosphatemia, increased calcium β-phosphate product, hyperparathyroidism, and reduced 1,25-dyhydroxy-vitamin D levels [20]. High serum phosphate concentrations and calcium β-phosphate product, by activating inorganic phosphate transporter 1 (Pit-1) receptors, trigger both tissue calcification and transdifferentiation of the vascular smooth muscle cells (VSMCs) to an osteoblast-like phenotype [20, 21]. Low serum albumin concentrations, often present in some CKD patients, may enhance calcium deposition by

increasing ionized precipitable calcium fraction [20]. Uremic serum may also induce vascular calcification and osteoblastic differentiation of VSMCs in the absence of high phosphate concentrations [22]. Factors in uremic serum that may be responsible for the calcification process are elevated parathyroid hormone and reduced vitamin D levels [22]. The secondary hyperparathyroidism, by promoting enhanced bone resorption with endogenous release of calcium and phosphorous, plays an additional critical role in vascular calcification [23]. Reduced vitamin D levels may predispose to cardiomyocyte and vascular smooth muscle hypertrophy [23].

The relationship between increased arterial stiffness and renal function, however, is not limited to patients with substantially impaired renal function and ESRF. It has also been reported in individuals with mild to moderate renal insufficiency. In a group of never-treated individuals with slightly elevated serum creatinine levels (serum creatinine >130 μmol/l or ≥1.47 mg/dl) and normal or mild uncomplicated hypertension, an inverse relationship between arterial stiffness and renal function was noted [24]. Serum creatinine concentration was the only predictor of the increased arterial stiffness. It can be postulated that with declining renal function, changes in serum phosphate concentrations – although still within the conventional reference range – may trigger vascular calcification and cause increased arterial stiffness. Interestingly, dose-dependent associations between serum phosphate concentrations, even within the conventional reference range, and CVD outcomes were reported in individuals free of CVD and CKD [25]. In contrast, other studies showed no substantive difference in arterial stiffness between individuals with and without mild to moderate CKD; microalbuminuria was the only index that correlated with arterial stiffness [26].

Diffuse nonocclusive medial calcification and increased arterial stiffness are the more dominant forms of vascular pathology in adolescents and young adults with CKD. These morphologic changes are associated with systolic hypertension, wide pulse pressure, LVH, coronary hypoperfusion, further renal damage, congestive heart failure (CHF), and sudden death [27] (Fig. 1.2).

1.3.2.3 Endothelial Dysfunction

Impaired endothelial function occurs early in renal disease and has been attributed to a number of potential causes [15]:

1. Reduced clearance of endothelial nitric oxide synthase (e-NOS) inhibitor asymmetric dimethyl arginine (ADMA), which leads to reduced bioavailability of endothelial nitric oxide
2. Activation of angiotensin II, which induces oxidative stress
3. High levels of homocysteine
4. Chronic inflammation
5. Dyslipidemia
6. Endothelial progenitor-cell deficiency [28]

Endothelial dysfunction contributes significantly to the initiation and progression

of CVD in CKD. It exacerbates arterial-luminal narrowing and arterial-wall stiffening by allowing development of intima–media thickening, medial hypertrophy, and calcification [15].

1.3.2.4 Uremia-Related CVD

A significant number of uremic patients with ESRF manifest: (1) symptoms of myocardial ischemia with no evidence of significant coronary artery disease by coronary angiography; (2) CHF generally resistant to therapy. These clinical conditions result from functional and morphologic features specific to the uremic state [11, 29, 30]. With worsening renal function and onset of ESRF, uremic patients characteristically have hypertension, anemia, hyperactive circulation due to arteriovenous fistulae, increased arterial stiffness, and LVH and cardiac dilatation as a result of pressure and volume overload and abnormal metabolic profile [30]. The structure of the myocardium itself also is altered in a manner that is characterized by intramyocardial coronary artery thickening, reduced myocardial capillary density, and increased interstitial myocardial fibrosis [30]. All these factors cause a cardiomyopathy which is specific to the uremic state and is known as uremic cardiomyopathy. In these patients, clinical manifestations include heart failure, ischemic heart disease even in the absence of coronary artery disease, arrhythmias, and sudden cardiac-related death.

1.3.3 Course of CVD in CKD

It is well established that terminal stages of CKD are associated with markedly elevated CVD burden. CVD morbidity and mortality are 100 times higher in ESRF patients compared with age- and gender-matched individuals with no kidney disease [9, 12]. CKD is a well recognized risk factor for accelerated CVD. There is a strong, continuous correlation between increased risk for CVD events and impaired renal function. The relationship between CKD and CVD, however, is not linear but exponential. The risk begins in the early stages of renal impairment and increases continuously to 20–30 times higher than in the general population as renal damage progresses to ESRD. This risk is evident at an eGFR of <50–60ml/min/1.73m^2 and increases sharply when eGFR drops <45ml/min/1.73m^2 [31–33].

1.4 CVD in Kidney Transplant Recipients

Although kidney transplant recipients recover adequate renal function, CVD remains an important cause for morbidity and mortality: mortality rates are twice as high as

in age- and gender-stratified samples of the general population. The most likely explanation is the high prevalence of conventional risk factors, such as hypertension, diabetes mellitus, LVH, and dyslipidemia, and novel risk factors unique to transplantation itself, including the direct effects of immunosuppressive drugs or organ rejection. In contrast, compared with the dialysis population, kidney transplant recipients have a lower CVD mortality rate, probably due to removal of kidney (uremia)-related specific risk factors [34].

1.5 Cardiac Disease as a Promoter of Kidney Dysfunction

CKD itself may result from underlying CVD. That heart disease has a negative impact on the kidney is well established. Primary disorders of cardiac function without evidence of overt kidney disease can initiate and perpetuate renal functional impairment and progressive kidney disease [35].

The relationship between disturbed cardiac dynamics and renal dysfunction is complex, and probably multifactorial. In acute myocardial failure, disturbed hemodynamics prevail. Reduced cardiac output and the associated underfilling of the systemic and renal circulation trigger a series of compensatory vascular responses characterized by increased systemic and renal vascular resistance and activation of several neurohormonal factors, including the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), and vasopressin release [35, 36]. These hemodynamic responses tend to maintain systemic blood pressure but reduce renal plasma flow, GFR, and perfusion of renal tissues, initiating the onset of acute kidney injury (AKI), a term used to denote rapid decline in renal function [36]. The enhanced neurohormonal factors cause sodium and water retention leading to further worsening of myocardial and renal functions. The incidence and severity of AKI correlate with the severity of acute cardiac decompensation. AKI is more severe in patients with reduced LV ejection compared with those with preserved LV function, achieving an incidence of >70% in patients with cardiogenic shock [37]. The frequent need for contrast agents for diagnostic purposes is an additional threat to the kidney, leading to further renal insufficiency.

In chronic heart failure, the pathophysiologic mechanisms underlying the impaired renal function are not well delineated. The low cardiac output, through contributory, does not appear to be a major determinant of renal dysfunction. In fact, no correlation has been demonstrated between GFR and LV ejection. Patients with chronic heart failure and preserved LV ejection have similar GFR as those with impaired LV ejection [38].

Other pathophysiologic mechanisms may contribute to worsening renal function. In chronic heart failure, the excessive and prolonged activation of neurohormonal factors, through their hemodynamic influences, and activation of inflammatory cascade cause damage to various organs, including the heart, kidney, and vasculature [39]. Anemia, which is often present in these patients, leads to cardiomegaly, wors-

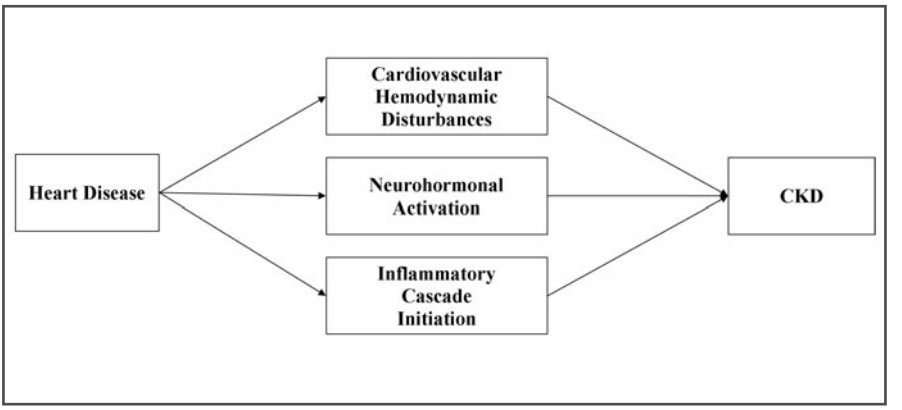

Fig. 1.3 Heart–kidney interactions

ening cardiac hemodynamic indices, and increased B-type natriuretic peptide. In turn, high B-type natriuretic peptide levels have been associated with accelerated progression of CKD to ESRF [40].

Old age, diabetes mellitus, hypertension, and macro/microvascular disease are additional contributors to worsening renal function in patients with chronic CHF.

It remains unclear, however, whether heart disease with no evidence of hemodynamic failure can impair renal function. There are no clinical studies that evaluate the impact of cardiac disease with preserved myocardial function on renal function. However, in an experimental model of cardiorenal association in rats, myocardial infarction after unilateral nephrectomy was associated with an increase in serum creatinine, proteinuria, focal segmental glomerulosclerosis (FSGS), and myocardial failure [41]. Renal functional and morphologic changes correlated with the size of the myocardial infarct. In contrast, no increase in serum creatinine, proteinuria, or FSGS were observed in rats with unilateral nephrectomy alone or myocardial infarction alone [41]. These interesting data suggest that cardiac disease can initiate renal dysfunction and progressive kidney disease only when associated with myocardial failure in an already compromised renal function (Fig. 1.3).

Cardiac disease may also be linked to CKD by other undefined mechanisms. In autopsy studies of individuals without clinically overt coronary heart disease dying from violent or natural causes, coronary atherosclerosis was strongly associated with nephrosclerosis [42]. These findings imply similar mechanisms underlying the pathobiology of coronary atherosclerosis and nephrosclerosis.

1.6 Conclusions

CKD and CVD are strongly related. In primary renal disease, renal impairment is associated with a high CVD burden of conventional and kidney (uremia)-specific

factors, which lead to a wide spectrum of clinicopathologic entities such as accelerated atherosclerosis, arteriosclerosis, endothelial dysfunction, and cardiomyopathy. Although the relationship between CKD and CVD is continuous, CVD risk becomes significant when GFR is <50 ml/min/1.73m^2.

Primary cardiac disease can initiate renal dysfunction and progressive kidney disease in the context of myocardial failure on an already compromised renal function. Disturbances in CV hemodynamics, activation of neurohormonal systems, and inflammatory cascade are the underlying mechanisms.

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Cardiorenal versus Renocardiac Syndrome 2

M. Sarraf, A. Masoumi, R.W. Schrier

Abstract Many national registries and epidemiological observations have revealed a strong correlation between morbidity and mortality of patients with cardiovascular disease and kidney dysfunction. In patients with heart failure, renal dysfunction is highly prevalent. Even mild to moderate renal dysfunction in patients with congestive heart failure, i.e., cardiorenal syndrome, leads to significant increase in morbidity and mortality. The mechanisms underlying this complicated syndrome are not well elucidated, but the kidney is known to be responsible for the sodium and water retention in heart failure. Without better understanding the pathophysiology of this complex interaction between the heart and kidney, the outcome for these patients remains poor. Moreover, renal parenchymal disease is a pathogenic factor to cardiovascular disease independent of the role of traditional risk factors. More than 88% of patients with chronic kidney disease never reach end-stage renal disease, as the majority of them die due to cardiovascular disease. Thus, understanding the role of renal parenchymal disease as an independent cardiovascular risk state – i.e., renocardiac syndrome – is very important. In this chapter, we discuss the importance of renal function in the pathophysiology of congestive heart failure. We also elaborate on the novel understanding of chronic kidney disease and its role in cardiovascular disease progression. It should be stated that there may be involvement of both the cardiorenal and renocardiac syndromes associated with a systemic disease, such as with diabetes mellitus.

Keywords: Cardiorenal syndrome • Renocardiac syndrome • Congestive heart failure • Diabetes mellitus • Hypertension • Chronic kidney disease • Homeostasis

2.1 Introduction

The interaction between kidney and heart is very important for hemodynamic control and regulatory functions. The kidney plays the central role for body fluid volume

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homeostasis, electrolyte balance, and blood pressure regulation. The cross-talk between heart and kidney occurs at multiple levels, including the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system (SNS), natriuretic peptides, endothelin, and antidiuretic hormones [1, 2]. Therefore, understanding these two delicate systems is crucial to improve the management of patients with heart and kidney disease.

As obesity is a pandemic in developed countries, it has become the main driver of important epidemics of diabetes mellitus (DM) and hypertension (HTN). Hence, it is not surprising that the prevalence of heart failure (HF) and chronic kidney disease (CKD) continues to escalate. Furthermore, it has been shown that even mild to moderate deterioration of kidney function correlates with higher morbidity and mortality in patients with HF and acute coronary syndrome [2, 3]. Thus, with the aging of the population, and the epidemic of obesity, DM, and HTN, understanding the mechanisms of renal dysfunction as a pathogenic factor for cardiovascular disease (CVD) is imperative. Mounting evidence demonstrates that CKD (stage 3 and higher) increases the risk of atherosclerosis, HF, valvular disease, and dysrhythmias that lead to sudden cardiac death in many cases.

2.2 Heart Failure as a Cause of Kidney Failure (Cardiorenal Syndrome)

A hallmark of HF is sodium and water retention by the kidneys. Although HF impairs sufficient blood supply to the organs, it is the kidney's retention of salt and water that leads to congestion and the clinical symptoms and signs of HF. Thus, understanding the relationship between the heart and kidney, the so called cardiorenal axis, is very important in HF. Much of the challenge of successfully managing HF lies in navigating between fluid overload and deteriorating renal function. Unfortunately, despite substantial research on cardiorenal syndrome, a clear definition has not yet developed. The National Heart, Lung, and Blood Institute (NHLBI) Working Group defines cardiorenal syndrome as "the result of interactions between the kidneys and other circulatory compartments that increase circulating volume and symptoms of heart failure and disease progression are exacerbated. At its extreme, cardio-renal dysregulation leads to what is termed 'cardio-renal syndrome' in which therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function" [4].

2.2.1 Ventricular Dilation in Congestive Heart Failure

Regulation of body-fluid volume is determined by cardiac output (CO) and systemic arterial resistance [1, 2, 5–7]. These two components maintain the integrity of the arterial circulation, which is the primary determinant of renal sodium and water

excretion in HF. If CO decreases (e.g., systolic HF) or systemic arterial resistance decreases (e.g., high-output HF), arterial underfilling leads neurohormones activation and hemodynamic changes in the kidneys, which lead to renal sodium and water retention (Fig. 2.1). This expansion of extracellular fluid (ECF) causes an increase in preload and ventricle dilation, which causes deleterious effects on the myocardium [2]. Cardiac dilation results in remodeling of the left ventricle (LV) and increased myocardial oxygen demand secondary to relative myocardial ischemia [2]. Furthermore, cardiac dilation can cause functional mitral insufficiency that leads to lower output from the LV to the aorta, as well as to pulmonary venous HTN. In early stages of HF, ventricular dilation is associated with an increase in brain natriuretic peptide (BNP). In healthy individuals, exogenous BNP increases glomerular filtration rate (GFR), sodium and water excretion, and vasodilatation while decreasing RAAS and SNS activation and vasopressin release; it also causes tubular sodium reabsorption [2, 8]. Thus, BNP may contribute to maintaining ECF balance despite mild LV dysfunction [1, 2]. However, the protective effect of BNP is blunted by worsening or advance HF. This blunting is due to renal vasoconstriction, reduced sodium delivery to the distal nephron where natriuretic peptides inhibit sodium reabsorption, [2] secondary hyperaldosteronism [2], and down-regulation of atrial natriuretic peptide (ANP) receptors [1].

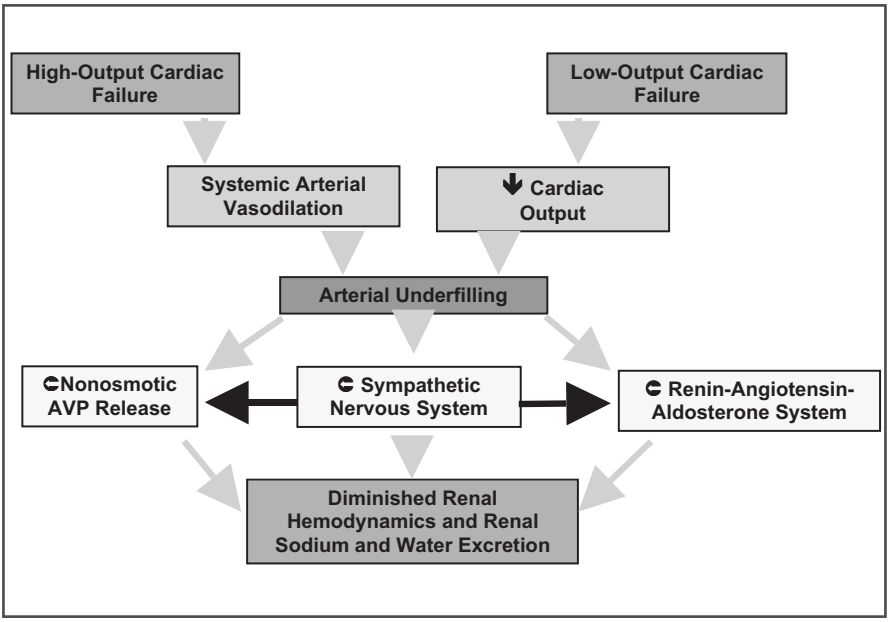

Fig. 2.1 Pathophysiology of acute decompensated heart failure (reproduced from [6], with permission)

2.2.2
Left Ventricular Mass Index and Congestive Heart Failure

Congestion and elevated preload cause increased transmural myocardial pressure and increased LV mass index. LV hypertrophy (LVH) is a strong independent risk factor for mortality due to increased risk of systolic and/or diastolic dysfunction, higher rate of fatal arrhythmias, and sudden cardiac death. Moreover, LVH decreases the ratio of capillary density to myocardium and leads to further ischemia and dysfunction of the myocardium [2]. In patients with risk factors for heart or kidney disease, there are a number of mechanisms that lead to LVH (see below).

2.2.3
Blunted Atrial–Renal Reflexes and Chronic Heart Failure

Under normal circumstances, any increase in atrial pressure decreases arginine vasopressin (AVP) release through the vagus nerve (so-called Henry-Gauer reflex), reduces renal sympathetic tone, and increases ANP, to maintain total body water and salt balance [2]. In HF, however, these reflexes are blunted in the low-pressure circulation secondary to reflexes initiated in the high-pressure arterial circulation, i.e., counteracting arterial baroreceptor unloading, leading to elevated SNS and RAAS activation, parasympathetic nervous system withdrawal, renal vasoconstriction, and sodium/water retention [2, 9].

2.2.4
Neurohormones and Chronic Heart Failure

Any decrease in CO activates a series of compensatory mechanisms through which the integrity of cardiovascular homeostasis is achieved. These compensatory mechanisms consist of RAAS, SNS, natriuretic peptides, and AVP release. Understanding of these compensatory mechanisms is crucial for managing these patients.

2.2.4.1
Renin–Angiotensin–Aldosterone System

The RAAS is activated in HF and has an important role in initiating and maintaining edema [2, 5, 10]. Increased renin secretion occurs early in biventricular failure, which leads to stimulation of angiotensin II (AngII). Increased plasma renin activity has direct correlation with mortality [1, 2] and is a potent SNS stimulator [2], which increases systemic vascular resistance. Moreover, AngII is one of the causes of myocardial remodeling through diverse physiologic effects. It stimulates the central neural centers associated with increased thirst. It also increases the activity of ganglionic nerves via its effects on the autonomic nervous system [1]. There is experi-

mental evidence for increased levels of angiotensin concentration in the central nervous system in HF patients [11]. In the brain, the increased level of AngII (SNS stimulator) and decreased level of nitric oxide (SNS inhibitor) potentially can abrogate the baroreceptor sensitivity in experimental CHF [11], and baroreceptor perturbation ensues. Thus, decreased baroreceptor activity leads to increased renal sympathetic tone, which results in further sodium retention by different mechanisms (Fig. 2.2). AngII also serves as a systemic vasoconstrictor to compensate for the initial decrease in stroke volume associated with ventricular failure. Importantly, AngII increases aldosterone synthesis [12], which increases renal sodium reabsorption and causes sodium retention. In healthy individuals, an "escape" from renal salt-retaining effects of aldosterone occurs usually after a 3-day period [1], thus avoiding edema formation. The escape phenomenon does not occur in HF due to increased sodium reabsorption at the proximal tubule, which results in decreased sodium being delivered to distal nephrons, the site of aldosterone action. AngII, elevated SNS activity, and elevated aldosterone levels are involved in the increased proximal tubular reabsorption in HF. Therefore, these patients continue to experience enhanced sodium retention, which leads to pulmonary congestion and edema [1, 12]. Aldosterone may also increase collagen synthesis and fibrosis of the failing myocardium [12].

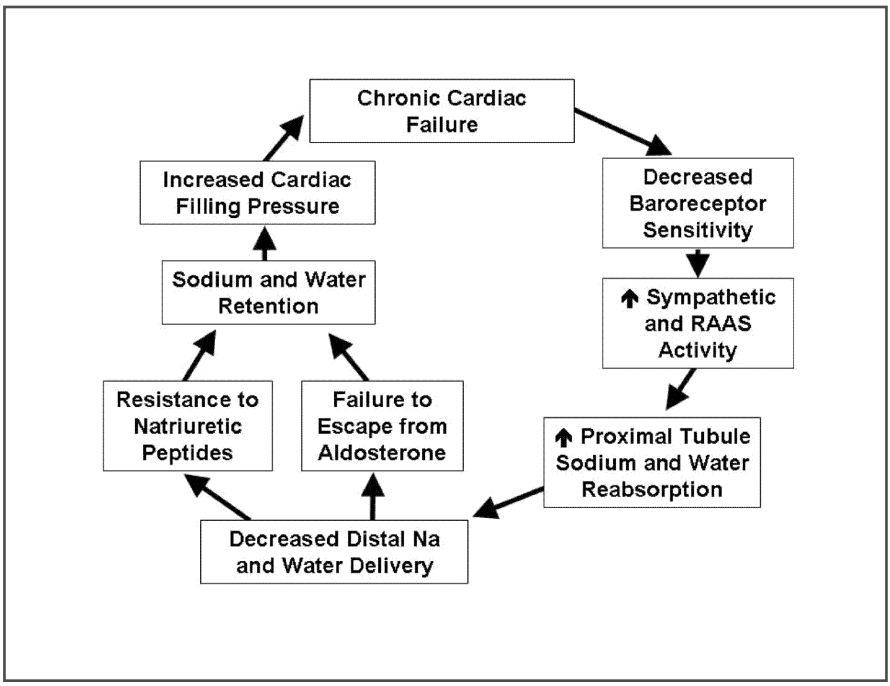

Fig. 2.2 Role of decreased baroreceptor sensitivity, and activation of RAAS and SNS in expansion of water and sodium retention as well as worsening HF. *Na* sodium (reproduced from [2], with permission)

2.2.4.2 Sympathetic Nervous System

One of the earliest adaptations in HF is SNS activation. This is evident even in the mild and early stages of HF. This response is due to loss of the inhibitory effect of baroreceptors on the arterial side and excitatory inputs from the nonbaroreflex peripheral chemoreceptors and "metaboreceptors" of muscles. Under normal circumstances, the vagus nerve is the major autonomic driver of the heart. As HF ensues, the parasympathetic effect is taken over by sympathetic activation. Therefore, with worsening HF, the plasma level of catecholamines rises. Catecholamines have a vital role in HF. It is well demonstrated that in HF there is a decrease in cardiac norepinephrine (NE) levels, whereas plasma NE is elevated [13]. This decreased cardiac NE is the result of maximal turnover of myocardial NE. Thus, the failing myocardium cannot respond adequately to sympathetic stimulation, as NE turnover rate has already been maximized. It is also well recognized that elevated plasma NE levels in HF patients correlates with increased mortality [14]. Meanwhile, renal effects occur secondarily to SNS activation. Stimulation of α-adrenergic receptors on the proximal tubule of the nephron enhances sodium reabsorption, whereas β-adrenergic receptors in the juxtaglomerular apparatus stimulate the RAAS [2]. Furthermore, in HF, postglomerular capillary pressure falls and oncotic pressure rises, further enhancing proximal tubular reabsorption [2].

The purpose of SNS activation is to maintain myocardial contraction, blood pressure, and renal hemodynamics [1]. However, this goal is achieved at the expense of increased myocardial energy consumption, which potentially can worsen ischemia when myocardial oxygen delivery is limited, as in patients with LVH [2]. Increased catecholamine levels can augment the risk of fatal arrhythmias and sudden cardiac death. It is also demonstrated that elevated NE levels has direct toxic effect on the myocardium and enhances myocardial apoptosis [1].

2.2.4.3 Arginine Vasopressin

AVP, the antidiuretic hormone, is secreted from the posterior pituitary gland and released secondary to volume depletion and increased osmolality. In HF, there is nonosmotic release of this peptide [2]. AVP stimulates vasculature V1 receptors and increases systemic vascular resistance while V2 receptor stimulation in the principal cells of the collecting duct increases water reabsorption and leads to hyponatremia. AVP also enhances urea transport in nephron collecting ducts, thereby increasing serum blood urea nitrogen (BUN). Figure 2.3 shows the potential combined effects V1 and V2 vasopressin receptor stimulation on increased cardiac preload, afterload, coronary artery restriction, and cardiac remodeling. These combined effects increase ventricular-wall stress, dilatation, and hypertrophy – factors that increase mortality risk in HF patients.

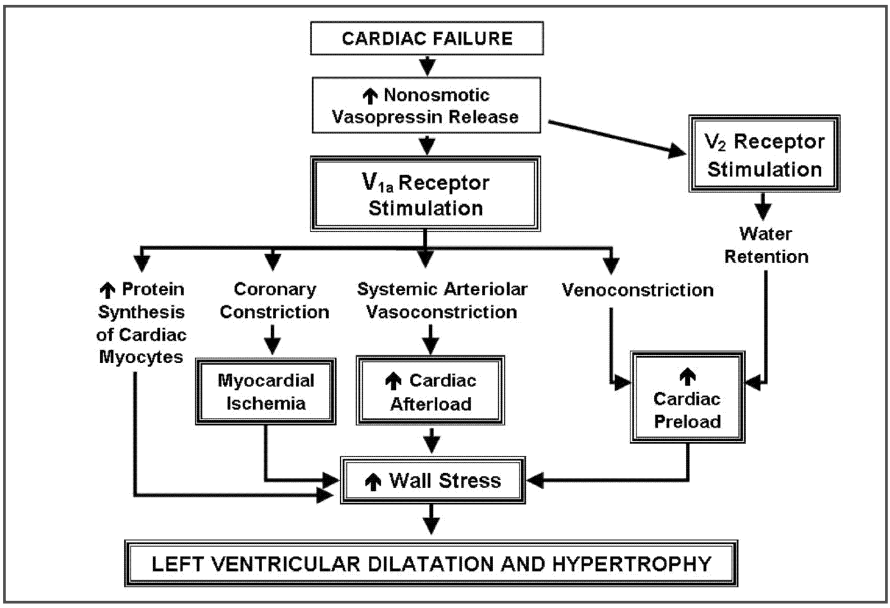

Fig. 2.3 Vasopressin stimulation of V2 and V1a receptors can contribute to events that worsen cardiac function (reproduced from [2], with permission)

2.2.5 Cardiorenal Intersection in Heart Failure

Retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention and Treatment trials [15] demonstrated a 41% increase in the risk of all-cause mortality in both trials when estimated GFR (eGFR) is <60 ml/min as assessed by the Cockcroft–Gault equation.

Baseline CKD has also been associated with increased morbidity and mortality risk in patients hospitalized for acute decompensated HF (ADHF) [16, 17]. Two biomarkers commonly measured on chemistry panel are BUN and serum creatinine. These are extensively studied in acute HF registries and clinical trials. In an analysis of the Acute Decompensated Heart Failure National Registry (ADHERE), using the classification and regression tree (CART) analysis approach, admission of BUN greater then 43mg/dl was associated with the best identifier of in-hospital mortality, followed by systolic blood pressure and serum creatinine as the second- and third-best identifiers [18]. This finding was confirmed by another retrospective analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME–CHF) [19]. In this study, investigators found that not only admission BUN but change in BUN during hospitalization had the most important impact on the 60-day outcome. Furthermore, in another investigation, Gottlieb et al. demonstrated that even a small change in serum creatinine as low as 0.1mg/dl is associated with worse outcome in hospitalized ADHF patients [20].

Finally, the investigators of the Candesartan in Heart Failure – Assessment of Reduction of Mortality and Morbidity (CHARM) study demonstrated that every 10 ml/min decrease in eGFR increased the adjusted hazard ratio (HR) of cardiovascular death or readmission to the hospital by 10% [1.10; 95% confidence interval (CI) 1.07–1.13, $p<0.001$] [21].

In patients with HF, comorbid CKD can result from intrinsic renal disease, hemodynamic abnormalities, or a combination of the two. CKD and HF share common risk factors, such as atherosclerosis, renovascular disease, HTN, and diabetes. Therefore, CKD and HF might frequently coexist. Diminished renal perfusion is frequently a consequence of the hemodynamic changes associated with HF and/or its treatment. Severe pumping failure leads to low cardiac output and hypotension. Neurohormonal activation produces sodium and water retention, elevated central venous pressure, and vasoconstriction, thus leading to increased afterload and low cardiac output. Diuresis can cause hypovolemia, reducing preload, and use of intravenously administered vasodilators can lead to hypotension [2]. In addition, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, angiotensin-converting enzyme (ACE) inhibitors, and AngII receptor blockers (ARBs) can all decrease renal perfusion [22]. The resultant diminished eGFR can lead to worsening kidney function, even in the absence of intrinsic renal disease. In patients with HF, there is a correlation between renal insufficiency and circulating levels of neurohormones. RAAS activation leads to renal hypoxia, vasoconstriction, intraglomerular HTN, glomerulosclerosis, tubulointerstitial fibrosis, and microalbuminuria/proteinuria [23]. Similarly, SNS activation causes proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall of intrarenal blood vessels [24]. Furthermore, increased cardiac preload is associated with increased renal venous pressure [25]. Renal perfusion pressure is equal to mean arterial pressure minus left atrial pressure (as an index of renal venous pressure). Elevated central venous pressure has been shown to decrease GFR and cause sodium and water retention [25]. Additionally, the increase in renal venous pressure stimulates the RAAS [25], which results in worsening hemodynamics of the failing myocardium. Therefore, elevated LV end-diastolic and venous pressure not only impairs forward flow, i.e., cardiac output, but can also contribute to renal dysfunction by increasing renal venous pressure. AngII-induced vasoconstriction of the efferent glomerular arteriole helps preserve GFR in patients with HF and renal dysfunction. Neurohormonal blockade with ACE inhibitors and/or ARBs may impair this vasoconstriction and reduce eGFR, leading to a small rise in serum creatinine. Although initially worrisome, especially given the mortality risk associated with similar acute increases in serum creatinine in patients with HF, the resultant decrease in glomerular hyperfiltration seems to be renoprotective over the long term and supports continuation of these therapies in the absence of bilateral renal artery stenosis [19, 26, 27]. This beneficial effect of ACE inhibitors is proven in a prospective study in nondiabetic patients with HF who had a serum creatinine as high as 5 mg/dl [26]. However, volume-depleted patients might be at high risk of worsening renal function due to this efferent arteriolar vasodilation. Therefore, restoring and maintaining a normal volume status before and throughout therapy with a neurohormonal blocking agent may help alleviate the initial acute decline in renal function.

In addition to the adverse affects of HF on renal function, renal dysfunction adversely affects cardiac function, producing a vicious cycle in which renal dysfunction impairs myocardial function, which subsequently leads to further impairment of renal function. As a result, renal dysfunction is a major determinant of HF progression, congestion, and recurrent decompensation and hospitalization [15]. Neurohormonal activation is the common pathway between renal dysfunction and HF (see "Renocardiac Syndrome"). Both HF and renal dysfunction produce neurohormonal activation [28]. This activation increases volume and pressure load on the heart, reduces myocardial oxygen supply, promotes deleterious myocardial remodeling, and accelerates atherosclerosis [28]. The etiology of renal dysfunction in patients with HF is complex, and several factors may be at work in the same patient.

2.3 Chronic Kidney Disease as a Pathogenic Factor for Cardiovascular Disease (Renocardiac Syndrome)

The incidence and prevalence of CKD is increasing in the United States [29, 30]. The majority of patients with CKD will die of CVD before reaching end-stage renal disease (ESRD). CKD accelerates the course of coronary artery disease (CAD) independent from traditional atherosclerotic risk factors. It is also associated with LVH, valvular disease, and cardiac arrhythmias. Thus, for patients with ESRD, as the extreme type of CKD, sudden, unexplained death is common and is often attributed to CVD.

2.3.1 Accelerated Atherosclerosis in Chronic Kidney Disease

As stated earlier, with the aging of the population and the epidemic of obesity, which leads to a rise in DM and HTN, the increase in incidence and prevalence of CKD is inevitable. The definition of CKD is a decrease in eGFR to <60ml/min/1.73m^2. This is accompanied by reduced renal parenchymal mass and partial loss of normal regulatory functions, such as blood pressure regulation, erythropoiesis, and other vascular-protective processes. A high prevalence of events therefore occurs in this patient population (Fig. 2.4) [30]. The Framingham Heart Study [31] determined the traditional risk factors of CVD such as age, sex, HTN, DM, smoking, and dyslipidemia. However, these risk factors do not fully explain the prevalence of CVD in this patient population, which prompted identification of novel risk factors such as anemia, oxidative stress, endothelial dysfunction, elevated homocysteinemia, elevated lipoprotein (a) [Lp(a)],chronic inflammation, and vascular calcification – all of which occur in CKD.

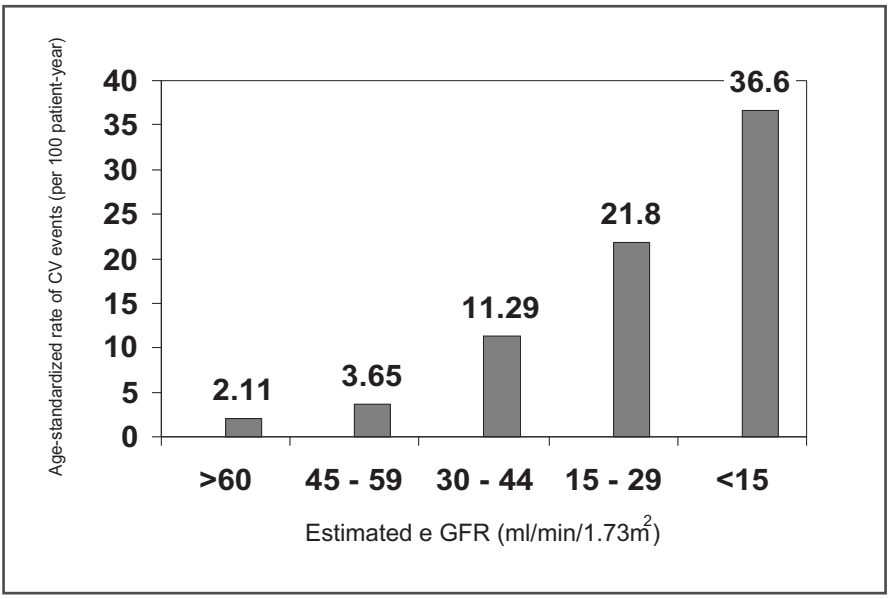

Fig. 2.4 Age-standardized death rates from cardiovascular (CV) events according to estimated glomerular filtration rate (eGFR) among 1,120,295 ambulatory adults (reproduced from [30], with permission)

2.3.2 Role of Traditional Risk Factors and Cardiovascular Outcomes in Patients with Chronic Kidney Disease

2.3.2.1 Hypertension

As GFR decreases by worsening CKD, blood pressure rises and is more difficult to control due to aberrant activation of the RAAS and SNS [32].This results in increased afterload, left LVH, increased myocardial oxygen demand, and augmented sheer stress at the endothelial level. RAAS activation leads to further SNS stimulation, reactive oxygen species (ROS) production, and nuclear factor kappa B (NF-κB)-mediated proinflammatory gene expression [32], which leads to increased risk of atherosclerosis. It also increases oxidation of low-density lipoprotein (LDL) receptors [33], thus further enhancing the risk of atherosclerosis. On the other hand, SNS activation also leads to stimulation of renin release, increased ROS production, and apoptosis of the myocardium [32]. With decreasing GFR and increasing HTN, shear stress in the vessel wall increases and leads to further risk of atherosclerosis and acute plaque rupture, and ultimately to increased risk of acute coronary syndrome [34].

2.3.2.2
Diabetes Mellitus

Diabetes and HTN usually occur at the same time in patients who will later develop CKD. More than 40% of patients with ESRD have DM, and >50% of patients with DM have kidney involvement [29]. In patients with DM type 2, elevated insulin levels act as a strong growth factor for arthrosclerosis, in addition to a dyslipidemic state. Additionally, DM is the most common risk factor for microalbuminuria, a strong surrogate for vascular endothelial injury. Microalbuminuria is a reflection of endothelial and vascular injury – not only at the level of the glomeruli but throughout the body – and is associated with vascular risk factors that relate to vessel damage (Fig. 2.5). In patients with and without diabetes in the Heart Outcomes Prevention Evaluation (HOPE) [35], microalbuminuria was associated with an increased relative risk of myocardial infarction (MI), stroke, or CVD mortality. Additionally, the risk progressively increased with escalating levels of microalbuminuria. Moreover, microalbuminuria increases with the decline in eGFR, further complicating the CKD, which leads to enhanced CV complications. In a subgroup analysis of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, 880 patients with type 2 DM were analyzed for urinary albuminuria excretion (UAE) by 24-h collection and for LV mass (LVM) by the Cornell voltage criteria. In this retrospective analysis, investigators found a positive correlation between log UAE and LVM. During 5 years of follow-up, survivors had significantly lower LVM (8.62 ± 0.11 vs. 9.88 ± 0.45; $p = 0.0140$) and lower UAE (154.60 ± 16.53 vs. 446.62 ± 114.11; $p = 0.0003$) than nonsurvivors. These findings were independent of glucose, blood pressure, and cholesterol control [36].

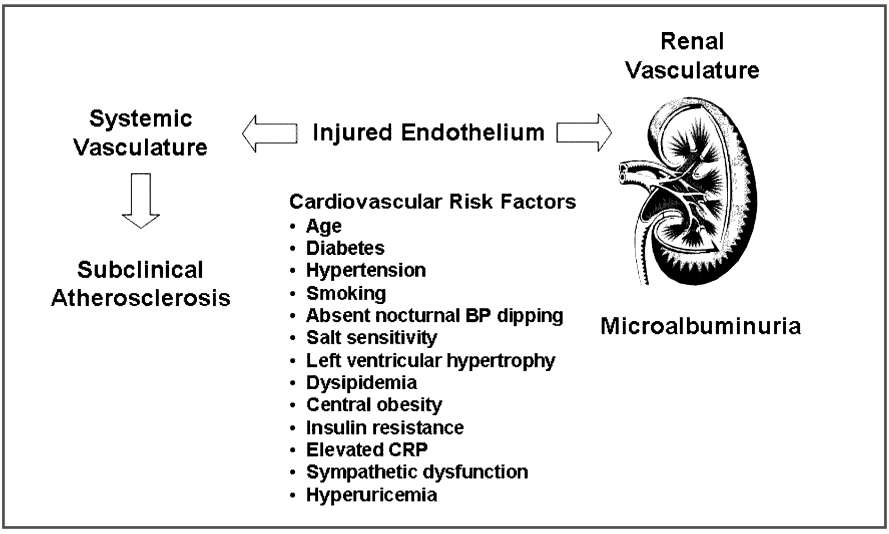

Fig. 2.5 Microalbuminuria and vascular disease (reproduced from [33], with permission)

2.3.2.3 Dyslipidemia

Dyslipidemia develops during the early stages of CKD due to significant changes in apolipoproteins (Apo) that usually precede changes in plasma lipid levels. Decreased high-density lipoproteins (HDL) due to decreased levels of Apo-A1 and Apo-A2, and increased triglyceride due to increased level of plasma Apo-CIII (a potent inhibitor of lipoprotein lipase), are the hallmarks of dyslipidemia in CKD patients [37]. Additionally, inflammation is a major contributing factor in patients with CKD, as it decreases albumin concentration, an important carrier of free cholesterol to the HDL from peripheral tissues. Moreover, in CKD, total LDL concentration does not change significantly, yet the atherogenic LDL particles increase due to RAAS activation and higher inflammatory milieu of the disease [33]. Lastly, there is strong correlation between CKD stage and dyslipidemia severity [33, 37]. Therefore, it seems self-evident that treatment of dyslipidemia with statins or other antilipid medications should change the outcome in favor of lower CVD outcomes.

There are two prospective randomized controlled trials in patients with ESRD [38, 39]. In Die Deutsche Diabetes Dialyse Studie (4D Trial), 1,200 type II diabetic patients on hemodialysis participated. They were randomized to atorvastatin 20 mg/day or placebo for 4 years. All patients were randomized within the first 2 years of starting hemodialysis. Surprisingly, there was a nonsignificant (8%) relative risk reduction (95% CI 0.77–1.10; $p = 0.37$) on the combined primary end point of cardiac death, nonfatal MI, or stroke [38]. This negative outcome was observed despite a significant reduction in total cholesterol and LDL. There was a significant reduction of combined cardiac events (death from cardiac causes and nonfatal MI); however, this finding was associated with a significant increase in fatal stroke [38]. The more recent clinical trial, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) studied 2,776 patients who had been on hemodialysis for at least 3 months prior to study entry and who received rosuvastatin during the trial. For the primary end point of cardiovascular death, nonfatal MI, or nonfatal stroke, there was no significant difference between the rosuvastatin and placebo arms despite a 43% reduction in LDL cholesterol and 11% reduction in high-sensitivity C-reactive protein (hs-CRP) in the treatment group after a median follow-up of 3.8 years (HR= 0.96; 95% CI] 0.84–1.11; $p = 0.59$) [39].

In patients with CKD stages 3 and 4, there is one prospective randomized controlled trial: Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND IT). In this primary prevention trial with a 2 by 2 factorial design, 864 patients with microalbuminuria were randomized to fosinopril or matching placebo and to pravastatin or matching placebo. The mean follow-up was 4 years. Pravastatin resulted in a nonsignificant 13% reduction [0.87 (95% CI 0.49–1.57); $p = 0.649$] [37]. However, the study was limited due to the small number of patients studied. Another landmark primary prevention statin trial was the Heart Protection Study (HPS), which enrolled 20,000 patients with increased risk of death from CVD due to diabetes, coronary heart disease (CAD), and other atherosclerotic diseases.

Patients were randomized to simvastatin 40 mg daily or placebo [37]. In this 5-year study, the investigators performed a retrospective analysis of 1,329 CKD patients with serum creatinine ranging from 1.3 to 2.3 mg/dl. There was a relative risk reduction of 28% (95% CI 0.72–0.85; $p = 0.05$) [37]. The same result was confirmed in a subgroup analysis in the Cholesterol and Recurrent Events (CARE) study, in which 1,700 patients with eGFR <75 ml/min were evaluated for the efficacy of pravastatin 40 mg per day versus placebo. There was a 28% relative risk reduction (95% CI 0.55–0.95; $p = 0.02$) over 5 years [37]. The ongoing Study of Heart and Renal Protection (SHARP) is examining the effect of a combination of simvastatin and ezetimibe versus simvastatin alone on subsequent vascular events in patients with CKD stages 3–5 [40].

2.3.3 Novel Risk Factors in Cardiovascular Disease Progression in Patients with Chronic Kidney Disease

2.3.3.1 Anemia

Anemia is a relatively early complication of CKD, and its prevalence depends on the hemoglobin (Hb) cutoff point used in different studies. However, the most commonly accepted definition of anemia by the World Health Organization (WHO) is an Hb <13 g/dl for men and <12 g/dl for women. It is estimated that 20% of patients with stable coronary disease and 30–60% with HF have anemia. The resulting decrease in Hb reduces oxygen-carrying capacity, which leads to anemia symptoms such as fatigue and shortness of breath. Moreover, the body compensates by increasing CO through vasodilatation (due to increased nitric oxide release in chronic anemic states). These compensatory mechanisms lead to neurohormonal changes, most importantly, RAAS and SNS activation. These changes and the reduced oxygen-carrying capacity adversely affect cardiac function. In addition, CKD patients are chronically exposed to higher levels of neurohormones, HTN, and anemia, which lead to LVH. In fact, LVH is the cardiac abnormality most commonly associated with anemia and is a strong predictor of mortality. Levin et al. found that the prevalence of LVH increased progressively with declining creatinine clearance (CrCl) levels: 26.7%, 30.8%, and 45.2% for CrCl >50 ml/min, 25–49 ml/min, and <25 ml/min, respectively [41]. For every 1 gram decrease in Hb, there was a 6% increase in LVH risk [41]. Thus, it is reasonable to conclude that patients are anemic long before they reach ESRD due to the association of LVH and severity of anemia. However, it is important to note that the causality of this relationship has not yet been completely proven. It is also worthy of discussion that multiple randomized studies in advanced CKD, i.e., stages 3 and 4, and ESRD patients have failed to show LVH regression after implementation of recombinant erythropoietin therapy. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study investigated 1,432

patients with CKD. This trial compared the effect of epoetin-α to the correction of moderate Hb (11.3 g/dl) versus a higher target of Hb (13.5g/dl). Findings for primary endpoint (i.e., death, MI, hospitalization for CHF, and stroke) showed this treatment was not beneficial and was actually harmful (HR = 1.34; 95% CI 1.03–1.74; p = 0.03), as it significantly increased death rate and negative cardiovascular outcomes. There was also a trend toward higher hospitalization for CHF (p = 0.07) [42].

2.3.3.2 Oxidative Stress

Oxidative stress has been extensively studied in patients with endothelial dysfunction and accelerated lipid accumulation in atherosclerotic plaque [32, 33]. Oxidative stress has profound atherogenic effects, as ROS combine with nitric oxide, resulting in endothelial dysfunction [32, 33]. Patients with CKD and ESRD have a significant elevation of oxidative stress due to increased inflammation levels and neurohormone stimulation (see above) [32].

2.3.3.3 Endothelial Dysfunction

The endothelium modulates vascular tone by balancing vasodilators (nitric oxide and prostacyclin) and vasoconstrictors (catecholamine, thromboxane, AngII, endothelin-1, antidiuretic hormone). In patients with CKD, this balance shifts in favor of more vasoconstriction due to increased levels of the nitric oxide synthase inhibitor asymmetric dimethyl arginine (ADMA) [43], along with elevated endothelin production and RAAS and SNS hyperactivity. The end result of this neurohormonal storm is increased blood pressure and atherosclerosis. Also, it reduces perfusion to vital organs, such as the heart, either by disturbing coronary perfusion or microcirculation.

2.3.3.4 Lipoprotein (a)

Lp(a) is similar to LDL in structure, except for an additional glycosylated Apo-B100 linked to Apo(a). It is highly atherogenic by a myriad of mechanisms, including macrophage foam cell stimulation, inhibition of endothelium fibrinolytic activity through impaired activation of plasminogen, and endothelial-derived reactivity reduction [33]. Lp(a) is an independent risk factor for cardiovascular mortality in patients with ESRD. In a prospective follow-up of patients with ESRD, Lp(a) was 43% higher in this patient population compared with the general population. Other studies indicate that there are up to sixfold higher levels of Lp(a) in patients with severe nephrotic syndrome [44].

2.3.3.5
Hyperhomocysteinemia

Homocysteine is a product of methionine metabolism. More than two thirds of homocysteine is excreted in the urine. Therefore, when eGFR declines, it is likely that hyperhomocysteinemia develops. A 5-year prospective study of 14,916 male physicians aged 40–84 years [45] revealed a 3.4-fold increased risk for MI in men with elevated homocysteine levels. CKD is one of the most common causes of hyperhomocysteinemia, and by the time CKD reaches stage 5, 90% of patients have a moderate degree of hyperhomocysteinemia, i.e., >15 μmol/l. A meta-analysis of observational studies demonstrated that an increment of 5 μmol/l increases the risk of ischemic heart disease and stroke by 70% and 80%, respectively. A number of observational and meta-analysis studies suggested the association between higher levels of homocysteine and increased CVD outcomes. Also, numerous mechanisms have been proposed for the causation of worse outcome in patients with hyperhomocysteinemia including reduction of HDL by inhibiting Apo-AI synthesis, direct vascular toxicity, changes in genomic DNA methylation and an increase in oxidation of LDL cholesterol. Yet, three large randomized vitamin interventional trials demonstrated that lowering of homocysteine level does not reduce CV outcomes in patients without CKD [46–48]. Similar results in patients with ESRD confirm similar finding, i.e., lack of benefit for lowering homocysteine levels and changes in CVD outcome [49].

2.3.3.6
Inflammation and High-Sensitivity C-Reactive Protein

Inflammation and atherosclerosis are tightly associated through the entire spectrum of atherosclerosis – from fatty streak formation to plaque formation and acute coronary syndromes (ACS). Among a handful of inflammatory biomarkers studied, hs-CRP remains one of the most important biomarkers for short-term, in-patient prognostication and long-term outcome prediction, and as a primary prevention screening tool for CVD risk assessment [50]. In CKD, elevated levels of inflammatory biomarkers, including CRP and interleukin-6 (IL-6), are additive to the traditional risk factors on the vascular endothelium. Moreover, IL-6 enhances production of CRP in the liver [33], which binds to the Fc receptor of the immunoglobulin protein and subsequently activates the complement cascade [33]. This places CKD patients in a chronic inflammatory state. In a moderately sized study of nearly 400 patients with ESRD, there was a strong relationship between serum hs-CRP >1 mg/L and higher mortality compared with those with lower hs-CRP level (44% vs. 18%; $p < 0.001$).

The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) studied 17,802 apparently healthy men and women with hs-CRP >2.0 mg/L assigned to rosuvastatin or placebo. After a mean follow-up of 1.9 years, the rates of the primary end point (a composite of MI, stroke, and death from cardiovascular causes) were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR for rosuvastatin

0.56; 95% CI 0.46–0.69; $p < 0.00001$) [50]. However, as stated earlier, AURORA [39] failed to show any benefit of statin therapy in patients with ESRD despite lowering hs-CRP and LDL cholesterol, indicating the complex understanding of vasculopathy of patients with advanced kidney disease. The ongoing SHARP trial [40] results will determine whether reducing hs-CRP and LDL cholesterol by statin therapy will change CVD outcome in patients with CKD stages 3 and 4.

2.3.3.7
Accelerated Coronary Calcification

With decreasing eGFR <60 ml/min/1.73m^2, phosphorus excretion diminishes [33] and leads to hyperphosphatemia. The elevated level of phosphorous stimulates the release of parathyroid hormone (PTH), which ultimately mobilizes calcium from the bone matrix. This sequence can potentially accelerate the risk of vascular calcification [33]. As CKD progresses to more advanced stages, this process accelerates simultaneously. Thus, coronary calcification, as measured by computed tomography (CT) is an invariable finding (88%) in younger patients with ESRD (20–30 years of age) compared with matched controls (5%) [51]. Noncalcium phosphate binders have been shown to lower the risk of coronary and aortic artery calcification in patients with ESRD. Reducing LDL cholesterol via binding capacity in the small bowel may be involved with these binders. This has led to a reduced coronary artery calcium score as measured by CT scan, yet CVD outcome of these patients remained poor despite improved coronary artery calcium score.

2.3.3.8
Other Novel Risk Factors

There is ongoing research on other novel biomarkers that might have either an association or causation relationship to worsening CVD outcomes in patients with CKD, such as diminished transforming growth factor (TGF)-1β level or disordered mineral metabolism. Data on such biomarkers or mechanisms are not as strong as those discussed here. Clearly, the cardiorenal and renocardiac relationship are a rapidly evolving area of research, and much more remains to be learned.

2.4
Chronic Kidney Disease and Valvular Heart Disease

Valvular and vascular calcifications are strongly interrelated. Nearly 25% of patients with CKD and 50% with ESRD have aortic and mitral annular calcification [52]. Approximately 80% of patients of ESRD have a murmur of aortic stenosis. Surprisingly, neither of these two major valvular abnormalities progresses to the

point that conservative management becomes futile, unless they become infected. This can occur in ESRD patients due to catheters, shunts, and exposure to needles that occur three times a week [52]. In patients with ESRD, if valve surgery becomes inevitable, there is no difference in outcome between mechanical and tissue valves. Therefore, it is reasonable to choose the tissue valve to avoid anticoagulation, because warfarin can accelerate vascular calcification in patients with ESRD and increase the risk of bleeding from the hemodialysis access site.

2.5 Chronic Kidney Disease and Arrhythmias

Common chemistry abnormalities of patients with CKD or ESRD, such as hyperkalemia, uremia, acidosis, and calcium/phosphorus dysregulation, are associated with higher rates of arrhythmia. Structural heart disease secondary to CKD/ESRD, such as LVH, valvular abnormalities, conduction system calcification, and HF can independently worsen the outcome of arrhythmias in this population. Therefore, specific attention to short- and long-term management of patients with CKD is necessary. As stated previously, HF and CKD/ESRD often coexist. Intracardiac defibrillator placement for secondary prevention of fatal ventricular arrhythmias is standard care. In the study by Wase et al. [53], investigators found a significant increase in defibrillation threshold in patients with CKD stage 3 and ESRD.

2.6 Conclusions

Kidney function remains the single most important prognostic marker in patients with HF in acute deterioration or in long-term therapy. Worsening kidney function may be one of the strongest surrogates of RAAS and SNS activation. Given the increased morbidity and mortality associated with comorbid renal dysfunction, recognizing which factors are involved in an individual patient and eliminating those factors whenever possible is an essential component of HF management. Conversely, CKD is not just a marker but a pathogenic factor in progression of heart disease or worsening the outcome of patients with heart disease. The metabolic milieu and vascular pathobiology of the CKD state offers an opportunity for development of diagnostic and therapeutic targets to improve the outcome of patients with cardiorenal or renocardiac syndrome.

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Section II
Crosstalk between the Cardiovascular System and the Kidney

Non-Pressure-Related Deleterious Effects of Excessive Dietary Sodium

3

A. Mimran

Abstract After demonstration of a positive correlation between sodium intake and arterial pressure in large population studies, the effect of rather short-term reduction in sodium intake demonstrated the efficacy of this nonpharmacological therapy. In addition, a positive relationship between urinary sodium (the most reliable estimate of salt intake) and left ventricular mass was found in normotensive and hypertensive cohorts independent of blood pressure. In recent years, cardiovascular morbidity has been positively correlated with increasing sodium intake, despite one contradictory study. The role of non-pressure-related effects of dietary sodium is discussed to bring additional and convincing arguments to support a large-scale attempt to reduce sodium intake by 30–50%.

Keywords: Sodium intake • Hypertension • Target organ damage • Aldosterone • Albuminuria • Cardiovascular mortality

3.1 Introduction

The role of dietary sodium as a determinant of blood pressure (BP) was demonstrated by the linear and positive relationship between sodium intake (estimated by 24-h urinary sodium excretion) and BP in cross-sectional population studies. Of interest, the slope of this relationship tended to be steeper with increasing age, thus suggesting that sodium sensitivity tends to be more prevalent with older age [1]. In addition, it has been shown that short-term as well as long-term moderate reduction of salt intake is associated with a decrease in BP in normotensive and hypertensive individuals. In the Dietary Approach to Stop Hypertension (DASH) study conducted on 412 individuals with a BP range 120–159/80–95 mmHg, moderate reduction of salt intake from 150 to 100 mmol/day (from 9 to 6 g/day) during a 4-week period was associated with a decrease in systolic arterial pressure (SAP) of 2.1 mmHg. The fall in SAP was amplified when sodium intake was reduced to 50 mmol/day (–4.4

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Cardiorenal Syndrome. Adel E. Berbari, Giuseppe Mancia (Eds.)

mmHg) [2]. In a systematic review and meta-analysis of randomized controlled trials conducted in normotensive and hypertensive populations, reduction of sodium intake by an average of 35 and 47 mmol/24 h at 13 and 60 months of follow-up, respectively, was associated with a fall in BP by 8/4.5 mmHg in hypertensive patients. No relationship between changes in sodium intake and BP was found [3].

During the last two decades, and following two reports on a positive correlation between left ventricular mass (LVM) and urinary sodium excretion independent of BP [4, 5], additional arguments favored the non-pressure-related effects of dietary sodium on subclinical target-organ damage and cardiovascular morbidity and mortality.

3.2 Measurement of 24-Hour Urinary Sodium is the Gold Standard for Estimating Sodium Intake

In clinical research, measurement of 24-h urinary sodium excretion, which represents approximately 85% to 90% of sodium intake measured by dietary recall, is the most reliable estimate of sodium intake, despite individual day-to-day variations in food availability and personal preferences, resulting in a variation coefficient of approximately 20% [6]. When the difference in natriuresis was assessed between individuals who regularly add salt before tasting food and those who do not, it amounted to approximately 25%. The use of the sodium to creatinine ratio on a single-spot urine sample, which is probably more convenient for population studies, may not yield reliable estimations. This is due to the age- and gender-related difference in urinary creatinine excretion reflecting a different muscle mass (for a given sodium intake, the sodium to creatinine ratio will be higher in elderly individuals and women). Overall, studies using 24-h urinary sodium excretion reported an approximately 20% lower sodium intake in women [6].

3.3 Influence of Sodium Intake on Subclinical Organ Damage

In essential hypertension, the presence of LV hypertrophy (LVH) is a strong and independent predictor of increased cardiovascular morbidity and mortality. More recently, microalbuminuria corresponding to albuminuria of 30–300 mg/24 h or 20–200 μg/min) (i.e., below the detection limit afforded by dipsticks), which was considered a good marker of renal risk in patients with insulin-dependent diabetes, has emerged as a reliable predictor of cardiovascular risk in large population studies [7] and essential hypertension [8]. Interestingly, the increase in risk is already found for urinary albumin excretion (UAE) well below the classically proposed threshold value of 20 μg/min (corresponding to 2.5 and and 3.5 mg/mmol creatinine in men and women respectively) and as low as 5 μg/min or urinary to creatinine values of 6.6 mg/g (0.66

mg/mmol) in men and 15.2 mg/g (1.52 mg/mmol) in women [9]. Of interest, no study has concentrated on the prognostic significance of each risk factor (LVH or albuminuria alone), or the combination of both. In several trials, a positive correlation, independent of BP level, was found between LVM index (LVMI) and sodium intake, estimated by nocturnal natriuresis or 24-h urinary collection [5, 6]. In a large cohort of 336 normotensive (BP <140/90 mmHg) individuals and 503 patients with never-treated essential hypertension, a progressive increase in age- and gender-adjusted LVMI, UAE, and albumin-to-creatinine ratio with increasing level of sodium intake (estimated as the average of two measurements of 24-h urinary sodium excretion) was observed in both normotensive and hypertensive populations. The regression line slope between systolic arterial pressure (the strongest determinant of LVMI and UAE) and LVMI or UAE was progressively steeper from the lowest to the highest quintile of urinary sodium excretion. As shown in Fig. 3.1, in a group of 450 never-treated patients with essential hypertension, the prevalence of LVH, microalbuminuria, or both clearly increased from the lowest to the highest quintile of natriuresis. Of interest, age and BP were similar in all groups [6]. These observations favor a modulating effect of dietary sodium on the response of the heart, kidney, vasculature, and probably other target organs to the chronic impact of high systemic pressure.

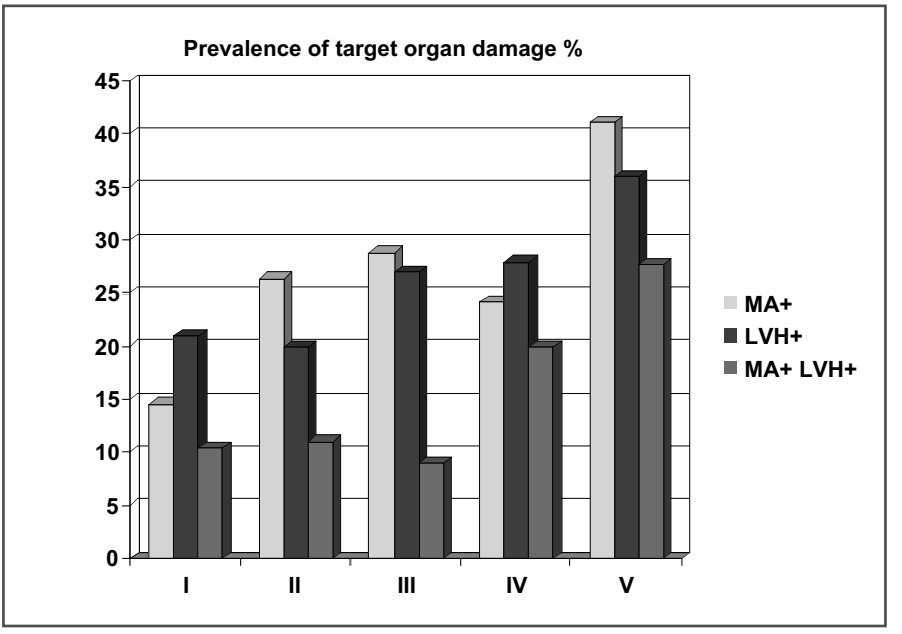

Fig. 3.1 Prevalence of left ventricular hypertrophy (LVH ≥ 125 g/m^2 in men and 110 g/m^2 in women), microalbuminuria [(MA) ≥20 μg/min in 24-h urine collection], or both (MA+ LVH+) according to quintiles of 24-h natriuresis adjusted to gender in 450 never-treated patients with essential hypertension aged ≥40 years. Mean values of age and blood pressure were similar in all groups

In contrast, other studies failed to detect any influence of sodium intake (estimated as the sodium to creatinine ratio on a single-spot urine sample) on LVM, independent of BP [10]. As mentioned earlier, this discrepancy may be related to the uncertainties associated with measuring sodium to creatinine ratio, especially in elderly individuals.

In our cohort, it was observed that pulse pressure, a marker of elastic arterial stiffness and a predictor of cardiovascular events [11] increased with increasing sodium intake in individuals older than 40 years.

3.4 Does the Influence of Dietary Sodium on Target-Organ Damage Translate into a Difference in Risk?

In Japanese patients with essential hypertension, salt-sensitive BP, in contrast to salt resistance, was associated with increased risk of cardiovascular events, independently of BP [12]. This observation was confirmed in a group of hypertensive individuals investigated by Weinberger et al. [13].

Two analyses of the same data base [the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES)] were conducted at two different periods. Whereas Alderman et al. [14] concluded that a low salt intake could be deleterious, He et al. [15] reported that in overweight individuals, a 100-mmol increase in sodium intake (estimated by dietary recall) was associated with an increase in stroke incidence of 32%, coronary heart disease mortality of 44%, and overall cardiovascular mortality of 61%. In an adult Finnish population of 2,436 individuals with a remarkably high sodium intake as estimated by 24-h natriuresis (>159 and 119 mmol/day in 75% of men and women, respectively), dietary sodium predicted mortality and risk of coronary heart disease independently of BP and other cardiovascular risk factors. In fact, for a 100-mmol increase in sodium intake, cardiovascular morbidity increased by 45%, but no influence on acute stroke was detected [16]. A meta-analysis of prospective studies conducted in 14 cohorts (total >100,000 individuals in whom >5,000 events were reported) showed that for a difference in salt intake of 86 mmol/day, an increase in the risk of stroke (by 23%) and cardiovascular disease (by 14%) was detected [17].

3.5 Studies on the Effect of Salt Restriction

In 38 patients with untreated hypertension, dietary sodium reduction by approximately 50% for 6–12 months was associated with a decrease in LVM of 9%, only when LVH was present at baseline. No correlation between changes in arterial pressure and cardiac weight was found [18]. Although some studies suggest that consistent dietary

sodium reduction is associated with favorable changes in large-artery function [19], assessment of the influence of sodium reduction on progression with time of large-vessel stiffness, independent of changes in BP, is clearly needed.

3.6 Is Reduction in Dietary Sodium Associated with a Reduction in Cardiovascular Risk?

In the Trial of Nonpharmacologic Interventions in Elderly (TONE) study [20], a cohort of 681 patients with controlled hypertension (systolic pressure <145 and diastolic pressure <85 mmHg) and aged 60–80 years was divided into four groups: sodium reduction alone, weight reduction alone, combined weight and sodium reduction, and usual lifestyle. In individuals submitted to sodium reduction, efforts were made to maintain 24-h urinary sodium at ≤80 mmol/day. After a follow-up period of 28 months associated with a decrease in natriuresis of 45 mmol/day, overall reduction of BP by 4.6/2.2 mmHg, similar in overweight and nonoverweight individuals, was observed. During follow-up, 43% of the sodium reduction group remained free of elevated BP (vs 27% in the control group), whereas 36% remained free of a trial endpoint consisting of elevated BP, resumption of medication, or cardiovascular event in the sodium-restricted group (vs 21% in the control group).

3.7 Evidences in Favor of a Direct Effect of Dietary Sodium

In animal studies, dietary sodium restriction was shown to prevent the development of cardiac hypertrophy, independently of BP changes, in hypertension induced by chronic infusion of angiotensin II [21]. In normal rats, a diet containing 8% sodium chloride for more than 4 weeks and begun in adult animals was associated with LVH independently of differences in BP [21, 22]. Interestingly, initiation of a high-sodium diet immediately after weaning and until the age of 5 months (in an attempt to mimic the human situation) showed that a substantial increase in LVM index and carotid cross-sectional area was already achieved with a diet containing 2% sodium chloride (NaCl) and was aggravated by 8% NaCl in the absence of any effect on BP [23]. Of note, at the end of the studies, a consistent reduction in glomerular filtration rate by approximately 40% associated with a threefold increase in albuminuria was observed only in rats ingesting the 8% NaCl diet [23]. Cardiac and renal changes associated with long-term increase of sodium intake may, in fact, result from a profibrotic effect of sodium associated with overexpression of transforming growth factor beta-1 (TGF-β1), as observed in cardiac and renal tissues from normal and spontaneously hypertensive rats [24].

A few studies provide arguments for a renal protective effect of dietary sodium

restriction. In the 5/6 renal ablation model, dietary sodium reduction (from normal to 20% of normal), started shortly after injury and continued for 8 weeks, prevented the progressive increase in BP and proteinuria, independently of changes in intraglomerular pressure [25]. Progression of nephropathy associated with streptozotocin-induced diabetes was also blunted by long-term sodium restriction [26].

3.8 Mechanism(s) Involved in the Deleterious Effect of Salt

As demonstrated in Table 3.1**,** the mechanism(s) linking sodium intake and the enhancement of hypertension-associated target-organ damage (LVH, albuminuria, stiffening of large arteries) remain unclear. Several clinical and experimental studies are in favor of non-pressure-related prohypertrophic and possibly profibrotic effects of excessive dietary sodium. Although it is unequivocal that salt intake plays an important role in regulating BP, the mechanisms whereby salt raises BP and induces direct cardiovascular organ damage are not clear.

In humans, chronic changes in sodium intake are associated with significant and parallel variations in plasma sodium concentration [27]. In cultured neonatal rat myocardial myoblasts and vascular smooth muscle cells (VSMC), a change in sodium concentration from a median of 146 to 152 mmol/L was associated with a consistent increase in cell volume, protein content, and the rate of protein synthesis – highly suggestive of cellular hypertrophy [28]. The hypothesis that small changes in plasma sodium concentration may influence endothelial cell stiffness was tested using atomic-force microscopy, a technique able to measure stiffness of living human endothelial cells grown in culture. An increase in plasma sodium concentration from 137 to 142 mmol/L and above had no effect on endothelial cell stiffness; however, after incubation of cells with aldosterone (0.45 μM), a sharp rise in cell stiffness occurred in response to sodium. This effect was prevented by addition of eplerenone or amiloride (1 μM concentration). Nitrite release (as a measure of nitric oxide production) was reduced only in the media of cells exposed to a high concentration of sodium and aldosterone. These studies demonstrate that an increase in sodium con-

Table 3.1 Putative mechanisms of the deleterious cardiovascular effects of excessive dietary sodium through blood pressure increase independent of blood pressure

- Endothelial dysfunction through excessive generation of free radicals
- Enhancement of microalbuminuria
- Enhancement of concentric remodelling of the left ventricle
- Increased stiffness of large vessels
- Excessive generation of free radicals
- Up-regulation of type1 angiotensin II receptors
- Down-regulation of type 2 angiotensin II receptors
- Overexpression of tissue aldosterone synthase
- Up-regulation of transforming growth factor beta-1 (TGF-β1)

centration may result in alteration of endothelial function or that aldosterone requires the presence of high sodium to exert its deleterious vascular effect [29]. An increase by 10 mmol/L of sodium concentration of the medium of aortic VSMC was associated with a marked increase in angiotensin II type 1 (AT1)-receptor messenger RNA (mRNA) and a rise in vascular AT1-receptor density in response to a 6-week increase in sodium intake [30]. Although a chronic increase in sodium intake is associated with profound reduction in the circulating level of renin and angiotensin II, no change in cardiac angiotensin II content has been observed [31]. In addition to upregulation of AT1-receptor expression and density [31], it was shown that the cardiac hypertrophic response to high dietary salt was associated with an increase in LV tissue angiotensin-I-converting enzyme mRNA activity in rats [32].

Activation of angiotensin II type 2 (AT2) receptors may function as an antihypertrophic mechanism, whereas downregulation would tend to enhance the response to renin–angiotensin system stimulation. In a recent study, it was observed that a high-salt diet is associated with a consistent decrease in AT2 receptor mRNA, protein, and vasodilatory effect in isolated small-diameter arteries [33].

It is well established that high dietary sodium is indispensable to the development of cardiovascular changes associated with aldosterone administration [34]. The contribution of aldosterone to structural cardiovascular changes resulting from a chronic increase in sodium intake was suggested by the finding of doubling in the cardiac production of aldosterone, aldosterone synthase activity, and cytochrome P11B2 (CYP11B2) expression, despite no change in arterial pressure, and a drastic reduction in plasma concentrations of renin and aldosterone and increased cardiac level of AT1 mRNA [22]. In rats, the role of aldosterone in cardiorenal changes associated with long-term (from weaning to 5 months of age) increased salt intake was assessed by administering spironolactone. Treatment with a mineralocorticoid receptor blocker during the final 2 weeks of the study resulted in reversibility of LVH and alteration in renal function associated with this period of excessive salt intake [23].

In patients with resistant hypertension, it was recently demonstrated that proteinuria was higher only in individuals with high urinary aldosterone excretion within the highest tertile of natriuresis [35]. This suggests that consistent reduction of sodium intake may have a major effect on BP and proteinuria in patients with resistant hypertension.

Endothelial dysfunction may be the consequence of excessive generation of reactive oxygen species (as suggested by an increase in isoprostanes) and/or increased circulating concentrations of the endogenous inhibitor of nitric oxide synthase, asymmetrical dimethylarginine (ADMA). In a recent study, plasma concentration of isoprostanes [36] or ADMA [37] was consistently increased after sodium loading only in individuals with salt-sensitive hypertension. Moreover, the change in ADMA was entirely prevented by combined sodium and potassium loading [37]. In rats maintained on a high salt diet for 1 week, increased plasma concentration of 8 isoprostanes was found, together with enhanced renal production of superoxide anions related to increased renal expression and activity of nicotinamide adenine dinucleotide phosphate, reduced (NADPH) oxidase. Moreover, a fall in BP was observed in response to chronic administration of the superoxide dismutase mimetic Tempol at

a dosage shown to reduce superoxide level in kidney and vessels [38]. In rats maintained on a high-sodium diet from weaning to 5 months of age, an increase in cardiac and aortic production of reactive oxygen species was also observed [21].

TGF-β is a family of polypeptides with complex effects on organ development, cell growth and differentiation, extracellular matrix protein expression, immune responses, angiogenesis, and tissue repair [39]. When a normal (1%) or high (8%) sodium diet was given from 8 to 16 weeks of age to normotensive Wistar-Kyoto and spontaneously hypertensive rat (SHR), a disproportionate (with respect to the modest rise in arterial pressure) widespread fibrosis of heart and kidney developed in both strains maintained on the high-sodium diet. Fibrosis was paralleled by overexpression of TGF-β1 in hearts and kidneys [39]. In normal rats, study of the time-course of the effect of high (8%) vs low (0.3%) sodium diet showed that kidney production of TGF-β1 mRNA and urinary TGF-β1 excretion were markedly enhanced as early as 1 day after the start of the high-sodium diet and persisted during the 2-week experiment without any elevation of systemic pressure. Of interest, diuretic administration in rats maintained on high-sodium intake had no effect on the excessive production of TGF-β resulting from salt loading [40]. Whether TGF-β1 promotes organ fibrosis directly or through salt enhancement of the profibrogenic effect of vasoactive hormones such as angiotensin II, aldosterone, or endothelin remains unclear.

3.9 Conclusions

There is sufficient argument favoring the need for a substantial reduction of sodium intake as an intervention aimed at reducing BP, reducing the need for drug treatment and the number of antihypertensive agents administered to hypertensive individuals, preventing progression from normotension to hypertension, and more importantly, from prehypertension to hypertension.

In the USA, although the recommended salt intake is approximately 6 g (100 mmol) per day, the estimated intake (2005–2006) was 10.4 g in men and 7.3 g in women, corresponding to 170 and 120 mmol per day, respectively. In order to explore the impact of reduced, even modest, dietary salt on public health, a computer simulation of coronary artery disease (CAD) was undertaken in US adults aged 35–84 years, and the authors extended the model to assess stroke. It was projected that a reduction of salt intake by 3 g (50 mmol/day) could be associated with an annual decrease in new cases of CAD by 60,000–120,000, stroke by 32,000–66,000, myocardial infarction by 54,000–99,000, and total mortality by 44,000–92,000 per year. Interestingly, a significant benefit would still be achieved in response to a salt intake reduction of 1 g/day [41]. Based on a fall in BP expected from meta-analysis of randomized studies [17], it was calculated that a decrease in salt intake of 6 g/day would be associated with reduced CAD of 18% and stroke of 24%. These figures could correspond to preventing 35,000 deaths from stroke CAD per year in the UK, and expectation of 2.5 million worldwide.

Since 75–80% of ingested salt comes from processed foods rather than salt added during preparation or consumption of meals; several countries, including the UK, Japan, Finland, and Portugal, have adopted rationing policies. Efforts for substantially reduced salt intake (by 30–50%) – concentrating on comprehensive labeling of processed foods through collaboration with the food industry, as well as public education – may be considered the most important measures for reducing dietary sodium intake.

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Regulation of Vascular and Renal Cells by Common Mediators in Health and Disease: Role of the Renin–Angiotensin System in the Pathophysiology of Hypertension and Cardiovascular Disease

4

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Abstract In the classic view of the renin angiotensin system (RAS), angiotensin II (AngII) is the main effector peptide. Circulating RAS regulates physiological responses, whereas the local RAS is activated during tissue injury and contributes to pathological processes, including cell proliferation/apoptosis, fibrosis, and inflammation. AngII has direct effects on these processes through activation of mitogen-activated protein kinase (MAPKs) and Smad and nuclear factor kappa B (NF-κB) transcription factors. In addition, AngII recruits important secondary mediators, such as transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), and chemokines. AngII binds to the angiotensin type 1 and 2 (AT_1 and AT_2) receptors mediating different cellular responses. Both angiotensin-converting enzyme (ACE) inhibitors and AngII receptor antagonists (ARA II, targeting the AT_1 receptor) have demonstrated their therapeutic efficacy in protecting the cardiovascular system and kidneys in humans. Some AngII degradation peptides are also biologically active. Aminopeptidases promote the generation of AngIII and AngIV, two N-terminal degradation products, whereas ACE-2 catalyzes generation of Ang-(1-7). AngIV has been reported to bind to the AngIV-binding-site insulin-regulated aminopeptidase (IRAP) and to promote inflammation in vascular cells. Ang-(1-7) activation of the Mas receptor may be beneficial in vascular injury but increases kidney inflammation.

Keywords: Angiotensin II • Atherosclerosis • Cardiovascular disease • Fibrosis • Inflammation • Kidney

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4

4.1
Renin–Angiotensin System in Vascular and Renal Diseases: From the Classic View to the New and Complex System

The classic view of the renin–angiotensin system (RAS), where angiotensin II (AngII) is the main effector peptide, is shown in Fig. 4.1. The circulating RAS regulates physiological responses, whereas the local RAS contributes to pathological processes, including cell proliferation/apoptosis, ECM accumulation, and inflammation. Activation of local RAS components, mainly elevated angiotensin-converting enzyme (ACE) activity and therefore AngII levels, has been demonstrated in many chronic diseases, such as hypertension, cardiovascular diseases (myocardial infarction and atherosclerosis), kidney diseases, and diabetes, supporting the importance of this system in different pathologies [1, 2]. Besides AngII, its degradation peptides also present diverse functions. The two N-terminal degradation products, AngIII and AngIV, are generated by different aminopeptidases (AP) and regulate important biological functions [3]. Ang-(1-7) can be formed by ACE-2, independently of ACE, and participates in cardiovascular responses [4].

In recent years, a combination of classic physiopharmacological techniques, modern genomics, and protein chemistry methods has characterized novel components of RAS [4], and a more complex picture, shown in Fig. 4.2, has emerged. These components are: Ang IV-binding-site insulin-regulated aminopeptidase (IRAP), ACE-2) the renin receptor, and the Ang-(1-7) receptor Mas. In particular, recent identification of the Ang-(1-7)-forming enzyme ACE-2 and Mas has added further insights into the RAS [4]. ACE-2 may play a role as negative regulator of ACE. Moreover, ACE-2, besides generating Ang-(1-7), hydrolyzes apelins, dynor-

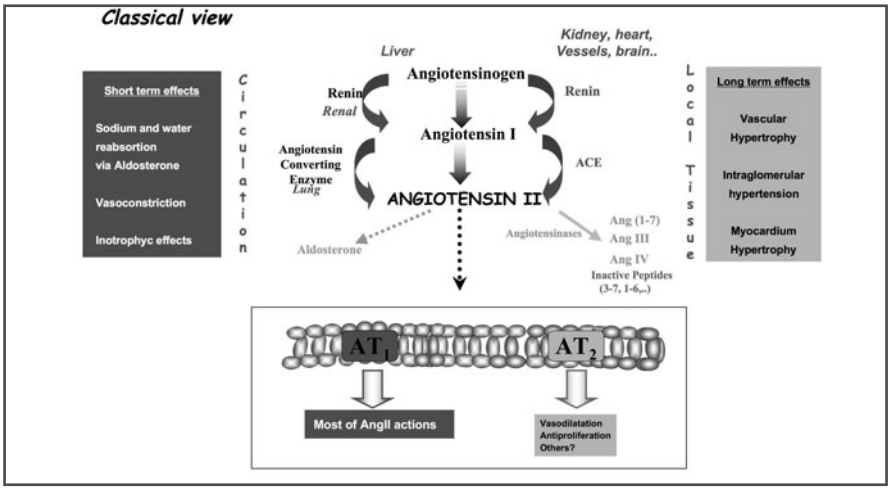

Fig. 4.1 Classic renin–angiotensin system (RAS). *ACE,* angiotensin-converting enzyme

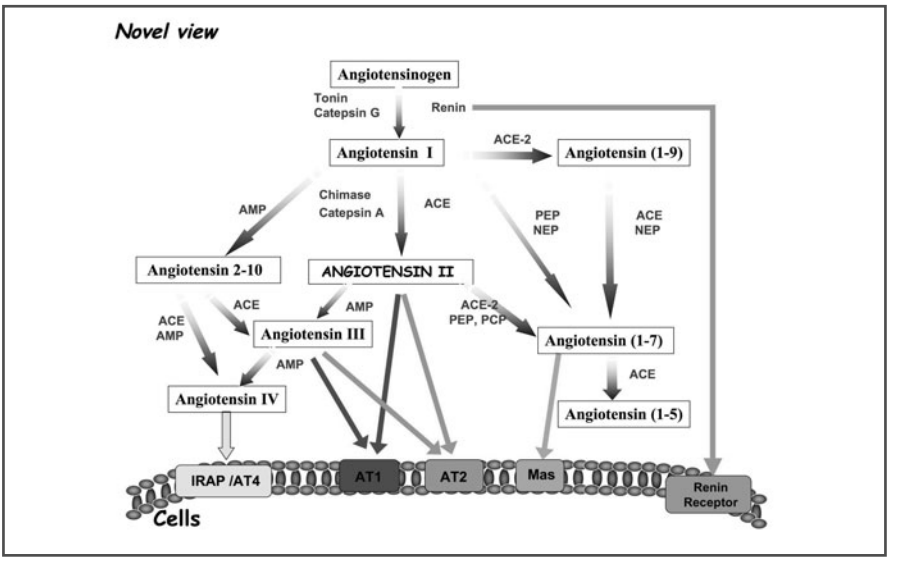

Fig. 4.2 Novel components of renin–angiotensin system. *ACE*, angiotensin-converting enzyme; *AMP,* amino-peptidase; *APN,* aminopeptidase N; *IRAP,* insulin-regulated aminopeptidase; *NEP,* neutralendopeptidase; *PCP,* prolylcarboxypeptidase; *PEP,* prolylendopeptidase

phin A 1-13, des-Arg-bradykinin, and other peptide substrates. These peptides have biological actions that are relevant for renal and vascular injury, as summarized in Table 4.1. In this chapter, we review the role of the RAS components in cardiovascular and renal pathology.

Table 4.1 A partial overview of renal and vascular effects of angiotensin peptides

Peptide	Receptor	Vascular effects	Renal effects
AngII	AT1	Vasoconstriction Cell-growth regulation Inflammation Fibrosis	 Cell growth regulation Inflammation Fibrosis
AngII	AT2	Vasodilatation Inhibition of cell proliferation Apoptosis Fibrosis Inflammation	 Inhibition of cell proliferation Apoptosis Inflammation
AngIV	AT4	Cell Growth Inflammation	Cell growth
Ang(1-7)	Mas	Vascular protection: lower BP	Promotes inflammation

BP, blood pressure

4.2 Pharmacological Blockade of Renin–Angiotensin System in Vascular and Renal Diseases

Blockade of the RAS, by ACE inhibitors or angiotensin type 1 (AT_1) antagonists is one therapeutic strategy widely used in several clinical conditions. These drugs have proven beneficial effects in cardiovascular and renal diseases, which include improved cardiac and renal function and prolonged survival [5].

ACE inhibitors differ in their affinity for tissue ACE, and it has been suggested that tissue ACE affinity might be responsible for some of the beneficial properties of these drugs. ACE inhibitors interrupt the RAS by preventing conversion of the inactive peptide AngI to AngII, as well as its degradation products AngIII and AngIV (Fig. 4.3a). For this reason, their beneficial effects could be attributed to blockade of the cellular actions of AngII and its N-terminal degradation peptides. ACE inhibitors do not inhibit ACE-2 activity, therefore Ang-(1-7) levels could be increased and exert some potential beneficial effects through activation of the Mas receptor, including vasodilatation [4]. ACE inhibitors also increase plasma levels of bradykinin, which possesses vasodilator and tissue-protective properties. ACE inhibitors enhance nitric oxide availability, present antioxidant properties, and activate several kinases that could also contribute to their beneficial effects [5].

AngII elicits its cellular response through its binding to the AT_1 and AT_2 receptors. The AT_1 receptor participates in blood pressure control, cell growth regulation, and production of proinflammatory and profibrotic factors [1, 2, 6–9]. The beneficial effects of AT_1 antagonists are ascribed to blockade of these AT_1-mediated responses. However, blockade of the AT_1 receptor results in increased AngII levels

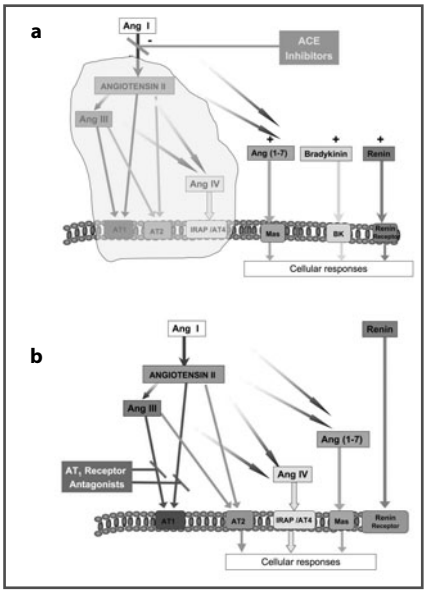

Fig. 4.3a, b Pharmacological blockade of renin–angiotensin system. View of the novel components. *Ang,* angiotensin; *ACE,* angiotensin-converting enzyme inhibitor; *IRAP,* insulin-regulated aminopeptidase

and increased Ang peptides [AngIII, AngIV, and Ang-(1–7)] generation. Free AngII could bind to the AT_2 receptor and induce several cellular responses, including vasodilatation and inhibition of cell proliferation. In general, cardiovascular effects of the AT_2 receptor appear to be opposite to those of the AT_1 receptor, and for this reason, some authors have suggested that AT_2 counterbalances the vasoconstrictive, proliferative, and antinatriuretic actions of AT_1 activation [10]. However, there are no in vivo data that clearly confirm this idea. In addition, the other Ang peptides, through binding to their specific receptors, might also be involved in the observed effects of AT_1 blockade (Fig. 4.3b).

4.3 Common Responses to Angiotensin II in Vascular and Renal Diseases: Modulation of Fibrosis and Inflammation

AngII, the main peptide of the RAS and classically considered a potent vasoconstriction agent, is also a growth factor that regulates cell growth (proliferation/hypertrophy or apoptosis) and fibrosis [6–9]. In recent years, growing evidence suggests that AngII is a true cytokine that plays an important role in the inflammatory response [2] (Fig. 4.4).

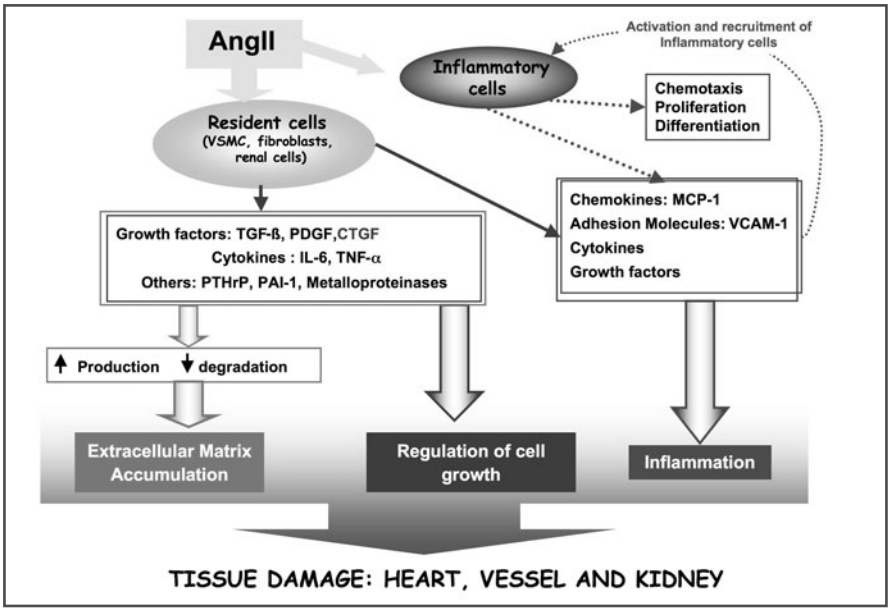

Fig. 4.4 AngII regulates cell growth, fibrosis, and inflammation. *Ang,* angiotensin; *MCP-1,* monocyte chemotactic protein-1; *PAI-1,* plasminogen-activation inhibitor-1; *PDGF,* platelet-derived growth factor; *PTHrP,* parathyroid-hormone-related protein; *TGF-β,* transforming growth factor beta; *TNF-α,* tumor necrosis factor alpha; *VCAM-1,* vascular cell adhesion molecule-1; *VSMC,* vascular smooth muscle cells

4.3.1
Angiotensin II and Cell Growth Regulation in Vascular and Renal Diseases

AngII regulates cell growth, although the response depends on cell type and cellular conditions. Most studies have shown that in vascular smooth muscle cells (VSMC), mesangial cells, and fibroblasts (both cardiac and renal), AngII via AT_1 receptor induces cell proliferation, whereas in cardiomyocytes and tubuloepithelial cells, it promotes cell hypertrophy [6–9]. In vitro studies have demonstrated that AT_2 stimulation inhibits the growth of various cell types, including VSMC, mesangial, endothelial cells, cardiomyocytes, and cardiac fibroblasts [6–9]. However, results of in vivo studies in the cardiovascular system are controversial [10]. Some experimental studies, using in vivo transfer of the *AT2* gene and AT_2-knockout mice showed that AT_2 can inhibit VSMC growth in vivo. Administration of an AT_1 antagonist to AT_2-knockout mice decreases vascular lesion to a lesser extent than in wild-type mice, supporting the hypothesis that AT_2 stimulation could exert beneficial effects during AT_1 blockade [11]. However, opposite results have also been reported, implicating the AT_2 receptors in cardiac hypertrophy and fibrosis [12]. In AT_2-knockout mice with AngII-induced hypertension, left ventricular hypertrophy and interstitial collagen type I deposition were absent [13]. Moreover, it was recently shown that AT_2-receptor deficiency aggravates renal injury and reduces survival in chronic kidney disease in mice [14]. These contrasting results emphasize that the role of AT_2 in human diseases needs to be investigated.

4.3.2
AngII Regulates Fibrosis via AT_1 receptor: Role of CTGF and Smad Signaling Pathway

AngII via AT_1 regulates ECM accumulation, both in vascular and renal cells. AngII-induced fibrosis is mediated by the endogenous production of profibrotic growth factors, such as transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF) [15]. The relationship between AngII and TGF-β in fibrosis is well known (reviewed in [7, 15, 16]). ACE inhibitors and AT_1 antagonists diminish TGF-β expression and fibrosis. In cultured vascular and renal cells, AngII stimulates TGF-β expression, and the blockade of TGF-β diminishes some AngII responses, including ECM accumulation. Although TGF-β is one of the main regulators of fibrosis, therapeutics strategies blocking TGF-β actions have not afforded the expected beneficial effects, probably because TGF-β has anti-inflammatory properties [16].

TGF-β transmits signals to the nuclei by activating the Smad pathway. AT_1 blockade diminishes Smad pathway activation and fibrosis in the model of renal injury caused by unilateral ureteral obstruction (UUO) in myocardial infarction in rats and in the aorta of AngII-infused rats (reviewed in [16]). We recently showed that AngII via AT_1 activates the Smad signaling system independently of TGF-β (Fig. 4.5), both in rat VSMC and cultured human tubuloepithelial cells [17, 18]. In tubular cells, AngII induced an initial, TGF-β-independent, rapid activation of Smad signaling (Smad2 phosphorylation, nuclear translocation, and increased DNA-binding activi-

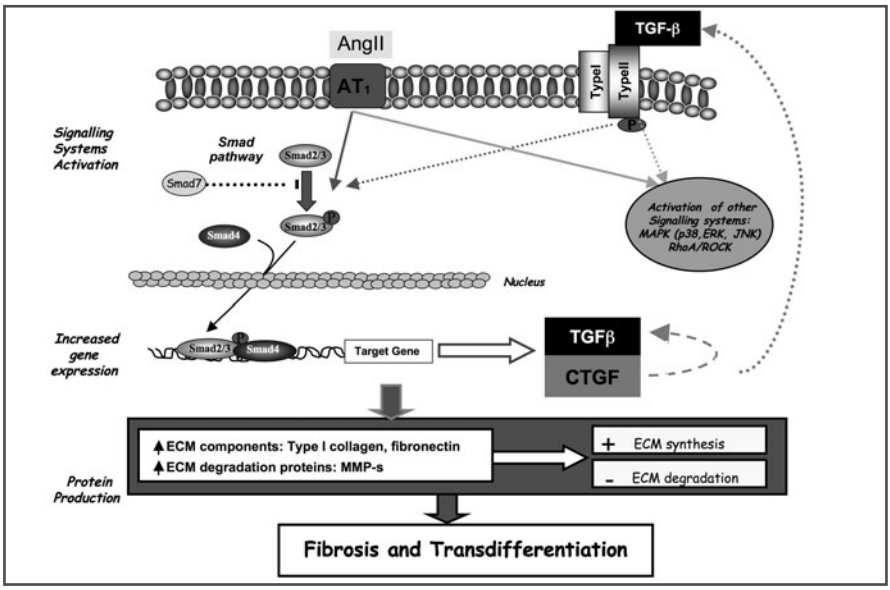

Fig. 4.5 AngII contributes to fibrosis through regulation of Smad pathway and other intracellular signaling systems. *Ang,* angiotensin; *CTGF,* connective tissue growth factor; *ECM,* extracellular matrix; *MMP,* matrix metalloproteinase; *TGF-β,* transforming growth factor beta

ty). This was followed by a delayed TGF-β-dependent Smad-dependent transcription observed after 24 h. Similar findings have been described in VSMCs and cardiac myocytes [16, 17]. There is cross-talk between mitogen-activated protein kinases (MAPKs) and Smad pathways (reviewed in [16]). Overexpression of constitutively active members of the ras/MAPK-ERK kinase/extracellular signal-regulated kinase (ras/MEK/ERK) cascade promotes Smad3-dependent processes in kidney mesangial cells while blocking nuclear accumulation of Smads in epithelial cells. In VSMC, AngII activates the Smad pathway via MAPK activation. In human kidney (HK2) proximal tubular cells, we found that all three MAPK inhibitors [p38, ERK, and Jun N-terminal kinase (JNK)] significantly diminished AngII-induced Smad2 phosphorylation [18]. In rats infused with AngII for 24 h, the Smad pathway was activated in the kidney and remained elevated for up to 2 weeks. Upregulation of renal TGF-β gene expression [messenger RNA (mRNA)] was found at 72 h, whereas increased TGF-b protein levels were only observed at 2 weeks. These data indicate that in the kidney, in vivo, and similar to its actions on cultured cells, AngII causes rapid, TGF-β-independent, activation of the Smad pathway [18]. After 2 weeks of continuous AngII infusion induction of epithelial-to-mesenchymal transition (EMT) markers and renal fibrosis was observed. At this time, Smad activation and TGF-β upregulation were also found, indicating that in chronic infusion of AngII, activation of the Smad pathway by endogenous TGF-β could contribute to renal damage progression [18]. In the aorta of AngII-infused rats, we observed that Smad activation was associated with CTGF induction and occurs before ECM accumulation [17], but the relationship with TGF-b levels has not been evaluated.

Smad7 may function as a general negative regulator of TGF-β receptor signaling [16]. Transient transfection with Smad7, which interferes with receptor-mediated activation of Smad2 and Smad3, diminished CTGF, fibronectin, and type1 procollagen upregulation caused by AngII in VSMC [17]. Stimulation for 3 days with AngII induced transdifferentiation of tubuloepithelial to myofibroblast-like cells that was blocked by Smad7 transfection [18]. Smad7 overexpression blocks TGF-β-induced ECM production and renal fibrosis (reviewed in [16]). In different animal models, including UUO, experimental hypertension and peritoneal fibrosis induced by peritoneal dialysis Smad7 overexpression inhibited fibrosis [19, 20]. Different therapies designed to interfere with TGF-β, including neutralizing antibodies, antisense oligonucleotides, and decorin, have been shown to diminish renal fibrosis. However, these treatments are difficult to use in humans, and anti-TGF-β antibodies are only in initial-phase clinical trials [21]. RAS blockers are commonly used in human renal diseases because of their proven end-organ protective effects [14]. AngII blockers, besides inhibiting AngII actions, also interfere with TGF-β/Smad signaling, providing an important tool to hinder TGF-β and prevent the loss of functional renal tissue.

Several studies have demonstrated that inhibition of endogenous CTGF is beneficial for treating fibrotic diseases. In nephrectomized TGF-β1 transgenic mice and in diabetic nephropathy, CTGF inhibition, using antisense oligodeoxynucleotides, diminished renal interstitial fibrogenesis [22]. In human diabetic nephropathy, plasma CTGF contributes to prediction of progression to end-stage renal disease in patients with type 1 diabetes, suggesting that CTGF could be considered as a risk marker of diabetic renal and vascular disease [23, 24]. Moreover, studies in patients with chronic cardiac damage suggest that plasma CTGF levels can be used as a marker of cardiac dysfunction and myocardial fibrosis [25]. In VSMC and mesangial cells, blockade of CTGF by an antisense CTGF oligonucleotide diminished AngII-induced fibrosis, as shown by diminution of fibronectin and collagen production [17, 26]. Moreover, in tubuloepithelial cells, antisense CTGF oligonucleotides inhibited epithelial mesenchymal transition caused by AngII [27]. ACE inhibitors and AT_1 antagonists diminish renal and vascular CTGF overexpression and fibrosis [7, 15]. These results suggest that CTGF could be a novel antifibrotic target for hypertension-induced renal and vascular fibrosis (Fig. 4.6).

4.3.3 Role of Angiotensin II in the Inflammatory Response in Vascular and Renal Diseases

Studies done in cardiovascular and renal diseases have provided significant information about proinflammatory and immunomodulatory properties of AngII (review in [28]). This peptide regulates production of adhesion molecules, cytokines, and chemokines by infiltrating and local cells, and thus contributes to progression of vascular and renal lesions (Fig. 4.5). ACE inhibitors and AT_1 antagonists reduce inflammatory parameters and the number of monocyte/macrophages in tissue damage. Experimental hypertensive target-organ tissue injury is characterized by the presence of monocyte/macrophage infiltration into the vessel wall, as well as into other target

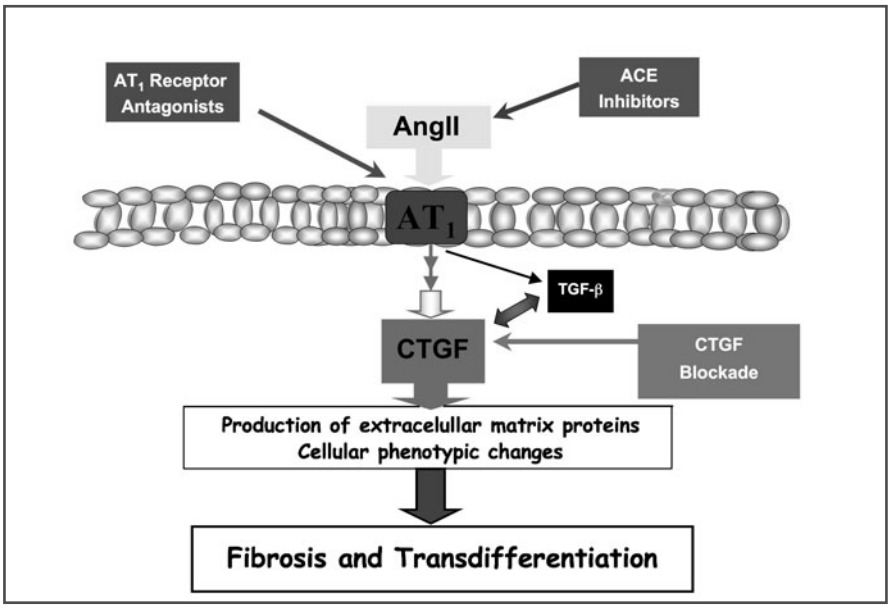

Fig. 4.6 Reninangiotensin system (RAS) blockade and fibrosis. Regulation of profibrotic factors such as connective tissue growth factor (CTGF) and transforming growth factor beta (TGF-β). *Ang,* angiotensin; *ACE,* angiotensin-converting enzyme; *CTGF,* connective tissue growth factor

organs, including kidney, heart, and brain. The systemic infusion of AngII in rodents also causes inflammatory response in the vasculature and kidney. These studies have shown infiltration of immunocompetent cells; induction of chemokines – such as monocyte chemotactic protein-1 (MCP-1) and regulated upon activation, normal T-cell expressed and secreted (RANTES), which regulate monocyte and leukocyte infiltration, respectively; upregulation of classic cytokines, including interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α); elevated levels of the Th1 cytokine gamma-interferon; and decrease in the Th2 cytokine IL-4 (review in [2, 28]).

AngII via AT_1 receptors upregulates many proinflammatory genes, such as vascular cell adhesion molecule-1 (*VCAM-1*), intercellular adhesion molecule-1 (*ICAM-1*), *IL-6*, and *MCP-1*, through activation of several intracellular signaling systems, including the nuclear factor kappa B (NF-κB), MAPK cascade, Rho proteins, and redox pathways (reviewed in [8, 9, 28]). Some experimental data suggest that AT_2 receptors are involved in inflammatory cell recruitment in the kidney. In different animal models of renal injury, including systemic infusion of AngII and UUO, only AT_2, but not AT_1, antagonists diminished the number of inflammatory cells. In these models, combined treatment with AT_1 and AT_2 antagonists blocked the inflammatory response, lowering the number of infiltrating cells and expression of proinflammatory genes to control levels (reviewed in [28]). In the UUO model, AT_2 blockade diminished TNF-α and RANTES overexpression, and the simultaneous blockade of both receptors abolished *MCP-1* gene upregulation [29].

Among the intracellular signaling systems involved in AngII-mediated inflammation, activation of the transcription factor NF-κB has special importance (review in [28]). This transcription factor regulates many inflammatory mediators, including chemokines and cytokines. In vivo, AngII activates the NF-κB pathway, both in the aorta and in the kidney. Both AT_1 and AT_2 receptors mediate NF-κB activation in cultured VSMC and mesangial cells, AT_1 is the main receptor implicated in tubuloepithelial cells, whereas AT_2 mediate NF-κB activation in endothelial cells. In experimental models of renal injury, NF-κB activation was partially diminished by AT_1 or AT_2 antagonists alone and was abolished by the combination of both receptor antagonists or by ACE inhibition. In the UUO model and spontaneously hypertensive rats (SHR), NF-κB inhibition attenuated renal interstitial inflammation. These data suggest that in some experimental renal diseases, blockade of AngII generation by an ACE inhibitor or its activity by combined blockade of both AT_1 and AT_2 receptors, as well as inhibition of NF-κB pathway, is able to fully stop the inflammatory process (Fig. 4.7). In human kidney diseases, renal RAS is activated. In diabetic nephropathy, elevated AngII generation was correlated with the presence of inflammatory-cell infiltration, activation of NF-κB, and proinflammatory gene overexpression [30]. These observations emphasize the importance of treatments that block AngII-induced inflammatory processes in human renal diseases.

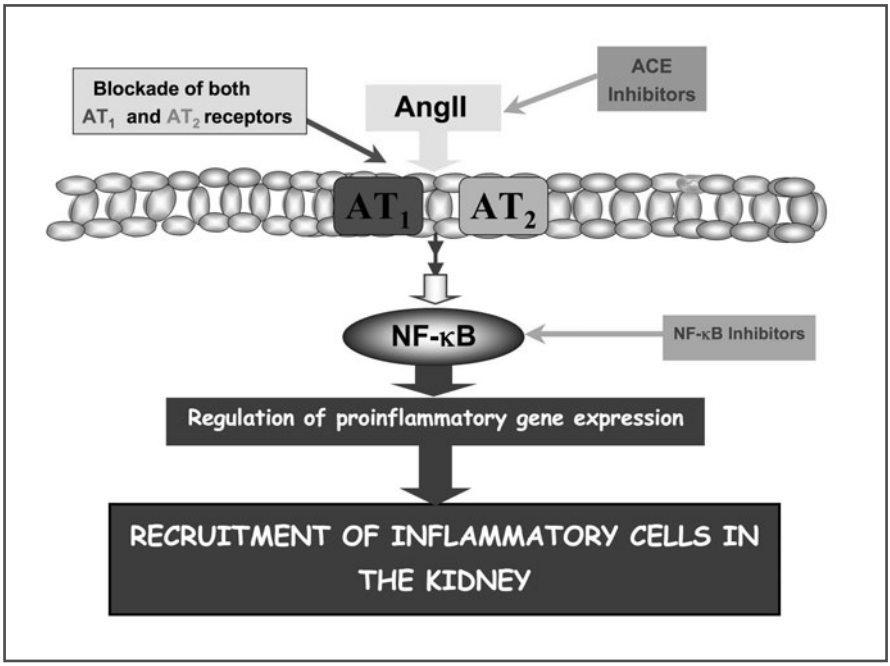

Fig. 4.7 Renin–angiotensin system (RAS) blockade and inflammatory response. *Ang,* angiotensin; *ACE,* angiotensin-converting enzyme; *NF-*κB, nuclear factor kappa B

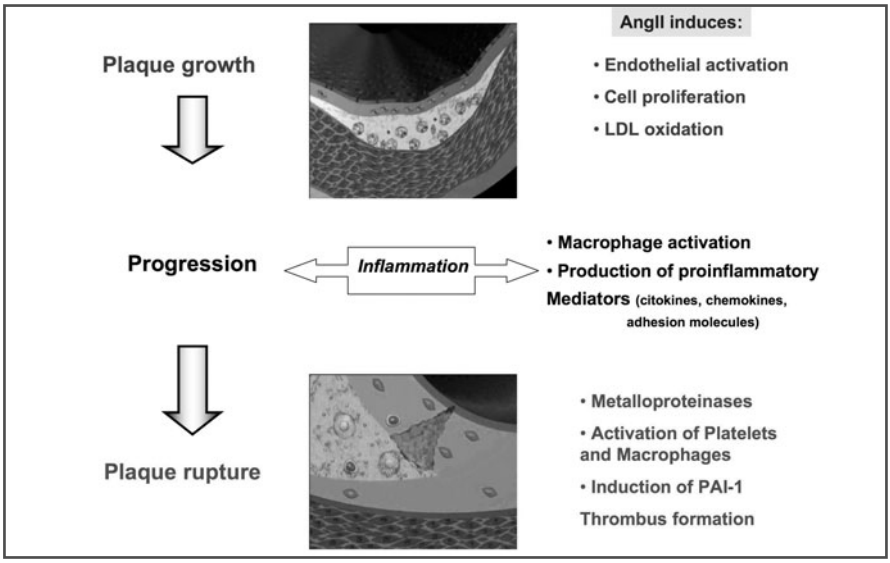

Fig. 4.8 AngII participates in growth, progression, and rupture of atheroma plaques. *LDL,* low-density lipoprotein; *PAI-1,* plasminogen-activation inhibitor-1

4.3.4 Active Role of AngII in Different Steps of Atherosclerosis

The involvement of AngII in the pathogenesis of human atherosclerosis has already been demonstrated. The earliest evidence came from experimental animal studies in models of vascular injury showing that RAS blockade diminished the presence of inflammatory cells and proinflammatory parameters (adhesion molecules, chemokines, and cytokines) in the lesion, serum, and circulating monocytes (reviewed in [28]). As shown in Fig. 4.8, AngII participates in all steps involved in atherosclerosis. In the initial phase of plaque formation, AngII induces endothelial activation and increases VSMC proliferation. AngII also contributes to progression of atherosclerosis through regulation of the inflammatory response: this peptide activates macrophages and resident cells to produce proinflammatory mediators. Finally, AngII is involved in plaque rupture by inducing metalloproteinases, which degrade collagen, and producing plasminogen-activation inhibitor-1 (PAI-1), and platelet activation leading to thrombus formation (reviewed in [28]).

4.4 Role of Angiotensin Peptides in Vascular and Renal Diseases

Among the Ang peptides, AngIV and Ang-(1–7) have been the best characterized from a functional point of view. AngIII shares many responses to AngII, acting

through the same receptors. In renal cells, AngIII induces cell proliferation and production of EMC and chemotactic proteins (reviewed in [3, 7, 28]).

4.4.1 AngIV in Cardiovascular Damage

AngIV binds to a specific receptor, namely, the AT_4. Some authors suggest that IRAP is the AngIV receptor [31]. There is a correspondence between AT_4 binding sites and IRAP, and they suggest that IRAP is a mixed enzyme/receptor that can act as a classic receptor, transferring extracellular information across the cell membrane (reviewed in [32]). However, more studies are needed to prove this hypothesis. AngIV can be generated by degradation of AngII, aminopeptidase N (APN), or other proteases, which could be activated during tissue damage, supporting the hypothesis of elevated AngIV levels in pathological conditions.

AngIV mediates important physiological functions in the central nervous system, including blood flow regulation and processes contributing to learning and memory, and they could contribute to vascular damage (reviewed in [32]). In the kidney, Ang IV increases renal cortical blood flow and decreases sodium (Na^+) transport in isolated renal proximal tubules [32]. VSMC and endothelial cells express *IRAP* gene and enzymatic activity, as well as AngIV-specific binding sites antagonized by divalinal [32]. AngIV regulates cell-growth responses in cardiac fibroblasts, endothelial cells, VSMC, and tubuloepithelial cells. In a model of vascular balloon injury, AngIV binding was increased in media, neointima, and the re-endothelialized cell layer, suggesting a role of AngIV in vascular wall remodeling following damage. In low-density lipoprotein (LDL)-receptor-deficient mice, hypercholesterolemia was associated with increased systemic angiotensinogen and angiotensin peptides (Ang II, III and IV). AngIV upregulates several proinflammatory factors and could participate in some steps of the inflammatory response. In VSMC, AngIV increases production of MCP-1, the main chemokine involved in monocyte recruitment, and upregulates expression of the adhesion molecule ICAM-1, which is involved in attachment and transmigration of circulating cells into damage tissue. AngIV also increases the expression of cytokines, such as IL-6 and TNF-α, contributing to perpetuation of the inflammatory response. ACE is expressed at the shoulder region of atherosclerotic plaques, and its activity is enhanced in unstable plaques. Therefore, local Ang peptides, may participate in plaque instability by activating inflammation. Thus, AngIV upregulates expression of the prothrombotic factor PAI-1 expression in VSMC, endothelial and renal cells, and also could participate in thrombus formation [32].

4.4.2 Ang-(1–7) in Renal and Cardiovascular Damage

In recent years, evidence has accumulated that Ang-(1–7) has cardiovascular protective effects [33–35] and counteracts detrimental effects of AngII under pathophysiological

conditions [36]. These effects may be may related to its vasorelaxation and blood pressure lowering effects through activation of the G-protein-coupled receptor Mas [4]. We recently showed that systemic infusion of Ang-(1-7) to wild-type mice induced an inflammatory response in the kidney characterized by interstitial inflammatory cell infiltration, activation of NF-κB, and upregulation of inflammation-stimulating cytokines such as IL-6 and MCP-1 [37]. Pharmacological blockade with Ang-(1-7) and/or AngII antagonists and studies in Mas-deficient mice demonstrated that these effects were Mas-dependent but did not involve AngII receptors. In vitro studies in tubuloepithelial cells confirmed that Ang-(1-7) activated NF-κB and induced inflammatory genes [37].

We also described that Mas deficiency preserved renal function in two models of renal damage (UUO and ischemia/reperfusion) and diminished inflammation, apoptosis, and tubulointerstitial fibrosis. Moreover, Ang-(1-7) infusion to UUO wild-type mice impaired the pathological outcome by aggravating the inflammatory response [37]. These results suggest that the pharmacological blockade of or the genetically generated deficiency for the Mas receptor prevents renal disease progression in the UUO model. In summary, Mas deficiency prevents renal inflammation, whereas Mas-dependent Ang-(1-7)-mediated cell signaling induces renal inflammation both under basal and pathological conditions. As inflammation is a key feature in chronic kidney diseases, including diabetic nephropathy, our data show that Ang-(1-7)/Mas axis is a novel player in renal inflammation and suggest a potential role for Ang-(1-7)/Mas-targeted therapy for renal failure.

4.3 Conclusions

AngII is a potent cytokine that regulates key process involved in the progression of cardiovascular and renal diseases. The current therapeutic strategies to block AngII actions (ACE inhibitors and ARA II) are among the best actual options for treating patients with those diseases. However, these drugs only slow disease progression, and more studies are needed to find better therapeutic targets.

The role of other components of the RAS (Ang peptides and their receptors) has only been investigated in cultured cells and experimental animal models. Future studies in humans will unveil the relevance of these novel RAS components in health and disease.

Acknowledgments
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Section III
Chronic Kidney Disease as a Risk for Cardiovascular Disease

Cardiorenal Continuum

5

J.A. García-Donaire, L.M. Ruilope

Abstract Atherosclerosis underlies the vast majority of vascular conditions that are a leading cause of death and serious morbidity or disabilities worldwide. Cardiovascular events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage, including vital organ damage—specifically, the kidney and the heart. A large percentage of patients attended at the clinic and admitted to hospital have various degrees of heart and kidney dysfunction. Disorders affecting one of them mostly involve the other. Such interactions represent the pathogenesis for a clinical condition called cardiorenal syndrome. Renal and cardiovascular diseases share the same etiopathogenic risk factors. If these factors are controlled, then atherosclerotic process evolution and further target-organ damage or cardiovascular events can be prevented. As the cardiorenal process advances, atherosclerotic vascular damage progresses, and subclinical organ damage can be detected. Chronic kidney disease is included at this stage, and a number of conditions associated with renal dysfunction become novel risk factors that may accelerate vascular damage

Keywords: Cardiorenal • Atherosclerosis • Continuum • Cardiovascular risk • Hypertension • Guidelines • Target-organ damage • Chronic kidney disease

5.1 Introduction

Hypertension is a highly prevalent risk factor that affects a large population worldwide [1, 2]. It promotes the development of coronary artery disease (CAD), stroke, renal and peripheral vascular disease, and largely contributes to increased cardiovascular disease (CVD) morbidity and mortality [3]. Regardless of the widespread

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Cardiorenal Syndrome. Adel E. Berbari, Giuseppe Mancia (Eds.)

knowledge about hypertension, the underlying mechanisms that contribute to the most common form of hypertension—essential hypertension—remain unclear, and individuals at the highest risk of developing hypertension must be identified in order to improve their CV status. Diverse studies support a basic role for the kidneys in the pathogenesis of essential hypertension. Cowley and Roman [4] reviewed six lines of evidence that show that renal dysfunction accompanies the development of all forms of hypertension in animal models. They described abnormal renal sodium excretion as one of the initial findings.

Adequate excretion of an increased sodium load due to high salt intake requires an elevation in glomerular pressure that, when maintained, can potentially lead to glomerular scarring and endothelial dysfunction. Frequently, a phase of glomerular hyperfiltration is observed in the early stage of arterial hypertension and diabetes. This phase can be followed by progressive renal damage with development of chronic kidney disease (CKD), to which a lower than normal number of nephrons at birth could contribute. Scarce data about the contribution of glomerular hyperfiltration to hypertension in humans are available, but during this phase of glomerular hyperfiltration, or later in patients with arterial hypertension and/or diabetes, microalbuminuria can develop [5]

CVDs are a leading cause of death and serious morbidity or disabilities worldwide, and CV events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage. This stage is called the cardiorenal continuum [6]. Fig. 5.1 displays an overview of the cardiorenal continuum, illustrating a simplified ver-

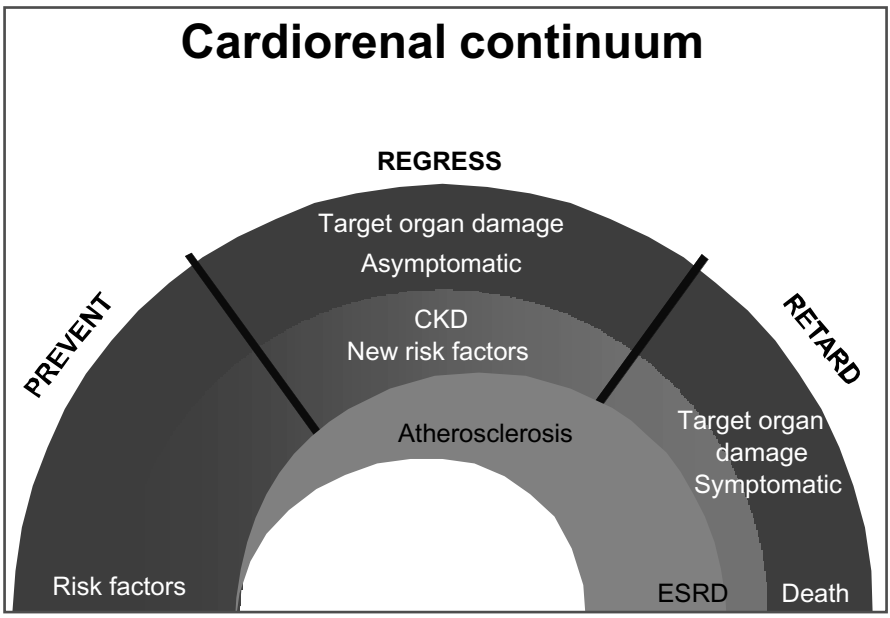

Fig. 5.1 Cardiorenal continuum

sion of the sequential occurrence of the atherosclerotic process from the first stage, in which CVD risk factors are detected and can be prevented if the conditions are appropriately controlled by implementing the optimal therapeutic approaches

Renal and CV diseases share the same etiopathogenic risk factors, including hypertension, dyslipidemia, glucose metabolism disturbances, cigarette smoking, obesity, and physical inactivity. If these factors are controlled, then atherosclerotic process evolution and further target-organ damage (TOD) or CV events can be prevented. Therefore, prevention can be carried out not just at the first stage but along the whole continuum. As the cardiorenal process advances, atherosclerotic vascular damage progresses, and subclinical organ damage can be detected. This is an intermediate stage in the continuum of vascular disease and a determinant of overall CVD risk. CKD is included at this stage, and a number of conditions associated with renal-function decline, such as anemia, secondary hyperparathyroidism, or accumulation of atherogenic substances, become new CVD risk factors and accelerate vascular disease. Therapeutic approaches at this point can regress CV damage, as shown in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, in which reduced urinary albumin/creatinine ratio (UACR) and regression of left ventricular hypertrophy (LVH) was associated with lower incidence of CV events [7]. Therefore, strict objectives regarding CVD risk factors must be set up. A large body of evidence is now available concerning the crucial role of TOD in determining the CVD risk of individuals with and without hypertension. If regression of CV damage is not achieved, the process advances to the development of CV events and progression of CKD to overt nephropathy and CVD. Although prevention strategies must be present along the continuum, interventions at this point should only retard the occurrence of CV and renal events [8]. This last stage represents the situation of further progression of vascular disease, leading to the appearance of symptomatic TOD (myocardial infarction, angina, stroke, transient ischemic attack, advanced chronic renal failure, and peripheral artery disease), which eventually will lead to end-stage renal disease (ESRD) or death. At this stage, the best we can do is to retard the likelihood of such events.

5.2 Cardiovascular Disease Associated with Renal Disease: Evidences Along the Continuum

Underlying the cardiorenal continuum is the pathophysiological continuum, which describes the progressive processes at molecular and cellular levels that manifest as clinical disease. A vast amount of research over the last two decades has provided considerably more knowledge regarding the therapeutic interventions that are able to intervene along the continuum.

Therefore, as CVD risk factors can be evaluated, the process begins. At this first stage of cardiorenal disease, preventative approaches are the most relevant strategies to disrupt disease progression [9]. In this sense, some data have demonstrated that

high-risk patients without evidence of renal damage may benefit from early therapeutic intervention. The multicenter, double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) assessed whether pharmacological intervention could prevent microalbuminuria in high-risk patients with no evidence of organ damage. The main results showed that intervention decreased the incidence of microalbuminuria [10]. Evidence from other ongoing trials will shed light on this issue, as will the Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) study–a placebo-controlled, multicenter, double-blind, parallel group study investigating the effect of the angiotensin receptor blocker (ARB) olmesartan medoxomil on the incidence of microalbuminuria in hypertensive people with type 2 diabetes and an objective of blood pressure <130/80 mmHg. In addition, ROADMAP will also analyze effects of olmesartan medoxomil on retinopathy and other microvascular circulations [11]. The results of the Diabetic Retinopathy Candesartan Trials (DIRECT) are designed to examine primary (incidence) and secondary (progression) prevention of diabetic retinopathy when blocking angiotensin II type 1 receptors with the ARB candesartan in patients with normoalbuminuric, normotensive type 1 diabetes, and secondary prevention only in patients with normoalbuminuric, normotensive, or treated hypertensive type 2 diabetes. This trial series will also support prevention strategies to block advancement of the atherosclerotic process that leads to development of CV damage [12].

Optimal management in people with several risk factors is crucial, especially when hypertension is associated with other conditions. Awareness that several antihypertensive agents may exert undesirable metabolic effects has antihypertensive treatment trials to investigate the incidence of new-onset diabetes. Almost all such trials with new-onset diabetes as an endpoint have shown a significantly greater incidence in patients treated with diuretics and/or beta-blockers compared with angiotensin-converting enzyme inhibitors (ACEIs), ARBs, or calcium antagonists [13–16]. Angiotensin receptor antagonists [17] and ACEIs [13] have been shown to be associated with significantly fewer new diabetes cases than were calcium antagonists. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is comparing telmisartan, ramipril, and their combination for preventing CVD morbidity and mortality in high-risk patients [18]. Telmisartan was the ARB selected for the ONTARGET Trial because it provides sustained antihypertensive activity over the 24-h between doses [19]. The comparator, the ACEI ramipril, was selected because in the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril was proved to reduce the incidence of CV events in a similar patient population [20]. Patients enrolled in ONTARGET have vascular disease (coronary artery disease, peripheral arterial occlusive disease, stroke) or diabetes with TOD. The primary outcome is a composite endpoint of CVD, death, stroke, acute myocardial infarction, and hospitalization for congestive heart failure (CHF). A variety of renal endpoints have also been included. The Telmisartan Randomized Assessment Study in ACE-I-Intolerant Subjects with CV Disease (TRANSCEND) is a parallel study within the ONTARGET Trial that is comparing the CV protective effect of telmisartan with placebo in patients intolerant of ACEIs [18]. The first results of this trial have been published and emphasize that the telmis-

artan was equivalent to ramipril in treating patients with vascular disease or high-risk diabetes and was better tolerated [21]. The combination of these two drugs was associated with more adverse events without an increased benefit. More evidence about prevention along the cardiorenal continuum is expected from this trial, including more than 150,000 patient-years of data. The Trial of Preventing Hypertension (TROPHY) hypothesized that early treatment with candesartan might prevent or delay hypertension onset. The main results showed that candesartan was better in preventing development of hypertension versus placebo [22]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) evaluated the benefits associated specifically with the use of statins among patients with hypertension [23]. Atorvastatin, which was added to the treatment therapy in more than10,000 patients with hypertension and additional CVD risk factors and a serum total cholesterol <6.5 mmol/L, reduced serum total cholesterol by 19.9% compared with placebo. This was accompanied by substantial benefits both with regard to total CV and renal events (36% reduction) and stroke (27% reduction). The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial was recently terminated prematurely because the predefined efficacy outcome was achieved and an interim analysis reported. The trial recruited more than 11,400 patients who received either amlodipine in combination with benazepril or hydrochlorothiazide in combination with benazepril. A primary composite endpoint of CVD morbidity or mortality was defined as death from CV causes, fatal or nonfatal myocardial infarction or fatal or nonfatal stroke, revascularization, or unstable angina requiring hospitalization. Treatment with amlodipine/benazepril significantly reduced CVD morbidity and mortality compared with hydrochlorothiazide/benazepril [relative risk (RR) 0.80; 95% confidence interval (CI) 0.71–0.90] [24]. Mechanical and chemical damage resulting from these interrelated CVD risk factors promote general progression of vascular damage that begins with endothelial dysfunction and atherosclerosis. This leads to end-organ damage, such as LVH, subclinical atherosclerotic vascular damage, and kidney injury that can be detected by microalbuminuria and renal function derangement [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or a slight increase in serum creatinine]. At this second stage, vascular damage processes may be regressed, and inhibition of the renin–angiotensin system (RAS) has been shown to be the most efficient pharmacological intervention along with strict control of CVD risk factors.

International guidelines devoted to arterial hypertension recognize microalbuminuria, elevated serum creatinine values, and reduced eGFR as major CVD risk factors that contribute to increased risk afforded by other coexisting factors [25–27]. The diagnosis of hypertension-induced renal damage in a hypertensive patient is usually based on reduced renal function and/or elevated urinary excretion of albumin. Renal function decline is classified in accordance with eGFR calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula that assesses age, gender, race, and serum creatinine [28]. Values of eGFR <60 ml/min/1.73 m^2 indicate CKD stage 3, whereas values <30 and 15 ml/min/1.73 m^2 indicate CKD stages 4 and 5, respectively [29]. The Cockcroft–Gault formula estimates creatinine clearance (CrCl) and is based on age, gender, body weight, and serum creatinine

[30]. This formula is applicable in the range >60 ml/min, but it overestimates CrCl in CKD stages 3–5 [31]. Both procedures help to detect mildly impaired renal function in the face of serum creatinine values that are still in the normal range.

Reduction in GFR and increase in CVD risk may also be inferred from increased serum levels of cystatin C [32]. Whereas elevated serum creatinine concentration or low eGFR (or CrCl) points to reduced rate of plasma filtered at the glomerular level, increased urinary albumin or protein excretion points to derangement in the glomerular filtration barrier, which allows increased albumin passage. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in those with either type 1 or type 2 diabetes [33]. However, only about 40% of those with type 2 diabetes will develop microalbuminuria and, of those, approximately 50% will develop microalbuminuria in the following 10 years [34]. In contrast, in both diabetic and nondiabetic hypertensive patients, microalbuminuria, even below the threshold values currently considered [35], has been shown to predict CV events. Several studies report a continuous relationship between CVD—as well as non-CVD—mortality and urinary protein/creatinine ratios >3.9 mg/g in men and 7.5 mg/g in women [36]. Thus, the term "microalbuminuria" may be misleading (because it falsely suggests a minor injury as well) and should, in theory, be replaced by the term "low-grade albuminuria" [37]. Microalbuminuria can be determined in spot urine samples (24-h or night-time urine samples are discouraged due to inaccuracy of urinary sampling) by indexing the urinary albumin concentration to the urinary creatinine concentration. Initial evidence concluding that microalbuminuria increases CVD risk came from observations involving high-risk patients [38]. Data from the HOPE study [39] confirmed the predictive value of microalbuminuria, which attained a predictive capacity similar to that of previous coronary artery disease and was equal for patients with and without accompanying diabetes. The relevance of urinary albumin excretion (UAE) as a CVD risk factor in patients with hypertension without diabetes and in the general population has also been demonstrated [40]. Some of these studies indicate that the relationship between urinary albumin and CVD risk is a continuum that starts below the established cutoff point indicated earlier. Definitely, both UAE and reduced GFR are independently associated with increased CVD risk, which is particularly elevated when both alterations coexist [41]. In fact, the prevalence of albuminuria, either micro or macro, increases as eGFR falls <60 ml/min/1.73 m^2 [42].

Patients developing ESRD are a minority in the group developing different forms of CKD. They could be considered survivors because CVD accounts for the majority of deaths of patients with CKD before the development of ESRD [43]. In turn, advanced CVD facilitates the development of CKD, and so the relationship between CKD and CVD becomes a vicious circle. That CKD and CVD are so closely related has resulted in increased interest in investigating the evolution of renal function in trials involving patients with hypertension, as well those with heart failure and post-myocardial infarction. This interest is fully justified, as in all these situations, renal function alterations are predictive for the development of CV events or death.

Even from the early stages, CKD adds to CVD risk in any patient with hypertension and in any patient presenting with established forms of CVD [44]. Reduction of CV events in the CKD population requires the implementation of effective integral

therapeutic interventions that protect both the kidney and the CV system. These interventions have to be implemented in the very initial stages of CKD, and strict blood pressure control is imperative in any patient with an elevated global CVD risk and high blood pressure. In the absence of other CVD risk factors, elevated blood pressure levels are required in order to consider patients as having high added CVD risks. In contrast, only high–normal blood pressure levels or even lower values are required for the same evaluation when patients present with three or more associated CVD risk factors, TOD, diabetes, or associated clinical conditions. Accordingly, patients with hypertension and a high added level of CVD risk can be found in any of the three stages of the CV and renal disease continuum. As soon as renal function exhibits minor derangements, CVD risk continues to increase until ESRD develops.

As renal function declines, TOD appears and CKD adds several clinical characteristics that raise the possibility of a CV event as atherosclerotic disease progresses. CKD-induced anemia and secondary hyperparathyroidism globally worsens outcomes in patients with and without myocardiopathies, and correction of these conditions is crucial to reduce absolute CVD risk [45, 46]. Among patients who referred to the authors' hypertension unit, 7.6% had a decreased renal function according to serum creatinine levels, and 25% had a decreased CrCl [47]. Community-based longitudinal studies demonstrated that CKD is an independent risk factor for the composite study outcome, including myocardial infarction, fatal CHF, stroke, and death [48]. In patients with essential hypertension and normal renal function (defined as eGFR >90 ml/min/1.73 m^2), those who developed CKD during 13 years of follow-up had a CV event rate 2.5 times higher than did those with preserved renal function [49]. As widely evidenced in the hypertensive population, the higher the CVD risk, the higher the CKD prevalence [50].

Evidence for the relationship between renal dysfunction and adverse CV events was initially documented in the ESRD population in whom the incidence of CVD death is elevated. Around 50% of individuals with ESRD die from a CVD—a CVD mortality rate much higher than the age-adjusted CVD mortality rate in the general population. This discrepancy is present across all ages, but it is most marked in the younger age group, in which the CVD mortality rate is >300-fold in ESRD patients compared with age-matched controls with normal renal function [51]. By the time ESRD occurs, 40% of patients have evidence of CHF, and 85% of those patients have abnormal LV structure and function.

The relationship between renal disease and CVD mortality has also been shown to extend to patients with more moderate degrees of renal impairment. Indeed, the majority of patients with eGFR <60 ml/min/1.73 m^2 die from CVD-related causes rather than progressing to ESRD. In addition, evidence of structural and functional cardiac abnormalities has been demonstrated. Data about cardiac structure in the renal insufficiency population has been described with echocardiographic techniques and comparable criteria for diagnosing LVH, detecting an LVH prevalence of 16% in patients with CrCl of >30ml/min and 38% in those with CrCl <30 ml/min [52]. Therefore, LVH is common in patients with renal insufficiency even before they progress to dialysis, and so prevalence of LVH correlates with the degree of renal functional deterioration. Many reports have shown that the relationship

between renal impairment and increased CVD mortality rate extends across the spectrum of renal dysfunction to cover the mildest degree of renal disease. Furthermore, this relationship appears to be maintained through populations with broadly diverse degrees of baseline CV health. LVH is an independent predictor of unfavorable prognosis in the hypertensive population, and, in the LIFE study, its relationship with albumin excretion was reported as being independent of age, blood pressure, diabetes mellitus, race, serum creatinine level, or smoking [53]. The prevalence of microalbuminuria was approximately twofold higher in patients with hypertension and eccentric or concentric LVH and minimally elevated in the group with concentric LV remodelling compared with patients with normal LV geometry. Although the clinical significance of impaired renal function and LVH in patients with hypertension is not yet fully understood, numerous reports link renal albumin leakage with morbidity and mortality.

The LIFE study also showed that the simple measurement of UACR further refines risk stratification by LV geometry and that patients with LVH have an increased risk of also having albuminuria, a situation that should be further investigated to improve treatment and counselling. The risk for CVD endpoints increases in a stepwise trend with higher values for UACR in patients with diabetes. Data indicate that albuminuria at a lower level than that usually used as a cut point in patients with diabetes defines patients at increased risk of CVD morbidity and mortality. UACR did not predict the risk of myocardial infarction. Perhaps diabetes itself is a strong predictor for CVD morbidity and mortality, partly overlapping the influence of albuminuria as a risk factor in the population with rather low levels of albuminuria. Other studies suggest that albuminuria at levels below established values is a risk factor for CHF in patients with and without diabetes, signifying that the relationship between albuminuria and CVD risk from other populations cannot be directly applied to non-diabetic hypertensive patients [54].

Strict control of all CVD risk factors and therapeutic action in order to regress already established vascular damage must be the cornerstone of the medical strategy, because, if not stopped, the cardiorenal continuum progresses to CKD (proteinuria, eGFR <30 ml/min/1.73 m^2), overt CVD, and stroke. Interventions at this point are focused on delayed development of CV and renal events [27]. CV events and consequent death are dramatically reduced when UACR is decreased and GFR decline is avoided. If renal decline progresses to the final stage, proteinuria will occur. In type 2 diabetes, data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial showed that changes in albuminuria in the first 6 months of therapy were approximately linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 months was associated with a 45% reduction in the risk for ESRD during later follow-up [55]. Furthermore, a secondary analysis of the Irbesartan in Diabetic Nephropathy Trial (IDNT) demonstrated that the risk for renal failure was reduced during the first year of the study when there were increases in proteinuria [56]. Subsequently, these two studies (IDNT and RENAAL) demonstrated that an ARB (irbesartan or losartan) was more effective than conventional therapy or a calcium channel blocker in slowing progression of nephropathy, regardless of blood

pressure control. Moreover, secondary analyses of these two large trials demonstrated that there was some interaction between the effect of the ARB and the levels of blood pressure that were achieved. It can also be concluded that optimal levels of blood pressure tended to magnify the renoprotective effects of ARB in both trials. In the large cohort of patients with hypertension, microalbuminuria, and type 2 diabetes who participated in the Microalbuminuria, Cardiovascular, and Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-HOPE), the ACEI compared with other treatments was more effective in reducing the incidence of overt nephropathy [57]. Furthermore, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study showed that treatment with the ARB irbesartan was much more effective than conventional therapy at both preventing the development of clinical proteinuria and favoring regression to normoalbuminuria in patients with microalbuminuria and type 2 diabetes, despite similar blood pressure control [58].

5.2.1 Global Therapeutic Approach Focused on Renal Outcomes

CKD progression, that is, reduced GFR, occurs at a variable rate, with a faster rate of decline generally noted among patients with diabetic nephropathy due to the presence of proteinuria. Several therapeutic options have been shown to be efficient in slowing the rate of renal function decline. Among these therapeutic treatments are blood-pressure-reducing drugs—preferably ACEIs and/or angiotensin II antagonists—low-salt and low-protein diets, and lipid-lowering drugs [59].

Unfor-tunately, for such treatments to be most efficacious and in agreement with the European Society of Hypertension/European Society of Cardiology guidelines, it is necessary to identify patients in an early stage of disease before significant loss of renal function has occurred. Such identification is simplified by the estimating GFR and measuring microalbuminuria in any patient with hypertension. UACR levels of approximately >2 mg/g or an estimated excretion rate of 2 mg/day are significantly associated with death from CVD, myocardial infarction, stroke, and elevated blood pressure. As a result, reductions in albuminuria levels during treatment translate to regression of a number of vascular abnormalities in hypertension and thus a decrease in risk in general. In patients type 2 diabetes and diabetic nephropathy, and also in patients with nondiabetic renal disease, data indicate that the extent of decreases in albuminuria during renin–angiotensin–aldosterone system intervention is associated with the degree of renal protection but also the degree of reduced CVD risk [60]. Reductions in both systolic and diastolic blood pressure are important in reducing albuminuria levels. Despite the firm relationship between blood pressure values and albuminuria, ACEIs and ARBs exhibit a more marked capacity to reduce microalbuminuria in patients with hypertension compared with a number of different therapeutic interventions, such as calcium antagonists, beta-blockers, or diuretics [61].

5

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Definition and Classification of Stages of Chronic Kidney Disease: Screening for Chronic Kidney Disease

6

T. Shafi, J. Coresh

Abstract Chronic kidney disease (CKD) is widely recognized as a public health problem. In this chapter, we review the basis for definition and classification of CKD as outlined in the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI). We also review the principles of screening and their applicability to CKD.

Keywords: Chronic kidney failure • Screening • End-stage renal disease

6.1 Introduction

Chronic kidney disease (CKD) is a significant public health problem with a wide range of severity. Later stages of CKD are associated with a high burden of comorbidities, and individuals with CKD are at a higher risk of progressive loss of kidney function leading to end-stage renal disease (ESRD), cardiovascular disease, and premature death. Early identification of individuals with CKD, especially those at the highest risk of CKD progression, may allow early diagnostic workup and implementation of therapies to reduce the risk of CKD progression and cardiovascular disease and reduce morbidity and mortality. The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) in the United States has been instrumental in leading the development of guidelines to identify and classify CKD [1]. These guidelines have greatly improved our understanding of the prevalence of CKD and the range of complications at different stages. Emphasis has now shifted toward early identification of individuals at the highest risk of complications of CKD and the need to test the efficacy of interventions.

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6.2 Definition of Chronic Kidney Disease

Glomerular filtration rate (GFR) is considered the best overall index of kidney function. Reduced GFR is a consequence of variety of acute and chronic glomerular, tubular, or interstitial injuries. Definitions of CKD incorporate measures of reduced function (GFR) and of renal parenchymal damage such as proteinuria and anatomical abnormalities. The operational definition of CKD proposed by the K/DOQI is the presence of kidney damage for at least 3 months. Kidney damage could be either: (1) pathological abnormalities, such as polycystic kidney disease, (2) presence of markers of kidney damage, such as proteinuria, or (3) GFR < 60 ml/min/1.73 m^2, with no other evidence of kidney damage [1].

K/DOQI guidelines emphasize the use of equations to calculate estimated GFR (eGFR). The recommended serum-creatinine-based equations are the Cockcroft–Gault equation or the Modification of Diet in Renal Disease (MDRD) Study equation in adults and the Schwartz and Counahan-Barratt equations in children. The MDRD Study equation has been widely used to estimate GFR, and reporting eGFR with serum creatinine by clinical chemistry laboratories has gained widespread acceptance throughout the world. The MDRD equation was developed from a sample of 1,628 MDRD Study participants [2]. The equation estimates GFR adjusted for body surface area and accounts for creatinine generation by adjusting for age, gender, and race. This equation was recently updated by a new serum-creatinine-based equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), a US National Institutes of Health (NIH)-sponsored initiative [3]. This new CKD-EPI creatinine equation was developed and validated using pooled data from 26 studies (12,150 participants) in which GFR was measured. The population included a larger number of African Americans and older individuals compared with the MDRD Study. The equation is at least as accurate as that of the MDRD Study for individuals with eGFR < 60 ml/min/1.73 m^2 and substantially more accurate for individuals with eGFR > 60 ml/min/1.73 m^2. It is expected that this new equation will improve decision making in individual patients and allow further refinement of CKD prevalence estimates. In particular, at the same serum creatinine, the CKD-EPI equation estimates higher GFR values than does the MDRD Study equation for younger or female individuals, who often have lower risk of complications.

6.3 Classification of Chronic Kidney Disease

The K/DOQI guidelines proposed a classification system for CKD based on the level of GFR and presence of kidney damage (Table 6.1) [1]. Stages 1 and 2 are differentiated by the absence (stage 1) or presence (stage 2) of markers of kidney damage, whereas stages 3–5 are based solely on eGFR. At each stage, an action plan is pro-

Table 6.1 Chronic kidney disease stages: K/DOQI classification and updates

K/DOQI classification			Updates				
Stage	Description	GFR	KDIGO		CARI	NICE	
1	Kidney damage with normal or increased GFR	≥ 90	"T" if kidney transplant		"P" if proteinuria		
2	Kidney damage with mild decrease in GFR	60-89				"P" if proteinuria	
3	Moderate decrease in GFR	30-59				Identify rate of progression	3a (eGFR 45-59)
							3b (eGFR 30-44)
4	Severe decrease in GFR	15-29					
5	Kidney failure	< 15		"D" if on dialysis			

CARI, Caring For Australians with Renal Impairment; *eGFR,* estimated glomerular filtration rate; *GFR,* glomerular filtration rate in ml/min/1.73 m^2; *KDIGO,* Kidney Disease: Improving Global Outcomes; *K/DOQI,* National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; *NICE* National Health Service – National Institute for Health and Clinical Excellence

posed, with the goal of reducing CKD progression and minimizing associated metabolic complications. The K/DOQI classification system is complementary to other clinical classifications, such as those based on the underlying pathology [immunoglobulin A (IgA) nephropathy, membranous nephropathy].

The emphasis of the K/DOQI classification system on eGFR rather than on serum creatinine overcomes many limitations of serum creatinine alone as a marker of kidney failure. Serum creatinine is not only dependent on renal creatinine clearance for elimination but also on creatinine generation. Creatinine generation depends on age, gender, race, and muscle mass. Individuals with reduced muscle mass, such as women and the elderly, can have serum creatinine within the normal range despite marked reduction in GFR. Finally, eGFR is expressed on an absolute physiologic scale (ml/min/1.73 m^2), emphasizing the value of standardized measurements (of serum creatinine) and comparisons across settings.

The K/DOQI classification system is widely accepted and endorsed by international societies and groups, including the Kidney Disease: Improving Global Outcomes (KDIGO) [4], the Canadian Society of Nephrology (CSN) [5], the Caring for Australians with Renal Impairment (CARI) [6], and the United Kingdom

National Institute for Health and Clinical Excellence (NICE) [7]. Table 6.1 presents the modifications proposed to the K/DOQI guidelines by these societies. K/DOQI guidelines suggest referral to a nephrologist for CKD patients with advanced disease (stages 4 or 5), proteinuria, rapid CKD progression, or uncontrolled hypertension or refractory hyperkalemia.

Development of definitions for CKD has allowed estimation of CKD prevalence across a wide spectrum of populations. In the United States, the most rigorous estimates for CKD are based on analysis of National Health and Nutrition Examination Surveys (NHANES) [3]. These prevalence estimates were recently updated using the new CKD-EPI creatinine equation. The overall prevalence of CKD in adults in the United States is 11.5% [95% confidence interval (CI), 10.6–12.4], which translates to 23.2 million people (95% CI, 21.3–25.0) in the United States with CKD. This estimate is somewhat lower than the estimated 13.1% based on prior estimates using the MDRD Study equation. The prevalence of CKD stages 1–4 based on NHANES 1996–2006 are 2.24% (stage 1), 2.56% (stage 2), 6.32% (stage 3), and 0.4% (stage 4). Prevalence estimates for stage 5 CKD treated with renal replacement therapies (kidney transplantation, peritoneal dialysis, hemodialysis) in the United States is available from the United States Renal Data System (USRDS) [8]. In 2006, 110,854 people reached ESRD, reflecting an age-, race-, and gender-adjusted incidence of 360 per million population, and 506,256 people were receiving renal replacement therapy, reflecting an age-, gender-, and race-adjusted prevalence of 1,626 per one million population. Global estimates for CKD based on the K/DOQI classification system have been widely reported. The prevalence estimates for populations with eGFR ≤ 60 ml/min/1.73 m^2 vary – from 4.9% based on clinical populations in the United Kingdom to 4.4% in Norway (The Nord-Trøndelag Health [HUNT 2] Study) to 11.2% in Australia (The AusDiab Kidney Study) [9, 10].

Whereas the K/DOQI classification system is a major improvement over the previous classification systems, it also has its limitations [11–13]. There are inherent errors and variability in eGFR, as well as in serum creatinine measurement. These errors can result in misclassification of individuals as having a disease if the diagnosis is based solely on eGFR. Many individuals, especially the elderly, with stage 2–3 CKD will never progress to ESRD, and the risk of death far exceeds the risk of ESRD in these individuals. Some fear that these individuals will undergo unnecessary diagnostic testing, whereas others suggest that knowledge about reduced GFR will allow administration of nephrotoxic medications to be avoided and medication side effects to be minimized by adjusting dosage and optimizing care for a wide range of complications – from cardiovascular disease to pneumonia [11–13].

6.4 Chronic Kidney Disease Screening

CKD is associated with a wide variety of complications, including volume overload, hyperkalemia, hyperphosphatemia, metabolic acidosis, anemia, and hypertension.

CKD is also highly associated with cardiovascular disease, and a recent summary statement of the American Heart Association concluded that CKD was an independent risk factor for cardiovascular disease [14]. In 4,893 participants of the Cardiovascular Health Study, there was a 5% higher risk of de novo cardiovascular disease per 10 ml/min/1.73 m^2 lower eGFR [15]. Microalbuminuria, defined as persistent urinary albumin excretion between 30 and 300 mg per day and albuminuria (>300 mg albumin excretion per day) are also associated with progression to ESRD and cardiovascular disease. In the 12,866 participants of the Multiple Risk Factor Intervention Study (MRFIT), followed for 25 years for ESRD development, dipstick proteinuria ≥ 2+ and eGFR ≤ 60 ml/min/1.73 m^2 were associated with a 41-fold higher risk of ESRD [16]. In the 85,421 participants of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study in the Netherlands, a twofold increase in urine albumin concentration in a spot specimen was associated with a 29% increase in cardiovascular mortality [17]. The cost of treating CKD and its complications is high. In 2006, CKD costs for Medicare patients in the United States accounted for almost one quarter of the general Medicare costs and exceeded $49 billion, representing a fivefold increase since 1993 [8]. Costs for ESRD treatment in 2006 were $23 billion, or 6.4% of the Medicare budget. The rising prevalence of CKD and its risk factors – including obesity, hypertension, and diabetes – availability of treatment to slow CKD progression and prevent cardiovascular disease, and the high cost associated with CKD provide a strong rationale for CKD screening.

The overall goal of screening for a chronic disease is early detection – prior to the development of overt clinical manifestations or complications. Early disease diagnosis should also provide an opportunity to initiate early treatment and prevent complications. An effective screening program can accomplish early detection and improve survival while minimizing unnecessary testing and costs. A screening program should be able to fulfill several criteria, as outlined by Wilson and Jungner in 1968 [18, 19]. Table 6.2 describes these criteria and their relevance to CKD screening. The majority of the screening criteria can be satisfied for CKD and provide the basis for developing screening programs in high-risk populations, such as older individuals and those with hypertension, diabetes, proteinuria, or family history of CKD.

An ideal evaluation of a screening strategy, such as that for CKD, will include randomization of individuals to early detection or standard of care followed by close monitoring for further testing, complication of testing, and disease and ultimately the benefit of screening on reducing mortality in a cost-effective manner [19]. Such an experimental design would reduce the risk of selection bias, lead-time bias, length-time bias, and overdiagnosis bias, all of which are well know to produce false-positive results in screening studies. No such trial of screening exists in CKD, and the available evidence for screening is based on observational studies (prospective and retrospective).

Albuminuria measurement as a screening strategy for CKD has been evaluated in several observational studies. In 2,527, participants of the PREVEND study, the ability of urinary albumin concentration and urine albumin to creatinine ratio in a morning void to detect microalbuminuria in a subsequent 24-h urine collection was evaluated. At a urine albumin concentration of 11.2 mg/L, the C-statistic for the receiv-

Table 6.2 Wilson-Jungner criteria for screening programs and their applicability to chronic kidney disease screening [19]

Criteria	Relevance to CKD
The condition sought should be an important health problem	CKD is common, with increasing prevalence of the disease as well as its risk factors
There should be an accepted treatment for patients with recognized disease	Early recognition of individuals with CKD allows opportunities for lifestyle modification and treatment with medications such as ACE-inhibitors and ARBs to control hypertension and slow CKD progression
Facilities for diagnosis and treatment should be available	Early stages of CKD can be managed by primary care physicians and advanced or rapidly advancing CKD can be managed by nephrologists. Infrastructure for this treatment exists
There should be a detectable preclinical stage	Advanced CKD (stages 4 and5) is preceded by preclinical stage often characterized only by laboratory abnormalities. These abnormalities may be present for decades prior to advanced stages of CKD
There should be a suitable test	eGFR calculated from serum creatinine and albuminuria are suitable tests for screening
The test should be acceptable to the population	Serum creatinine measurement and dipstick/urine testing are widely used in clinical practice and routine health monitoring
The natural history of the condition should be well understood	Natural history of CKD, with progression to ESRD and risk of cardiovascular disease is well described
A policy on who to treat as patients should be developed and agreed upon	Advance kidney failure treated with renal replacement therapy is covered by healthy policy and law. However, CKD has many outcomes and randomized evidence for risk reduction is limited to a few interventions and outcomes
The cost of case finding should be balanced with medical care availability	Targeted screening for CKD is likely to be cost effective (known for albuminuria[20]), but further evidence is needed of the full range of interventions and effectiveness for different outcomes
Screening should be a continuous process and not a one-time project	KEEP program is based on continuous screening of high risk populations

ACE, angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CKD,* chronic kidney disease; *KEEP,* National Kidney Foundation's Kidney Early Evaluation Program

er operating characteristic (ROC) curve was 0.92, and sensitivity and specificity were both 85% [20, 21]. Similar findings were noted in a study of 577 individuals in Karachi, Pakistan. Based on the ROC curve analysis, at a urinary albumin concentration of 2 mg/dl, sensitivity and specificity were 81% and 95%, respectively, for men and 43% and 97%, respectively, for women [22].

Few studies evaluated screening strategies for CKD using eGFR alone. Hallan et al. evaluated the effectiveness of screening by eGFR among 65,604 participants of the HUNT 2 Study in identifying individuals with CKD defined as eGFR ≤60 ml/min/1.73 m^2 [23]. The number of screened individuals needed to detect one case of CKD was 20.6 in the whole population but decreased to 8.7 if screening was restricted to those with hypertension, diabetes, or age > 55 years. Combination of eGFR and albuminuria may improve the yield of CKD screening and identify individuals at highest risk of progression, who are most likely to benefit from therapy. In the 12,866 participants of the MRFIT Study (followed for 25 years for ESRD development), dipstick 1+ proteinuria was associated with a threefold higher risk, ≥ 2+ proteinuria with a 16-fold higher risk, and a combination of eGFR < 60 ml/min/1.73 m^2 and ≥ 2+ proteinuria with a 41-fold higher risk of ESRD [16]. However, ESRD is relatively rare, and more common complications may dominate a needed cost-effectiveness analysis, the weakest link of which may be the need for more randomized trial data for a broader range of interventions and complications.

CKD is unlikely to be optimally treated by a single intervention. In a recent analysis of 8,530 participants of NHANES, age, gender, hypertension, diabetes, peripheral vascular disease, history of cardiovascular disease, congestive heart failure, proteinuria, and anemia were highly predictive of CKD. A scoring system was developed, with 1 point for each variable except age (50–59 years, 2 points; 60–69 years, 3 points; ≥ 70 years, 4 points) [24]. A score of ≥ 4 had a sensitivity of 92%, specificity of 68%, positive predictive value (PPV) of 18%, and negative predictive value (NPV) of 99% for the CKD diagnosis (defined as eGFR ≤ 60 ml/min/1.73 m^2).

A screening strategy for CKD targeting the highest risk groups – those with diabetes or hypertension, family history of diabetes, hypertension, or kidney disease – is likely to be most efficient and cost effective. A recent study analyzed the cost-effectiveness of serum creatinine reporting vs. automatic eGFR reporting in a hypothetical cohort of 10,000 individuals older than 60 years undergoing annual testing for more than 18 years [25]. Monte Carlo simulations demonstrated that with eGFR reporting, 13 fewer deaths and 29 fewer transitions to ESRD occurred over 18 years of repeated annual testing. Estimated GFR reporting, however, generated 11,348 more false-positive CKD cases compared with serum creatinine alone but resulted in 2,072 fewer patient years spent with undetected CKD. This suggests that interpretation of eGFR could be optimized by including additional patient risk factors. It is noteworthy that whereas risk factors may vary across outcomes, lower eGFR, higher albuminuria, diabetes, and hypertension increase the risk of most outcomes (e.g., ESRD, acute kidney injury, cardiovascular disease, infection, medical complications), whereas older age is associated with higher risk of most outcomes but lower risk of ESRD [26].

The National Kidney Foundation's Kidney Early Evaluation Program (KEEP)

screens for early detection of CKD. KEEP focuses on high-risk individuals, such as those with a personal history of diabetes or hypertension or a first-degree relative with diabetes, hypertension, or kidney disease. KEEP screenings include blood pressure (BP) measurement; blood testing for hemoglobin, plasma glucose, serum creatinine, and cholesterol; and urine testing for hematuria, pyuria, and microalbuminuria. Individuals with abnormal tests are provided on-site consultation with volunteering physicians and referred for further evaluation and testing. The KEEP program, launched in 2000, has screened more than 100,000 individuals, of whom 28.7% had CKD [27], with a prevalence of stage 1, 3.1%; stage 2, 4.8%; stage 3, 19.7%; and stages 4 and 5, 1.1%. This distribution demonstrates the program's ability to detect individuals in the early stages of CKD.

6.5 Conclusions

CKD is rising in prevalence and is now recognized as an independent risk factor for cardiovascular disease and mortality. Development of definitions and a classification system for CKD by the K/DOQI has led to an improved understanding of the CKD epidemiology and outcomes. The focus is now shifting toward improving eGFR prediction and identifying risk factors for CKD progression. Screening strategies for CKD in the general population continue to be a matter of active debate, and the present consensus is to limit screening to high-risk individuals. Interpretation of CKD stages should incorporate the level of eGFR and albuminuria, patient characteristics that determine the risk for different outcomes, and patient suitability for different risk-reduction strategies.

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Cardiovascular Disease Risk Factors in Chronic Kidney Disease: Traditional, Nontraditional, and Uremia-related Threats

7

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Abstract Cardiovascular disease remains the leading cause of morbidity and mortality in chronic kidney disease (CKD), and there is an urgent need to develop novel therapeutic strategies to reduce this excessive risk. In the context of uremia, this has been problematic, as the extremely high cardiovascular disease (CVD) risk seems to be the result of a complex interplay between a vast number of traditional, novel, and uremia-specific risk factors. Emerging evidence suggest that, in particular, endothelial dysfunction, oxidative stress, vascular calcification, and inflammation play major roles in initiating and promoting vascular disease in this patient group. New research into areas such as hormonal derangements may be help identify new vascular risk factors, unravel new rational pathogenetic pathways, and facilitate the more rapid development of novel, safe, and effective therapies.

Keywords: Cardiovascular disease risk factors • Uremia • Inflammation • Oxidative stress • Endothelial dysfunction • Hormonal derangements • Insulin resistance • Vascular calcification • Mineral metabolism • Secondary hyperparathyroidism • Homocysteine • Anemia • Dialysis • Dyslipidemia

7.1 Introduction

The life expectancy of chronic kidney disease (CKD) patients is reduced, and cardiovascular disease (CVD), including sudden death, stroke, acute myocardial infarction (AMI), and congestive heart failure (CHF), accounts for the majority of premature deaths in dialysis patients [1]. Among these, sudden death due to cardiac disease is the most common. The reasons for the unacceptably high incidence of CVD in CKD patients are not fully known. Besides a high prevalence of traditional risk factors, several uremia-specific processes, such as vascular calcification, inflammation (the response of vascular tissues to harmful stimuli), oxidative stress, anemia, and altered

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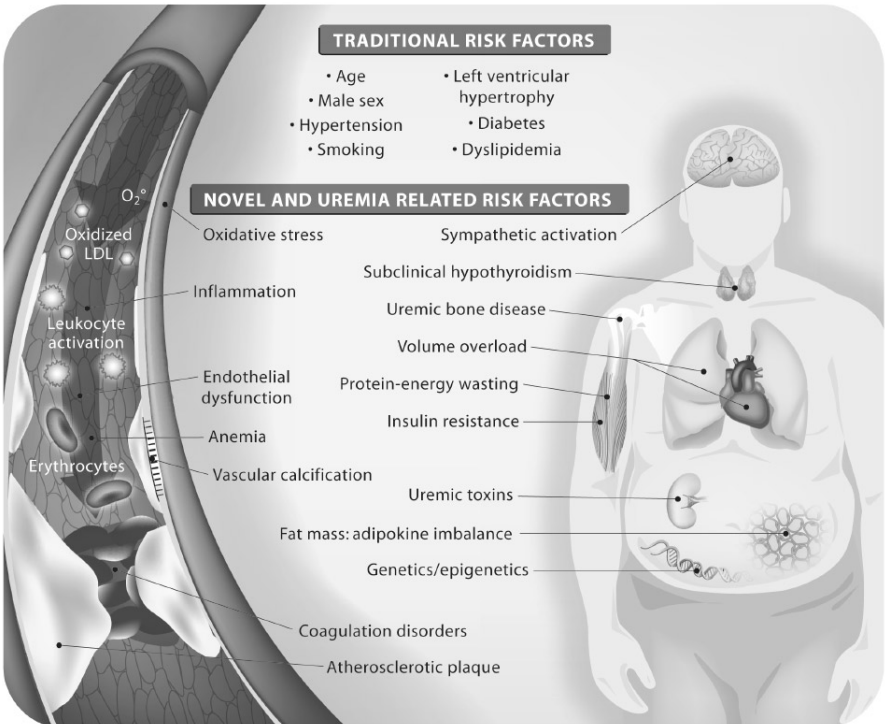

Fig. 7.1 Traditional and novel/uremia-specific cardiovascular risk factors in chronic kidney disease. Reproduced from [2], with permission.

energy metabolism, may contribute. Diminished estimated glomerular filtration rate (eGFR) is a powerful graded, independent predictor of CVD and all-cause mortality. In this chapter, we review the mechanisms of the main and most established risk factors known or suspected to increase CVD risk in patients with impaired renal function (Fig. 7.1).

7.2 Epidemiological Considerations

7.2.1 Difficulties in Describing Causes of Death

Precise information on the incidence and prevalence of CVD in CKD patients is difficult to obtain. It is clear that in this often-sedentary population, a clinical definition of CVD will underestimate the true prevalence and incidence of atherosclerosis and cardiovascular complications. Because premature CVD is the leading cause of

death in CKD patients, many clinical studies of purported cardiac risk factors and new treatments focus on death from cardiac disease as a primary end point. However, in our opinion, the use of cardiac disease mortality instead of all-cause mortality as an end point may be hazardous for many reasons. First, autopsies are infrequently performed in such patients, and the accuracy of death certificates is inherently problematic. Moreover, there are many examples of difficulties in defining the exact cause of death in CKD patients, such as in sudden cardiac failure. Finally, in many cases, it is difficult to ascribe death to a single cause in CKD. In our experience, most CKD patients die in a complex clinical picture, with vascular complications, protein-energy wasting (PEW), and multiple infections.

7.2.2 Effects of Changing Demographics and Race on CVD in CKD

As it has been demonstrated that the majority of CKD patients die before they reach dialysis [3], another aspect that needs to be considered when interpreting the literature is selection bias. Actually, because dialysis patients have usually survived many years of the unhealthy internal uremic environment, they could be considered to be survivors. At the same time, with better predialysis care and more liberal criteria for accepting a patient for dialysis, nephrologists are now treating older and sicker patients with renal replacement therapy (RRT). As a consequence, this will result in a dramatically increased burden of CVD in CKD patients and a higher prevalence of risk factors associated with older age, such as hypertension, dyslipidemia, vascular calcification, advanced glycation end products (AGEs), oxidative stress, and inflammation. When discussing the complicated interplay between traditional and novel risk factors, we should bear in mind that risk factors seldom operate in separate rigid compartments, and strong associations are usually found between traditional and novel risk factors. Striking differences in the cardiovascular mortality rate of dialysis patients from the USA, Japan, and Europe have been reported. As adjustments for traditional risk factors and different dialysis regimes do not affect these differences, it has been speculated that cultural habits, differences in diets, and/or genetic variations may contribute to the observed disparities. Moreover, as Asian dialysis patients treated in the USA have a markedly lower adjusted relative risk than Caucasians, it seems that diet and genetic factors play a role. Indeed, wide differences in mortality rates exist within the USA, where Caucasians in general have a higher mortality rate than Hispanic, Asian, and African American dialysis patients.

7.2.3 Reverse Epidemiology

Reverse epidemiology is the paradoxical observation that the well-documented associations in the general population between hypercholesterolemia, hypertension, obesity, and poor outcomes does not exist or even may be reversed in dialysis patients.

It should be mentioned that this phenomenon is not only observed in dialysis patients but also in geriatric populations and in patients with malignancies and CHF. Studies have suggested that this confounded epidemiology is due to the overriding effect of PEW and persistent inflammation [2].

7.3 Traditional Risk Factors

7.3.1 Age, Gender, and Smoking

As CVD is mostly a disease of middle-aged and older patients, the majority of patients receiving RRT are already at the age in which CVD is often prevalent. In patients older than 60 years, every additional year increases the mortality risk by about 3%. Male gender is another well-known risk factor for CVD in the general population, and it has been reported that the incidence of AMI is nearly 2.5 times more frequent in male than in female CKD patients in all age groups. However, older female patients will also be affected by an increased risk of CVD because of menopause – induced by age and/or comorbidity. It has been shown that about 70% of women on hemodialysis (HD) were menopausal before or after starting RRT, and the incidence of AMI was three to five times higher in female CKD patients than in the general female population at all age groups [4]. Smoking is, as in the general population, associated with CVD and premature death in CKD [5].

7.3.2 Diabetes Mellitus

North-American registry data shows that the number of diabetic patients annually admitted to RRT more than doubled from 1995 to 2000. Thus, diabetes mellitus has become the single most important cause of end-stage renal disease (ESRD). Survival of diabetic patients on RRT continues to be poor and is worse than in dialysis patients with any other underlying renal disease. The major causes of death in this patient group are coronary heart disease, such as myocardial infarction, angina, history of bypass surgery, percutaneous transluminal coronary angiography (PTCA), or pathology on coronary angiography. As most cardiovascular complications, particularly coronary atheroma, accumulate before diabetic patients enter RRT programs, there is definitely a need for improved care of the diabetic patient at the pre-ESRD stage. Diabetic patients with mild to moderate CKD who develop AMI experience an increased risk of cardiac complications, such as atrial and ventricular arrhythmia, atrioventricular (AV) block, asystole, pulmonary congestion, and cardiogenic shock [6].

7.3.3 Hypertension

Hypertension is a major risk factor for the development of atherosclerosis, stroke, and left ventricular hypertrophy (LVH), which is common (75–85% of patients) and not always well treated in the dialysis population. Although low blood pressure is associated with increased mortality in dialysis patients, hypertension predicts mortality in CKD patients before or at dialysis initiation. To explain these apparently conflicting findings, one must distinguish the roles of systolic pressure, diastolic pressure, mean arterial pressure (MAP), and pulse pressure. Isolated systolic hypertension with increased pulse pressure is by far the most prevalent blood pressure anomaly in dialysis patients owing to medial sclerosis of arteries with secondary arterial stiffening. Stiff vessels cause increased pulse-wave velocity, resulting in increased systolic peak pressure by a prematurely reflected pulse wave. The consequence is progressive LV dysfunction and ultimately CHF. Subsequently, this may result in lower MAP and diastolic pressure and increased risk for death from CVD. Taken together, these findings suggest a U-shaped relationship between blood pressure and mortality: isolated systolic hypertension and increased pulse pressure probably indicate high long-term risk in dialysis patients, whereas low mean and diastolic blood pressures predict early mortality. The "invisible" danger concerning hypertension is related to the fact that numerous CKD patients are "nondippers", i.e., experience no nocturnal fall in BP. Advancing experience suggests that sleep apnea is a frequent and often overlooked condition in CKD associated with nondipping blood pressure, sympathetic nervous system activation, and increased CVD risk [7].

7.3.4 Insulin Resistance

Many abnormalities associated with metabolic syndrome, including insulin resistance, are also found in different stages of CKD, a so-called "uremic metabolic syndrome". The etiology of insulin resistance in CKD is multifactorial, with contributions from fat mass accumulation, vitamin D deficiency, metabolic acidosis, inflammation, and accumulation of uremic toxins, which lead to acquired defects in the insulin-receptor signalling pathway. Although the quantitative role of insulin resistance in the composite outcome of CKD patients is unclear, one Japanese study showed that insulin resistance was an independent predictor of CVD mortality in dialysis patients [8].

7.3.5 Dyslipidemia

In the general population, hypercholesterolemia is a well-established risk factor for CVD morbidity and mortality. In the CKD population, this relationship is less clear,

as some of the major causes of CVD, such as cardiomyopathy and sudden death, may not be dependent on dyslipidemia. As with other chronically ill patients, low rather than high serum cholesterol levels predicts poor outcome in dialysis patients. This is likely attributed to the confounding effects of wasting and inflammation. Progressive loss of renal function leads to changes in plasma composition of blood lipids that are associated with vascular disease. Renal dyslipidemia is characterized by an atherogenic apolipoprotein profile, including decreased levels of apolipoprotein A (apoA)-containing lipoproteins and increased levels of apoB-containing lipoproteins. A hallmark of progressive CKD is increased levels of apoCIII, which may link inflammation and endothelial dysfunction to uremic dyslipidemia. Whereas total serum cholesterol levels in general are normal, or even low, high-density lipoprotein (HDL)-cholesterol is reduced; and low-density lipoprotein (LDL)-, intermediate-density lipoprotein (IDL)-, very-low-density lipoprotein (VLDL)-cholesterol, plasma triglycerides, and lipoprotein(a) [Lp(a)] levels are increased. Compared with HD patients, patients treated by peritoneal dialysis (PD) more often have both hypercholesterolemia and hypertriglyceridemia. Elevated Lp(a) levels have been reported to be associated with increased CVD mortality both in HD and PD patients. Two randomized controlled trials showed no benefit of statin treatment in dialysis patients [9, 10].

7.4 Nontraditional and/or Uremia-specific Risk Factors

7.4.1 Renal Failure Per Se

Recent data suggest an independent, graded association between reduced eGFR and the risk of death, cardiovascular events, and hospitalization [11]. Although the exact mechanisms by which a progressive loss of renal function may accelerate the atherogenic process are not well established, the prevalence and magnitude of a number of nontraditional CVD risk factors, such as oxidative stress, inflammation, vascular calcification, and accumulation of AGEs increases. Also, many other accumulating uremic retention solutes, such as asymmetric dimethylarginine (ADMA), guanidine, homocysteine, indoxyl sulphate, and p-cresol, may have direct proatherogenic properties. It should be emphasized that as kidneys also may produce substances, such as renalase, which may inhibit CVD, a loss of renal function may contribute to accelerated vascular disease via other mechanisms than retention.

7.4.2 Oxidative Stress

Besides atherosclerosis, oxidative stress may be implicated in the pathogenesis of many uremic complications, such as dialysis-related amyloidosis, PEW, and anemia.

As a result of reduced antioxidant systems (vitamin C and selenium deficiency, reduced intracellular levels of vitamin E, reduced activity of the glutathione system) and increased pro-oxidant activity associated with advanced age, high frequency of diabetes, chronic inflammatory state, and bioincompatibility of dialysis membranes and solutions, many laboratories have shown that uremic patients are subjected to enhanced oxidative stress. No evidence suggests that dialysis therapy reduces the overall burden of oxidative stress. Clinical evidence demonstrates that increased oxidative stress may promote accelerated atherogenesis and increased risk of atherosclerotic cardiovascular events [12]. Whereas four different pathways (carbonyl stress, nitrosative stress, chlorinated stress, and classical oxidative stress) of oxidative stress seem to be operative in CKD, evidence suggests that nitrosative stress plays a major role [3]. The most important enzymes capable of oxidizing LDL in vitro involved in reactive oxygen species (ROS) production are the superoxide producer nicotinamide adenine dinucleotide phosphate, reduced (NADPH) oxidase, the hydrogen peroxide producer superoxide dismutase, the nitric oxide (NO) producer nitric oxide synthase (NOS), and the hypochlorous acid producer myeloperoxidase (MPO). Also, AGEs in uremic patients can be generated as a consequence of increased ROS production and both N-carboxymethyl-lysine (CML) and pentosidine production. The relationship between AGE accumulation and CVD outcome is unclear. Although prospective studies of pentosidine and CML found no consistent association with mortality, one study showed that skin autofluorescence predicted mortality in HD patients [13]. In addition to having increased generation of pro-oxidants, CKD patients may also be subjected to decreased intake of antioxidants due to poor appetite and/or increased nutrient losses into the dialysate. Patients with signs of PEW and a low serum albumin (S-albumin) concentration have a significantly diminished plasma antioxidant capacity due to the diminished availability of thiol groups. It seems plausible that hypoalbuminemia and inflammation will have a synergistic effect on the risk for detrimental vascular effects, because whereas inflammation would generate increased production of oxidants by leukocytes, hypoalbuminemia results in reduced scavenging capacity for these oxidants. The implications of the findings of a generalized increase in oxidative stress associated with uremia have led to speculations that antioxidative therapy may reduce cardiovascular complications.

7.4.3 Hyperhomocysteinemia

Homocysteine (Hcy) is a nonprotein sulfur-containing amino acid that has attracted considerable interest by vascular researchers, as it may by several mechanisms mediate premature atherosclerosis and CVD. The prevalence of hyperhomocysteinemia in patients with advanced CKD is >90%. In contrast to the well-documented association between total Hcy (tHcy) and vascular disease in the general population, the association between tHcy and CVD is inconsistent in the setting of reduced renal function, with several reports showing low tHcy levels in CKD patients with CVD [14].

Although there are several putative reasons that may explain this paradoxical relationship, the strong association between tHcys and hypoalbuminemia, PEW, and inflammation seems to be the most important. As there is a strong positive correlation between tHcys and S-albumin, and hypoalbuminemia is such a strong risk predictor for poor outcome that this association may confound the impact of tHcy on vascular disease. Evidence suggests that treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in CKD patients despite significant reduction in homocysteine levels [15].

7.4.4 Inflammation

Inflammation may be defined as the response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation should be regarded as a protective attempt by the organism to remove the injurious stimuli as well as to initiate the tissue-healing process. Although proinflammatory cytokines may have acute beneficial effects, chronic systemic elevation, as in CKD, is detrimental. Chronic inflammation is characterized by the persistent effect of a causative stimulus, which leads to cell and tissue destruction and has deleterious effects on the body. In advanced CKD especially, the systemic concentrations of both pro- and anti-inflammatory cytokines are severalfold higher due to both increased production and decreased renal clearance. In addition, several dialysis-related factors (such as membrane bioincompatibility and thrombosed AV fistula) and nondialysis-related factors (such as infection, comorbidity, poor oral health, failed kidney transplants, genetic factors, diet) may contribute to a state of persistent inflammation. Robust and consistent evidence shows that even single measurements of various inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, long pentraxin 3 (PTX3), S-albumin, and white blood cell count, as independent predictors of mortality in CKD patients [3]. In the clinical setting, CRP testing has arisen as the prototypic marker of inflammation due to its reliability, low cost, and availability. However, many comparative studies on prognostic performance suggest that IL-6 may be a better outcome predictor in CKD [16]. Although CRP reflects systemic inflammation and predicts risk, emerging evidence suggests that CRP does not promote vascular disease. Indeed, although CRP haplotypes is associated with circulating CRP levels, an association to ischemic heart disease has not been observed [17]. As CRP is a moving target and levels fluctuate greatly over time (Fig. 7.2), being mainly influenced by processes such as transient infections and comorbidity, continuous monitoring of CRP is recommended, as it provides more precise information on the "real" inflammatory state [18]. In contrast to studies on the CRP gene, IL-6 gene polymorphisms appear to be associated with metabolic syndrome and premature vascular disease. Thus, evidence suggests that IL-6 acts as a promoter of vascular disease and wasting by actively participating in the processes of vascular calcification, muscle catabolism, anorexia, oxidative stress, hormonal derangement, cell ageing, and endothelial dysfunction [3]. PTX3 is a novel inflammatory media-

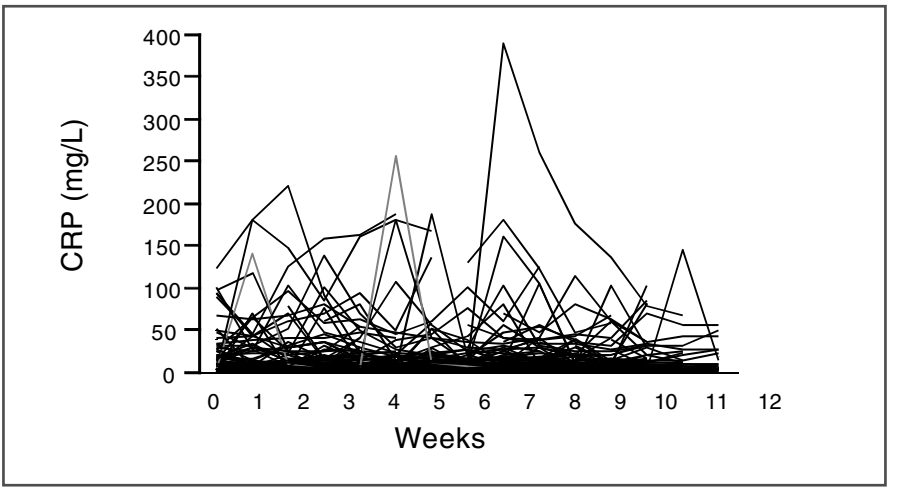

Fig. 7.2 Fluctuation of C-reactive protein levels during 12 consecutive weeks in 228 prevalent patients undergoing hemodialysis. Modified from [18].

tor of interest in the context of CKD, as evidence suggests associations with both endothelial dysfunction and albuminuria [19]. However, as many features known to mediate atherosclerosis, such as endothelial dysfunction, vascular calcification, insulin resistance, and increased oxidative stress, all are more or less associated with inflammation biomarkers, the association between chronic inflammation and CVD may also be indirect.

7.4.5 Endothelial dysfunction

Endothelium dysfunction is commonly observed in CKD, being an obligatory, prodromal phase in the atherosclerosis process that likely precedes cardiovascular complications. High oxidative stress and low availability of nitric oxide (NO) may be the main causes engendering endothelial CKD dysfunction. However, other factors inherent to the uremic milieu might further aggravate endothelial dysfunction, such as ADMA retention, anemia correction, inflammation, phosphate retention, and an imbalance in fat-derived adipokines. Emerging evidence suggests that detached circulating endothelial cells (CEC) serve as a potential marker of endothelial damage, arising as a strong predictor of future cardiovascular events in HD patients [20]. Normally, in response to ischemic insult and cytokine stimulation, endothelial progenitor cells (EPC) are mobilized from the bone marrow to act as "repair" cells in response to the endothelial injury. As to reduced numbers of and/or a functional impairment of EPC due to inflammation and/or toxic effects of retained uremic solutes, there seems to be an imbalance between CEC and EPC, which may predispose CKD patients to endothelial dysfunction.

7.4.6
Secondary Hyperparathyroidism and Mineral Metabolism

CKD is associated with disturbances of calcium and phosphate metabolism starting as early as in the GFR interval 15–60 ml/min. However, it was not until recently that attention was directed to the effect calcium and phosphate disturbances on the vasculature, potentially triggering accelerated calcifying atherosclerosis and arteriosclerosis. Indeed, hyperphosphatemia, serum calcium, and intact parathyroid hormone (iPTH) are more or less all mortality predictors in dialysis populations. The overall mortality risk prediction attributable to disorders of mineral metabolism is in the range of 17% for HD patients [21]. Supportive of a relationship between hyperphosphatemia, cardiovascular calcification, and mortality, an elevated serum phosphate level is associated with increased risk for valvular calcification and death from CVD [22].

7.4.7
Cardiovascular Calcification

Cardiovascular calcification is a process that may affect the arterial media, atherosclerotic plaques, and heart valves, respectively. A hallmark of medial calcification is arterial stiffness, which in the clinical situation manifests as increased pulse pressure. The pathophysiological role of plaque calcification is less clear, as it is mostly soft plaques, which rupture and cause AMI. However, it is now evident that the atherosclerotic calcification burden is a potent risk marker of cardiovascular events. In dialysis patients, valvular calcification affects the aortic and mitral valves specifically and contributes to progressive stenosis and associated morbidity [23]. In the general population, coronary artery calcification is infrequently observed in younger age groups. It is a phenomenon that increases with age, and the majority of people affected by vascular calcification are >65 years. In ESRD patients, on the other hand, extensive vascular calcification can be commonly observed in much younger age groups as well. The calcification process frequently starts before the initiation of dialysis treatment. The prevalence and extent of vascular calcification, arterial media calcification, and arterial stiffness have recently been shown to be strong predictors of CVD and all-cause mortality in dialysis patients [24].

Besides diabetes mellitus, abnormal calcium and phosphate metabolism and persistent inflammation, respectively, may – in the context of uremia – be two of the most important factors in the development of cardiovascular calcification [25]. Fetuin-A, an important inhibitor of vascular calcification, is down-regulated during the inflammation process, and low levels are linked to poor survival in dialysis patients [26]. However, fetuin-A is certainly not the only modifier of extraosseous calcification. Phosphate, calcium, and some proinflammatory mediators have the capacity to induce osteogenic differentiation, which is a transition of vascular smooth muscle cells toward osteoblast behavior. A system of calcification inhibitors (and inducers) is of major importance**,** as the extracellular calcium and phosphate environ-

ment must be formally considered as being "supersaturated" regarding the chemical solubility product of these ions in an aqueous solution [27]. Among those, leptin, matrix gla protein (MGP), tumor necrosis factor alpha (TNF-α), pyrophosphates, bone morphogenetic proteins (e.g., BMP-2 and -7), and osteoprotegerin (OPG), may be related to a process of accelerated vascular calcification in ESRD.

7.4.8 Autonomic Dysfunction

An important feature of CKD is decreased baroreflex sensitivity, which together with inflammation and wasting has been linked to increased risk of sudden death [28]. A further investigated indicator of the risk for sudden death is heart rate variability (reflecting autonomic dysfunction). Increased sympathetic nerve activity is commonly observed in CKD patients and predicts poor outcome [29]. The common occurrence of sleep apnea in patients with moderate and advanced CKD [30] is likely an important contributor to sympathetic overactivity.

7.4.9 Anemia

Anemia is a major cause of LVH and LV dilatation in ESRD. Although partial correction of anemia with erythropoietin results in regression of LVH [31], data does not suggest any cardiovascular outcome benefit of normalized hemoglobin [32]. The appropriate target hematocrit to minimize LVH or other CVD has not been defined. However, briefly summarizing guideline recommendations favors target hemoglobin of about 11 g/dl [33].

7.4.10 Hormonal Derangements

The loss of kidney function and the altered metabolic milieu in CKD affects hormone secretion and response of target tissues, causing a number of endocrine dysfunctions that may affect both PEW prevalence and future CVD risk. The most studied of these hormonal alterations is the growth hormone (GH) and insulin-like growth factor (IGF)-1 axis, both important physiologic regulators of growth, body composition, and kidney function. Perturbations in the GH–IGF-1 axis are responsible for many important CKD complications, such as growth retardation, PEW, atherosclerosis, and disease progression [34]. Other common hormonal disturbances in CKD are subclinical hypothyroidism and the low-T3 syndrome, present in 20% of CKD patients. Traditionally, decreases in plasma thyroid hormone concentrations in CKD have been interpreted as an attempt to conserve body energy stores by reducing the metabolic rate. However, thyroid alterations are associated with an increased risk for cardiovas-

cular events in the general population, and inflammation substantially down-regulates thyroid production. Thus, it has been hypothesized that these factors may constitute an intermediate link between inflammatory stress and impaired cardiovascular response in CKD patients [35]. Finally, the sex hormone profile is altered during the course of CKD. Male hypogonadism is present in as many as 50–70% of ESRD men. Testosterone decline is not only linked to reduced synthesis of both muscle protein and hemoglobin but may also be linked to atherosclerosis progression and artery vasoconstriction and/or hardening. Thus, the recently established link between male hypogonadism and increased cardiovascular mortality risk in dialysis patients will possibly bring back attention toward this therapeutic target [36]. Although recent randomized controlled trials in non-CKD patients with low doses of testosterone showed promising results in the form of lean body mass gain and improved metabolic profile [37, 38], interventional studies targeting cardiovascular outcome or cardiovascular death have, so far, not been conducted.

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Increased Levels of Urinary Albumin: A Cardiovascular Risk Factor and a Target for Treatment

8

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Abstract Excretion of albumin in the urine is highly variable, ranging from nondetectable quantities to grams. Increased levels of albuminuria are highly prevalent in healthy individuals and even more so in hypertensive and diabetic populations. The variable excretion of albumin in the urine is related to the risk for the individual to develop cardiovascular disease (CVD): absence or very low levels of albuminuria is associated with low risk, whereas the risk continuously increases (with no thresholds) with increasing amount of urinary albumin. The predictive power of urinary albumin levels for CVD risk is independent of other CVD risk factors. Leakage of albumin appears to be associated with a defect in vascular permeability, most likely caused by a defect in the glycocalyx layer. This defect appears to be not only present in the kidneys but also in other vascular beds, providing a potential explanation as to why increased albuminuria not only predicts renal disease risk but also CVD risk. Treatments that lower albuminuria are associated with cardiovascular protection, as demonstrated in randomized controlled trials of diabetic as well as hypertensive patients. There is preliminary evidence that albuminuria lowering also protects healthy individuals with elevated albumin excretion rates. In conclusion, albuminuria appears to be a sensitive marker for the susceptibility of an individual to develop CVD. Lowering albuminuria appears to be associated with cardiovascular protection. It may therefore be a suitable target for early primary prevention using cardiovascular protective therapy regimens.

Keywords: Albuminuria • Cardiovascular disease • Epidemiology • Pathophysiology • Cardioprotective treatment

8.1 Introduction

Albumin excretion into the urine was initially demonstrated to be a risk factor for progressive renal function loss. Recently, it has been established that individuals with

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increased albuminuria are also at risk for cardiovascular disease (CVD). The mechanism behind this relationship is not yet fully understood. This chapter discusses the potential clinical use of albuminuria in predicting the risk of CVD, the possible causality, and the clinical role of albuminuria in tailoring cardioprotective treatment.

8.2 Definition of Albuminuria

There appears to be consensus that, in physiological conditions, no or small amounts of albumin should pass through the kidneys into the urine. In case the amount of urine albumin exceeds 30 mg per day but remains below 300 mg per day, one speaks of microalbuminuria. If the level is above 300 mg per day, one talks about macroalbuminuria, overt albuminuria, or proteinuria [1] (for definitions, see Table 8.1). Using such definitions is important in clinical practice, as they offer the clinician and the patient an important tool to define what is normal and what is abnormal. Caution remains warranted, however, as the definitions of normal and abnormal are quite arbitrary. History teaches us that definitions of normal for other cardiovascular and renal risk markers, such as hypertension and cholesterol, are still being lowered. This is no surprise, as the relationship between blood pressure or cholesterol levels and CVD risk is continuous, and thus there is no specific threshold level. The same is true for the relationship between albuminuria and CVD and renal disease risk (*vide infra*). Thus, terms such as microalbuminuria and macroalbuminuria are practical as long as the medical community regularly checks the definitions of normalcy, as is the case for hypertension.

8.2.1 How Do We Measure Albuminuria?

8.2.1.1 Protein or Albumin?

Traditionally, leakage of plasma proteins into the urine was measured by quantifying the amount of total protein in the urine – so-called proteinuria. Commonly, the main component of this protein is albumin (>50%). With the need of measuring lower quantities of protein in the urine, the measuring technique required choosing a specific protein to be measured. This was albumin. Determining which plasma protein is the one we should measure is hard to define today. The different urinary proteins may reflect different pathologies. In case of low molecular weight proteins, renal tubular damage is likely to be the underlying condition; leakage of high molecular weight proteins into the urine most likely reflects renal glomerular damage. Measuring urinary proteinuria will, by definition, detect all different proteins, including low molecular weight and middle and high molecular weight proteins. In the event proteinuria is >1g/day, the

majority of that protein is usually albumin. Thus, the choice of measuring total protein versus albumin becomes arbitrary. However, in the event of lower total protein levels, the relative contribution of urinary proteins other than albumin increases, and the specific measurement of albuminuria is warranted.

In clinical practice, albuminuria is often chosen to measure renal disease and CVD risk, particularly in diabetic patients and in patients with essential hypertension. In nondiabetic patients, proteinuria is usually measured. Determining which protein is related to renal or CVD risk is as yet unknown. Albumin may qualify, as its size and charge is such that it will not easily pass the intact glomerular or vascular barrier. In the event of decreased barrier function, albumin will pass both the glomerular and vascular barrier. This might explain why albuminuria predicts both CVD and renal disease risk. Thus, to date, for CVD and renal disease risk stratification and for therapy monitoring, albumin appears to be the molecule of interest. However, it could also be that another plasma protein (cofiltered with albumin) is better related to renal and CV damage or damage prediction when one studies this in more detail [2].

8.2.1.2 Measurement Technique

Another ongoing important debate is which technique we should use to measure urinary albumin. Most common laboratory techniques use antibodies that bind to the albumin molecule (or its fragments) and subsequently detect the amount of formed complexes. It is important to realize that the antibodies used are raised against albumin derived from plasma. Whether this is an appropriate antibody is questionable, as urinary albumin may not have the same characteristics for antibody binding as plasma albumin due to the distinctly different environment of plasma and urine passing through the renal filter and tubules.

Indeed, when one measures urinary albumin with a nonimmunological technique such as high-performance liquid chromatography (HPLC), one detects more albumin compared with the antibody techniques. This opens up a whole new area of research. Not only is it important to truly quantify albumin but to verify whether and to what extent a new measurement technique alters the predictive power of this parameter on outcome [3].

8.2.1.3 Urine Collection

To measure urinary albumin, one needs to collect the urine. Traditionally, 24-h urinary collection is taken. This forces the patient to carry urine collection containers. Other, more practical, collection strategies involve a spot urine sample (the patient produces a urine sample at any time of the day) or a first-morning void (the patient collects the first morning urine after awaking). In case of a 24-h collection, one can

calculate the amount of albumin excretion per time. This allows standardized monitoring between patients and within a patient. The problem with urine portion collection techniques is that they can only quantify urinary albumin concentration, which could be problematic for standardization when the individual/patient has varying urinary albumin concentration from day to day or within a day. This problem can be overcome by using urinary creatinine excretion as a reference and dividing urinary albumin by urinary creatinine. The use of the albumin/creatinine ratio filters out the possible urinary concentration differences. However, the need for measuring creatinine introduces another bias. In addition to the measurement error of creatinine, the amount of creatinine may differ within (diurnal variation) and between (muscle mass) individuals. As all three collection (and correction) techniques are associated with different cutoff figures of normoalbuminuria, microalbuminuria, and macroalbuminuria (Table 8.1), the wide-spread clinical use of albumin as a risk marker is complicated. Standardization and guidelines are therefore desperately needed. Even if one collects accurately, day to day variation in albumin excretion appears to be present. Whether this is physiological or pathophysiological or still due to collection or even measurement errors remains hard to resolve. To avoid this variability as much as possible, multiple consecutive collections (three times) may help, as well as repeating collections three times with a week interval (modified from [1]).

The decision regarding the choice of collection or correction technique clearly depends on the goal. Obviously, the technique used should most accurately measure the true amount of albumin. In addition, the risk prediction properties of albuminuria should not be compromised by the technique used. An early and easy collection technique is preferable for screening purposes, whereas more accuracy and precision is required in for diagnoses. Several studies have shown that spot sampling is inferior to 24-h collection for albuminuria quantification [4]. Collection of a first-morning

Table 8.1 Definitions and threshold levels for urinary albumin according to the Kidney Disease: Improving Global Outcomes (KDIGO) consensus [1]

	24-hour urine collection, albumin excretion rate (mg/day)	Albumin concentration (mg/L)	Spot morning urine sample, albumin to creatinine ratio	
			mg/mmol	mg/g
Normal	<30	<20	<3 M <2.0 F <3.0	<30 M <20 F <30
Microalbuminuria	3–300	20–200	3–30 M 2.0–20 F 3.0–30	30–300 M 20–200 F 30–300
Macroalbuminuria	>300	>200	>30 M >20 F >30	>300 M >200 F >300

void, however, is an adequate technique and comparable to 24-h collection – both for albuminuria quantification and risk prediction [5]. Whether the creatinine correction (albumin/creatinine ratio) brings any added value over albumin concentration is questionable. For screening purposes, first-morning-void albumin concentration seems to be adequate. Whether creatinine correction is needed for monitoring and follow-up needs to be further studied.

8.2.1.4 Fresh or Frozen Sample?

Urine samples for albumin measurement should be fresh. There is no reason in clinical practice to store urine, as the results need to be directly available. However, for those involved in research studies with follow-up measurements of albuminuria, or those involved in large epidemiological studies, the need for urine storage may be present. In general, urine does not require special treatment after collection and can withstand many hours at room temperature without affecting urinary albumin measurement. However, freezing, particularly at –20°C, introduces clear and variable changes in the level of albumin measured in the sample. Changes increase with longer storage, which affects predictive properties of albuminuria in CVD risk [6]. The increased variability in urinary albumin observed during frozen storage may be due to factors such as urinary pH [7]. Correcting urinary pH or freezing at –70°C remains the best way to store urine samples if needed.

8.3 Epidemiology

Albumin excretion varies within the population. The majority of people have low levels of albumin excretion, some even below the detection limit. Around 10% have increased albumin excretion in the microalbuminuric range, and only a limited number of individuals have macroalbuminuria (proteinuria). The prevalence of microalbuminuria appears to be quite similar throughout the Western world. To date, studies have been carried out in Europe (Netherlands, Norway), Australia, and the USA, showing roughly the same distribution [8]. In the general population, individuals with diseases such as hypertension or diabetes have an increased prevalence of microalbuminuria (20%), although the numbers on this vary considerably between studies. However, even among individuals in the healthy (nondiabetic, nonhypertensive) general population, microalbuminuria is highly prevalent and is still predictive for cardiovascular outcome.

Increased levels of urinary albumin cluster with other CVD risk factors, such as age, body weight, smoking, diabetes, and hypertension. Individuals with either one or a combination of such conditions show a higher prevalence of microalbuminuria or proteinuria. Incident microalbuminuria is also higher in these cases. The increased

prevalence and incidence suggests that microalbuminuria may be the consequence of these other risk factors. However, microalbuminuria can be found in children and even babies [8]. This may suggest that microalbuminuria reflects early presence of vascular dysfunction, which may predispose the individual for other CVDs (and risk factors). Indeed, some studies show that microalbuminuria predicts new-onset hypertension as well as new-onset diabetes [9, 10].

8.4 Pathophysiology

The glomerular filter is designed to retain macromolecules within the vascular compartment. In case of a defective filter, one may expect to find several different macromolecules in the urine. Given its size, albumin would pass through the filter. However, its negative charge appears to prevent it from freely passing. The actual barrier within the glomerular filter that prevents albumin from passing was recently redescribed [11]. Apparently, the vascular endothelium plays an important role, in particular, a negatively charged glycocalyx layer that not only covers the glomerular endothelium but also the endothelial layer on various vascular beds. In case of endothelial dysfunction and changes in the glycocalyx, albumin may pass more readily into the vascular wall in multiple vascular beds. This may be the missing link, explaining why leakage of albumin into the urine is associated with CVD [12]. Albumin leakage may just reflect endothelial dysfunction, the latter causing CVD and renal disease risk. Alternatively, leakage may directly cause vascular disease through low-grade inflammation in the vessel wall.

8.5 CVD Risk Prediction

The predictive power of increased levels of albuminuria for renal disease risk are well described in patients with both type 1 and type 2 diabetes. Patients who develop microalbuminuria have marked increased risk of developing proteinuria and to progress to complete loss of kidney function. Mogensen wrote a seminal paper in 1984 describing the importance of microalbuminuria, not only as a renal-disease risk factor, but as a CVD risk factor in patients with diabetes [13]. It took some time until the importance of microalbuminuria as a CVD risk marker was further established (reviews [14, 15]). Although the risk for CVD in patients with type 1 diabetes is lower than in patients with type 2 diabetes, the CVD predictive effect of microalbuminuria is comparable for type 1 and type 2 diabetes [16].

Because of these findings, microalbuminuria was clearly linked to diabetes. The clinical applicability of microalbuminuria as a CVD risk predictor remained largely limited to diabetes, despite the fact that the Framingham study, established in 1984,

identified proteinuria as an important risk marker of (CVD) mortality in the general population [17]. It lasted 20 years before the predictive properties of microalbuminuria went beyond diabetes. Several important studies followed each other, such as the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project, the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, the Nord-Trøndelag Health (HUNT) study, and the European Investigation into Cancer–Norfolk (EPIC–Norfolk) study [18–21]. They all showed that, as in diabetes, microalbuminuria is predictive for cardiovascular events, even in individuals without diabetes (Fig. 8.1a–d). In addition, these studies clearly illustrat-

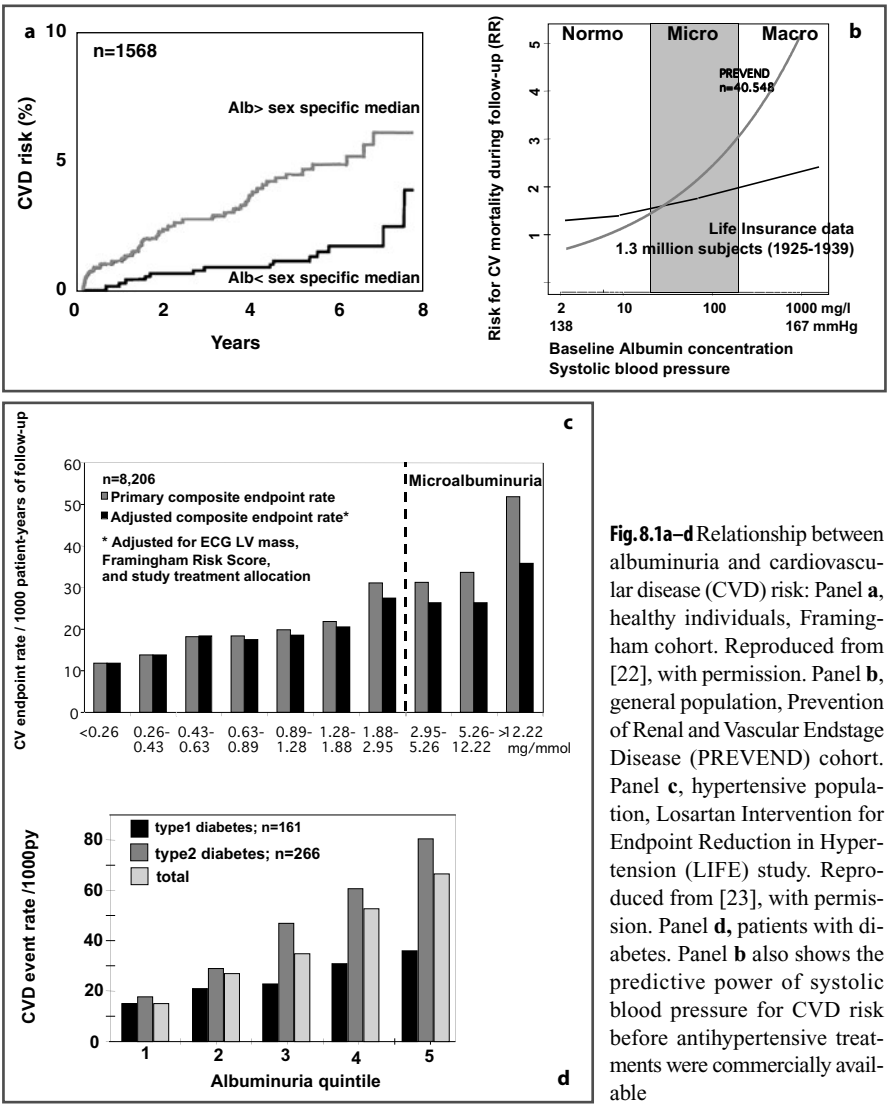

Fig. 8.1a–d Relationship between albuminuria and cardiovascular disease (CVD) risk: Panel **a**, healthy individuals, Framingham cohort. Reproduced from [22], with permission. Panel **b**, general population, Prevention of Renal and Vascular Endstage Disease (PREVEND) cohort. Panel **c**, hypertensive population, Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. Reproduced from [23], with permission. Panel **d,** patients with diabetes. Panel **b** also shows the predictive power of systolic blood pressure for CVD risk before antihypertensive treatments were commercially available

ed that the definition of microalbuminuria is still arbitrary, as the relationship between urinary albumin and CVD risk is continuous, with no clear lower or upper limit [19, 24, 25].

In the hypertensive patient, microalbuminuria has been shown to be an important CVD risk factor (reviewed [26]). Larger cohort studies confirmed this to be independent from other risk markers in the general hypertensive population (MONICA) [27] and a hypertensive cohort with left-ventricular hypertrophy (LVH), the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study [28]. Many (not all) guidelines recognize that the hypertensive patient with microalbuminuria is at increased CVD risk. Even in a mix of patients with increased CVD risk, such as the Heart Outcomes Prevention Evaluation (HOPE) study [29], microalbuminuria appears to be associated with increased CVD risk.

In the above studies, microalbuminuria was associated and clustered with other well-known CVD risk factors (age, smoking, diabetes, hypertension, LVH, being overweight, metabolic syndrome, serum creatinine). The question is whether microalbuminuria is an independent risk predictor. Careful correction for such factors, and post-hoc selection of "healthy" individuals in large general population cohorts, revealed the marked and overwhelming independent predictive power of microalbuminuria. This was confirmed by the recent Framingham data that elegantly shows that in normotensive, nondiabetic individuals with normal renal function, microalbuminuria remains a strong predictor for CVD [22].

Glomerular filtration rate (GFR) has been described in multiple studies as a powerful predictor for CVD risk. The relationship between CVD risk and microalbuminuria could thus well be driven by low GFR. However, data from the Framingham and PREVEND studies show that microalbuminuria relates to CVD risk independently of the GFR level [22, 30, 31].

8.6 Targeting Albuminuria for CVD Risk Protection

Clearly, microalbuminuria and proteinuria are independent predictors of CVD risk. Apart from risk stratification, to have any meaning in clinical practice, it must be shown that measures that reduce albuminuria or proteinuria are associated with cardiovascular protection. Several strategies are available to lower urinary albumin excretion in the microalbuminuric as well as in the proteinuric range. The albuminuria-lowering effect of antihypertensives, in particular, those that intervene in the renin-angiotensin-aldosterone system (RAAS), is well known. However, statins, glucosaminoglycans, and vitamin D analogues have proven to lower albuminuria [32–35]. Some of these strategies have showed cardioprotective characteristics in randomized controlled trials. However, few have been directed at albuminuria lowering per se to evaluate the effect on cardiovascular outcome. The Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA-2) study, evaluating the effect of the angiotensin-II-antagonist irbesartan, shows that

albuminuria can be substantially lowered in microalbuminuric hypertensive type 2 diabetic patients, and this is associated with renal protection and some degree of cardiovascular protection [36]. However, this study was not powered to address the effect on cardiovascular events. The PREVEND Intervention Trial (PREVEND IT) study is the only randomized trial that studied the effect of albuminuria lowering in healthy microalbuminuric individuals (other CVD risk factors were excluded). The study showed that reducing albuminuria with the angiotensin-converting enzyme (ACE)-inhibitor fosinopril tended to be cardioprotective (Fig. 8.2a) [37]. A recent post-hoc analysis of the LIFE study found similar results in hypertensive patients: the more the losartan lowered albuminuria, the lower the cardiovascular event rate, irrespective of the effect of other CVD risk factors (Fig. 8.2b) [38]. A post-hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that lowering albuminuria in patients

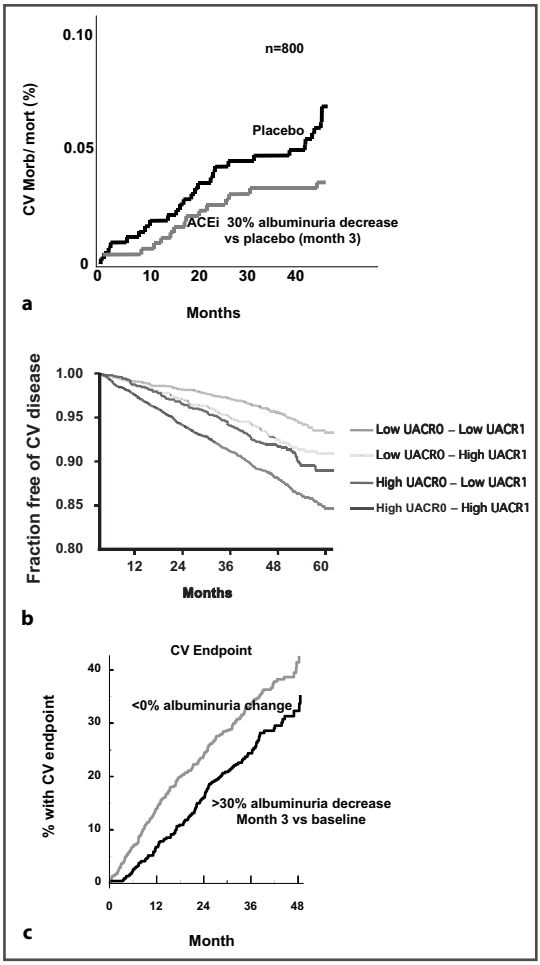

Fig. 8.2a–c Cardiovascular protection using therapies that lower albuminuria in different populations: Panel **a,** individuals from the general population: Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT); angiotensin-converting enzyme (ACE) inhibitor versus placebo. Panel **b,** hypertensive population: Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Reproduced from [23], with permission. Angiotensin receptor blocker (ARB) versus beta blocker. Panel **c,** patients with type 2 diabetes: Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial; ARB versus placebo. *UACR0* urinary albumin creatinine ratio at baseline, *UACR1* urinary albumin creatinine ratio at year 1

with nephritic-range albuminuria is also associated with cardiovascular protection (Fig. 8.2c) [38]. Future CVD trials involving drugs that target albuminuria more specifically are needed to resolve the issue of whether specific lowering of albuminuria results in cardiovascular protection and whether this is a cost-effective healthcare approach. Screening, specific targeting, and monitoring of increased urinary albumin levels may have distinct public-health implications in relation to CVD prevention [39].

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Microalbuminuria and Kidney Disease: An Evidence-based Perspective

9

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Abstract In the early 1960s, microalbuminuria was noted as a predictor of nephropathy and higher cardiovascular risk in patients with type 1 diabetes mellitus. Over the past four decades, however, the epidemiological evidence has become far stronger, implicating it as a cardiovascular risk marker than a risk factor associated with nephropathy. Microalbuminuria is also a marker of endothelial dysfunction, increased vascular leakage of albumin, and a marker of inflammation. In this context, it is also a marker for risk of developing hypertension and making it more difficult to control blood pressure if hypertension is already present. This chapter reviews the role of microalbuminuria as a marker of cardiovascular risk and nephropathy identifier. It also reviews the association of microalbuminuria with other cardiovascular risk factors and the pathophysiological association between microalbuminuria and vascular damage. In addition, the chapter reviews trial data that evaluated microalbuminuria for its prognostic significance on cardiovascular outcomes, as well as existing therapeutic interventions for reducing urinary albumin excretion in patients with high cardiovascular risk.

Keywords: Microalbuminuria • Kidney disease • Cardiovascular risk • Hypertension • Endothelial dysfunction

9.1 Introduction

More than 70 million Americans suffer from some form of cardiovascular (CV) disease, the single leading cause of mortality in both men and women, causing more than 850,000 deaths every year in the USA [1]. Microalbuminuria (MA) is a well-recognized predictor of CV disease morbidity and mortality in patients with or without diabetes [2–4]. Whereas early research focused on the relevance of MA as a risk factor, i.e., directly relating to the pathophysiology of the mechanism for kidney disease progression, data over the past decade has focused on its role as a predictor of

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CV disease [5]. As will be seen in this chapter, MA is a risk marker, i.e., it does not contribute to the pathophysiology of disease but is, rather, an indicator of underlying vascular inflammation. The proposed mechanisms primarily involve local injury to the vascular smooth muscle and endothelial cells through oxidative stress and subsequent changes in nitric oxide. These changes in vascular integrity are associated with an increase in a variety of proinflammatory cytokines, culminating in cell proliferation and increase in vascular permeability.

9.2 Definition of Microalbuminuria

According to the current definition, the term MA refers to urinary albumin excretion (UAE) of >30 mg/day and in the range of 20–200 mg/min (30–299 mg/day) [6]. Evidence from epidemiological studies suggest that UAE should be viewed as a continuum of risk for CV diseases, with the lower the UAE the lesser the CV disease risk [7].

There are three methods of collecting and measuring urinary albumin: (a) measuring albumin concentration or albumin creatinine ratio (UACR) in a random spot urine specimen; (b) measuring albumin concentration and simultaneously measuring creatinine clearance in a 24-h urinary collection; (c) measuring albumin levels in a timed urinary collection (e.g., overnight or over 4 h). Spot collection of morning urine requires knowledge of the factors that affect UACR measurement [8], (Table 9.1). UAE range is 25% lower during sleep than when awake. Furthermore, MA can vary daily from 40% to 100%. These largely biological variations are due to inflammation associated with a variety of factors ranging from high lipid or sodium ingestion to infections or underlying worsening of atherosclerosis. The American Diabetes Association recommends that at least two morning urine specimens collected within 3 months should be abnormal to consider patients as having MA [8]. Point of care testing is now available using a spot urine to assess presence and magnitude of MA and is used in screening programs around the world [9, 10].

Table 9.1 Factors that affect measurement of urine albumin and creatinine

Albumin excretion	Creatinine excretion
Blood pressure	Muscle mass
Salt intake	Race
Volume status	Gender
Fasting versus nonfasting sample	
Time of day	

9.3 Prevalence of Microalbuminuria

MA occurs in 30% of middle-aged individuals with type 1 or 2 diabetes and in 10–15% of individuals without diabetes [11]. Variations in prevalence are primarily due to patient selection or factors that affect albumin excretion (Table 9.2).

Table 9.2 Factors known to influence the development of microalbuminuria

Elevated blood pressure (systolic, diastolic, mean)
Increased body mass index
Insulin resistance (hyperinsulinemia)
Endothelial dysfunction
Decrease in high density lipoprotein levels
Smoking
Salt sensitivity
Increased age
DD-ACE genotype

9.4 Pathophysiology of Microalbuminuria

MA is more a marker than a pathogenic factor to the atherosclerotic process. There are several proposed hypotheses connecting MA to increase CV disease risk. All patients with MA have an elevated transcapillary escape rate of albumin. MA is more likely to be present if the patient has known CV disease risk factors, such as hypertension, hyperlipidemia, insulin resistance, and obesity. Inflammation markers, such as high-sensitivity C-reactive protein (hs-CRP), fibrinogen, interleukin 6 (IL-6); and indicators of procoagulatory state, such as von Willebrand factor (vWF), are usually elevated if MA is present [3, 12].

Whereas the fundamental mechanisms of vascular injury leading to MA are similar between individuals with and without diabetes, there are some differences. In patients without diabetes, generalized vascular leakiness is caused by alterations in defects in barrier membranes. These alterations are largely triggered by increased microvascular pressure, which leads to injury to the endothelium [12]. The resultant defect in endothelial permeability permits lipid influx into the vessel wall, contributing to atherosclerotic changes. Many other acute and chronic illnesses that mediate immune responses, including complement activation, macrophages, neutrophils, and endothelial stimulation, all contribute to this diverse inflammatory injury [12] (Fig. 9.1). In individuals with diabetes, albumin is glycated and associated with generation of

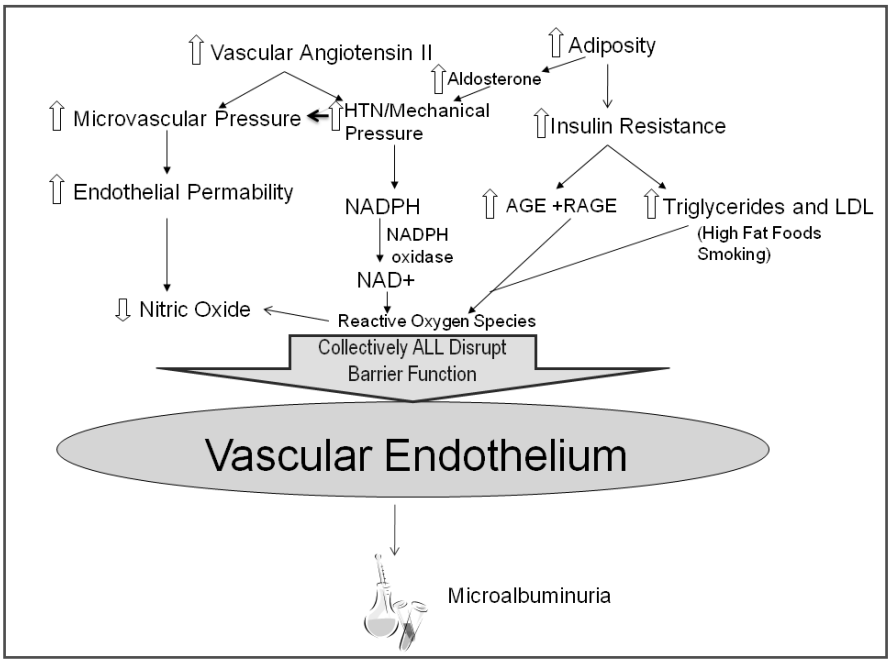

Fig. 9.1 Factors in the pathogenesis of increased endothelial permeability. *AGE,* advanced glycation end products; *HTN,* hypertension; *LDL,* low-density lipoprotein; *NAD+,* nicotinamide adenine dinucleotide; *NADPH,* nicotinamide adenine dinucleotide phosphate, reduced; *RAGE,* receptor for AGE

reactive oxygen species (ROS). In addition, many other factors, such as advanced glycation end products, ROS, and other cellular toxins contribute to vascular injury. Once such injury occurs, the effects of pressor hormones, such as angiotensin II, are magnified, resulting in faster progression of vascular injury. The end result is direct injury to epithelial cells of the glomerular membrane, vascular smooth muscle cells, and the podocyte basement membrane.

9.5 Cardiovascular Risk

9.5.1 Hypertension

Patients with hypertension are more likely to have MA than those with normal blood pressure. Likewise, people with MA are at greater risk for developing hypertension. The Nurses' Health Study showed an independent association between the level of urinary albumin and the development of hypertension in individuals who did not have diabetes or hypertension. This association between albuminuria level and risk of

hypertension extended into the high normal range, i.e., <25 mg/g [13].

The degree of MA correlates with the blood pressure level measured by either clinic or 24-h ambulatory blood pressure monitoring. In the Microalbuminuria: A Genoa Investigation on Complications (MAGIC) study, hypertensive patients with high normal levels of MA, in the range of 28–30 mg/day, had higher diastolic and mean blood pressure readings than did normoalbuminuric hypertensive patients [14]. Furthermore, the Gubbio Population Study with 1,567 participants revealed that non-diabetic individuals with MA had 18 mmHg higher systolic blood pressure when compared with those without MA [15]. Changes in circadian blood pressure patterns have also been described by Bianchi et al., who observed a blunted or absent nocturnal dipping of blood pressure in hypertensive patients with MA. A study of 63 hypertensive patients demonstrated that patients with a blunted, i.e., <10/5 mmHg or absent nocturnal dipping of blood pressure had higher levels of MA than patients with a normal dipping pattern [16].

9.5.2 Hyperinsulinemia

Insulin resistance and the accompanying hyperinsulinemia form a link between CV disease risk factors of metabolic syndrome and the development of CV disease.

Individuals with MA have lower insulin sensitivity and higher fasting insulin compared with individuals without MA. UAE level and MA prevalence were higher in patients with isolated impaired glucose tolerance than those with impaired fasting glycemia. MA increases as glycemic control worsens, and this effect is seen even in patients without frank diabetes. There is a significant graded relationship between the number of metabolic syndrome components and the corresponding prevalence of MA. These findings suggest that MA is strongly related to the components of metabolic syndrome and hence is a part of the International Diabetes Federation definition of metabolic syndrome [12, 17].

Not all the studies confirm an independent association between insulin resistance and MA. A 13-year follow-up study of individuals with long-standing hypertension demonstrated that MA did not predict increased insulin resistance, impaired insulin secretion, or increased traditional or novel markers of inflammation and endothelial dysfunction. Rather, it was associated with the rate of decline in kidney function [18]

Despite these disparate results, elevated insulin levels are associated with increased vascular inflammation, and hence the connection with MA in those with and without diabetes.

9.5.3 Endothelial Dysfunction

Endothelial dysfunction represents a common final pathway for macro- and microvascular diseases. Increased permeability of the endothelium allows atheroscle-

rotic lipoprotein particles [oxidized low-density lipoprotein (LDL) and others] to penetrate into the vessel wall. This influx generates oxygen free radicals, decreases nitric oxide production or bioavailability, and induces vasoconstriction. The end result of this cascade of events is the creation of an ideal environment for development of atherosclerotic plaques. Among the endothelial-dependent regulatory mediators, vWF remains the most extensively studied potential marker of endothelial injury. Plasma levels of patients with vWF are higher in those with essential hypertension and MA when compared with patients with normal albumin excretion. Furthermore, vWF has been associated with occlusive thrombosis, so increased plasma levels associated with vWF may directly contribute to the enhanced CV disease risk seen in those with endothelial dysfunction and MA [3, 12].

MA is associated with carotid atherosclerosis [19], and patients with MA have increased intima-media thickness of the carotid artery when compared with patients with normoalbuminuria. There is a linear relationship between both UACR and plaque initiation and UACR and plaque growth. The effect was similar for initiation of novel atherosclerosis (no plaque at baseline) and progression of already established atherosclerosis [20]. Vascular retinal changes and CV disease are also more common in hypertensive patients with MA than in normoalbuminuria patients. Interestingly, the incidence of hypertensive retinopathy is lower if MA is regressed with treatment. This vascular remodeling may be related to endothelial dysfunction [12]. MA as a marker of endothelial damage is also associated with cognitive decline in older people with impaired glucose tolerance, and this is mediated by large arterial stiffening [21].

9.5.4 Dyslipidemia

The relationship between MA and abnormalities in serum lipoproteins is well documented. These lipid abnormalities include higher levels for LDL-cholesterol, triglycerides, and lipoprotein A [Lp(a)]. The abnormality seen most consistently in all cohorts is a low high-density lipoprotein (HDL)-cholesterol. Loss of the protective effects of HDL-cholesterol together with elevations of proatherogenic lipoproteins has a significant contribution in MA development. A cross-sectional analysis showed that progressive increase in albuminuria was associated with elevations in intermediate-density lipoproteins and small, dense LDL particles. Elevations of atherogenic Lp(a) maintained a correlation with MA in a multivariate analysis of patients with essential hypertension. Although the picture is not entirely clear, data supports the notion that the mechanism of increased CV disease risk in patients with MA is in part related to an overall adverse lipid subfraction profile [12].

9.5.5
C-reactive Protein

Higher hs-CRP levels predict higher risk for CV events in patients with unstable angina and acute myocardial infarction. Levels of hs-CRP are elevated in patients with MA, supporting the concept that MA is a marker for vascular inflammation [22].

9.5.6
Genetic Associations

A variety of genetic polymorphisms are believed to contribute to the development of MA in patients with hypertension with or without diabetes. Elevated activity of the renin–angiotensin system (RAS) is an independent risk factor for CV disease. The United Kingdom Prospective Diabetes Study (UKPDS) and others demonstrated that angiotensin-converting enzyme (ACE) gene polymorphism is associated with MA. Patients with the DD-ACE genotype show an increased albumin excretion rate, but it is unclear as to whether this genotype alone is enough to cause MA [12, 23, 24].

9.5.7
Vascular Risk Assessment

MA is associated with several established adverse CV disease risk profiles [2, 4, 25]. In one report of 680 patients, the presence of hyperhomocysteinemia, a risk factor for atherosclerosis, was significantly associated with the level of MA. This was independent of type 2 diabetes or hypertension. The association of MA with an abnormal prothrombotic profile may not be surprising, as some conditions, such as endothelial dysfunction, are hypothesized to be a common link between both MA and atherosclerotic CV disease. MA also has an association with elevated brain natriuretic peptide (BNP). A study of 537 patients showed that elevated levels of both MA and BNP were predictors of overall mortality and first CV event. These relationships held even when plugged into the same model, and both factors were better predictors of CV disease mortality and events than was CRP [12].

9.6
Prognostic Implications

Data from large population studies indicate that MA is an important risk marker for CV disease and early mortality in patients with or without diabetes and/or hypertension. This is discussed in Chap. 8. The risk of myocardial infarction, stroke, CV disease mortality, and all-cause mortality increases as MA levels increase, starting at levels below the traditional normal definition for MA [7].

9

Yudkin and colleagues first reported an association between albumin excretion and higher risk of CV disease mortality and morbidity in nondiabetic individuals. Their report was followed by several large cohort studies and database analyses that solidified the relationship between higher UAE and adverse CV disease outcomes[26]. Agrawal et al. reported a significantly higher prevalence of coronary artery disease, stroke, and peripheral vascular disease among people with MA [25]. The prevalence of CV disease was 31%, 6%, and 7%, respectively, in nondiabetic hypertensive patients with MA compared with 22%, 4%, and 5%, respectively, without MA. In the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study the risk of ischemic heart disease was fourfold higher in nondiabetic patients with untreated or prehypertension [27]. An increase in overall mortality was seen in the nondiabetic subgroup of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, which showed that the primary composite endpoint of death, fatal and nonfatal stroke, and fatal and nonfatal myocardial infarction due to CV disease increased as albuminuria increased. Moreover, the risk was continuous over the range of albuminuria [4]. This relationship with MA levels and CV disease risk was also true in an analysis of the Nordic Diltiazem (NORDIL) study in hypertensive patients followed for 4.5 years [28]. These observations were also found in the European Prospective Investigation into Cancer–Norfolk (EPIC-Norfolk) study of more than 20,000 individuals from the general population in the United Kingdom [29], and in the largest general-population-based study to date – The Prevention of Renal and Vascular End-stage Disease Intervention (PREVEND) trial involving more than 40,000 residents of Groningen in The Netherlands [30]. The PREVEND trial found that the increase in CV disease mortality was independent of effects of other CV disease risk factors in the presence of MA. Lastly, the Heart Outcomes Prevention Evaluation (HOPE) study also provides a strong rationale for MA to be a risk marker for CV disease. Among the more than 9,000 participants in this study, the presence of MA increased the relative risk of the primary aggregate end-point (myocardial infarction, stroke, or death due to CV disease) in patients with or without diabetes (1.97 and 1.61, respectively) [2].

The level at which CV disease risk starts in the context of MA has been questioned. Data from the third Copenhagen City Heart Study involving more than 2,700 men and women showed that low MA levels – well below the conventional definition of MA, i.e., 5 μg/min – were associated with a twofold increased risk of coronary heart disease and death [31]. Similarly, the Nord-Trøndelag Health Study (HUNT) that included 2,000 healthy individuals from Norway found that MA was associated with a twofold increased risk in all-cause mortality starting at albuminuria levels in the normal range of 0.76 mg/mmol [32]. In this context, data from the 9-year follow-up of the PREVEND trial demonstrate a clear relationship between CV disease risk and albuminuria level into the normal range [33].

In contrast, not all data in people without diabetes consistently shows this increased CV disease risk with MA. A prospective 3.3-year follow-up study of more than 300 treated hypertensive men showed no increased CV disease risk. In this study, although target organ damage was more common among patients with MA, it was macroalbuminuria (>300 mg/day) that was associated with a poor prognosis

[34]. In patients with diabetes, however, the relationship between CV disease risk and MA level is more consistent. A meta-analysis showed that the overall odds ratio is 2.4 for total mortality and 2.0 for CV disease morbidity and mortality in type 2 diabetes if MA is present. Other studies observed that individuals with MA and type 2 diabetes have an approximate all-cause mortality of 8% and CV disease mortality of 4% annually. These values are up to four times higher compared with patients without MA [12].

9.7 Chronic Kidney Disease

Whereas elevated levels of albuminuria, i.e., >300 mg/day, predict kidney failure [33], MA is not a marker of kidney disease but of worsening endothelial dysfunction. Increases in MA over time despite good systolic blood pressure control, i.e., <130 mmHg, however, is indicative of worsening kidney function, and occult causes of inflammation, such as collagen vascular disease, or high sodium intake should be sought.

Only one clinical trial evaluated true kidney disease progression in people with MA: the Appropriate Blood Pressure Control in Diabetes (ABCD) trial. After a 7-year follow-up, there was no relationship between changes in MA and outcomes, as blood pressure was well controlled in both groups. Many other studies have used MA development as a marker of kidney disease, but these studies did not further our knowledge of disease prevention at this early stage of nephropathy. Thus, MA should be viewed as a CV disease risk marker, and progression into the macroalbuminuria range in the presence of appropriate treatment should be a red flag that kidney disease is clearly present.

In contrast to patients with MA, those who progress to proteinuria, i.e., >300 mg/day of urinary protein, clearly have kidney disease and are at high risk to progress to end-stage renal disease. Moreover, the magnitude of proteinuria is a predictor of kidney disease progression [35]. This concept is further supported by a cross-sectional study that evaluated the risk of kidney disease progression in the presence and absence of albuminuria in more than 4,400 people [36]. This study showed that albuminuria levels >200 mg/day were highly predictive of kidney disease progression, whereas glomerular filtration rate (GFR) levels were more predictive of CV disease risk.

It is important to note that *all* clinical outcome trials of nephropathy progression, positive for some therapeutic intervention, recruited patients with proteinuria >300 mg/day [37] (Table 9.3). Moreover, all trials in which patients showed the slowest nephropathy progression demonstrated a >30% reduction in proteinuria, usually with RAS blockers [38, 39] (Table 9.4). Thus, whereas the presence of MA is not indicative of kidney disease, its increase in the presence of blood pressure control treatment is a poor prognostic sign relative to kidney disease progression. Therefore, monitoring this laboratory marker should occur once or twice annually [40].

Table 9.3 Summary of long-term (≥3 years) outcome trials focused on progression to end-stage renal disease in people with advanced nephropathy

Patients without diabetes	Patients with diabetes
MDRD [41]	Captopril Trial [42]
AIPRI [43]	Bakris GL [44]
REIN [45]	IDNT [46]
AASK [47]	RENAAL [48]
REIN-2 [49]	ABCD [50][a]
Hou et al [51]	

AASK, African American Study of Kidney Disease; *ABCD,* Appropriate Blood Pressure Control in Diabetes; *AIPRI,* Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency Study; *IDNT,* Irbesartan in Diabetic Nephropathy Trial; *MDRD,* Modification of Diet in Renal Disease; *REIN,* Ramipril Efficacy In Nephropathy; *RENAAL,* Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

[a]Only the ABCD trial was negative for the primary outcome but had a cohort of patients with normoalbuminuria or microalbuminuria and glomerular filtration rates (GFR) >80 ml/min at baseline. All other studies had proteinuria >300 mg/day at baseline and GFR values well below 50 ml/min

Table 9.4 Summary of long-term outcome trials focused on proteinuria reduction in relation to advanced nephropathy progression

Increased time to dialysis (30-35% proteinuria reduction)	No change in time to dialysis (no proteinuria reduction)
Captopril [42]	DHPCCB arm–IDNT [46]
AASK [52]	DHPCCB arm–AASK [52]
RENAAL [48]	
IDNT [46]	

AASK, African American Study of Kidney Disease; *DHPCCB,* dihydropyridine calcium channel blocker; *IDNT,* Irbesartan in Diabetic Nephropathy Trial; *RENAAL,* Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

9.8 Therapeutic Intervention and Cardiorenal Disease Risk Reduction

The same factors that reduce the risk of nephropathy and CV disease also reduce the risk of developing MA, or if MA is already present, will increase the likelihood of normalization. Specifically, lifestyle modifications, including <3 g/day sodium diet, exercise, and reduced protein intake to 0.8 g/kg per day will reduce the risk of MA development or reduce the levels, if already present. Tight glycemic control with a glycated hemoglobin (HbA_{1c}) <7% will also reduce the amount of MA.

The most effective and reliable way to reduce CV events and preserve kidney function is achieving a blood pressure goal <130/80 mmHg in patients with macroalbuminuria, regardless of type 2 diabetes [6]. RAS blockers should be used as antihypertensive medications in patients with MA, as they also help decrease the amount of albumin in the urine.

The Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO)-HOPE substudy demonstrated that MA reduction does lead to improved CV disease outcomes. Among the 1,140 patients with diabetes and MA, patients treated with ramipril had a 20% lower UACR, accompanied by a 21% reduction in the primary outcome (myocardial infarction, stroke, or death due to CV disease) and a lower risk of developing overt nephropathy. These effects were independent of baseline MA levels [53]. Similar results were seen in LIFE study, which showed that the use of losartan decreased the occurrence of death, nonfatal myocardial infarction, and nonfatal stoke due to CV disease, and 20% of this effect was related to MA reduction [3, 54].

In people with early-stage nephropathy, i.e., stages 2 and 3a (GFR = 60–89 ml/min) with MA, there is no clear benefit on kidney disease progression by reducing MA independent of lowering blood pressure. This was exemplified not only in the ABCD trial but also in analyses in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) in which events regarding kidney disease progression were driven by patients with albuminuria and not those with normoalbuminuria or MA [50, 55].Thus, blood pressure lowering is the key goal for all patients with early-stage nephropathy and normoalbuminuria or MA.

9.9 Conclusions

Recent advances have allowed us a greater understanding of the epidemiology, pathophysiology, and clinical significance of MA among individuals with or without diabetes and hypertension. MA is clearly associated with increased CV disease risk and a higher prevalence of diabetic complications. Increase in MA when blood pressure and other risk factors are controlled portends a poor prognosis for kidney disease outcomes over time. Thus, annual MS measurement should be done in high-risk patients, such as those who are obese, have diabetes, or have other CV disease risk factors. Achieving target blood pressure should be the priority in treating patients with MA, and strong consideration should be given to using agents that block the RAS, such as ACE inhibitors and angiotensin receptor blockers (ARBs) as part of the treatment regimen, as they reduce albumin excretion to a greater extent than just lowering blood pressure. It must be kept in mind, however, that maximal antialbuminuric effects will not be achieved with these agents unless a low sodium diet is strictly followed.

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Cardiometabolic Syndrome

10

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Abstract Cardiometabolic syndrome is a common condition that is increasing in prevalence in the USA and developing nations. Epidemiological studies indicate a strong association between cardiometabolic syndrome and subsequent risks for diabetes and cardiovascular events. Accumulating evidence suggests it may also be a risk factor for incident chronic kidney disease (CKD) and cardiovascular events in individuals with pre-existing CKD. In studies of nondiabetic individuals, cardiometabolic syndrome was associated with a 30–100% increased risk for incident CKD. Among individuals with advanced CKD, cardiometabolic syndrome was associated with >100% increased risk for cardiovascular events, but findings in individuals with earlier stages of CKD were not consistent. Furthermore, the clinical utility of this syndrome and, in particular, its role in risk prediction, remains uncertain. Whereas the syndrome appears to be of value in identifying nondiabetic individuals at risk for developing cardiovascular disease (CVD) and CKD, it is unclear whether the diagnosis of cardiometabolic syndrome carries specific therapeutic implications. At present, most guidelines recommend therapies targeted at lifestyle modification and treatment of individual risk factors, whereas the role of pharmacological therapies targeting insulin resistance needs further study

Keywords: Cardiometabolic syndrome • Chronic kidney disease • Cardiovascular disease

10.1 Introduction

Cardiometabolic syndrome has been described as a clustering of common clinical and laboratory features that together confer a high risk for diabetes, cardiovascular events and cardiovascular-event mortality. The syndrome is highly prevalent in both

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developing and industrialized nations, with prevalence estimates ranging from 9–17% in China to 34% in the United States. The parallel increase in the worldwide prevalence of obesity, cardiometabolic syndrome, and chronic kidney disease (CKD) has sparked great interest in the role of cardiometabolic syndrome as a novel risk factor for both cardiovascular disease (CVD) and CKD. This chapter reviews the concept and definition of cardiometabolic syndrome, its role in CKD development and progression, and as a cardiovascular risk factor in CKD, and its clinical application in risk prediction and risk reduction.

10.2 Definition and Origins of Cardiometabolic Syndrome

The pathologic origins of cardiometabolic syndrome – also known as syndrome X, insulin-resistance syndrome, and metabolic syndrome – its definition, and its clinical utility are the subject of great debate. In 1988, Reaven postulated that insulin resistance and resulting hyperinsulinemia created a predisposition to a cluster of clinical conditions consisting of hypertension, atherogenic dyslipidemia, and impaired glucose tolerance, and thus was the underlying cause for increased CVD risk [1]. Since then, most authorities have focused on insulin resistance as the core unifying feature of this syndrome. Others have speculated that obesity, and abdominal obesity in particular, is sufficient to cause clinical manifestations of cardiometabolic syndrome independent of insulin resistance.

To facilitate recognition of cardiovascular risk associated with cardiometabolic syndrome and encourage research into cardiometabolic syndrome and insulin resistance, in 1998 the World Health Organization (WHO) proposed the first internationally accepted definition of metabolic syndrome. The International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) followed suit (Table 10.1) [2–6]. NCEP ATP III criteria are the most widely used in epidemiological studies, and diagnosis requires three of the following five criteria (Table 10.1):

- Impaired fasting glucose
- Central obesity
- Hypertension
- Elevated triglycerides
- Reduced high-density lipoprotein cholesterol (HDL)

Microalbuminuria is included as a criterion in the WHO definition but not in other definitions. Many authorities also recognize cardiometabolic syndrome as a proinflammatory and prothrombotic state, although these features are not included in the formal definition.

Obesity, physical inactivity, advancing age, and genetic factors are among the primary factors identified as causes of cardiometabolic syndrome. The mechanisms underlying the clinical manifestations of this syndrome involve a complex interplay between multiple organs reflecting, at its core, disordered energy homeostasis.

Table 10.1 Definitions of the cardiometabolic syndrome

	World Health Organization [4, 5]	NCEP Adult Treatment Panel III [2, 3]	International Diabetes Federation [6]
Diagnostic criteria	Glucose criteria plus two additional criteria	Three of the following five criteria	Central obesity plus two additional criteria
Glucose	Type 2 diabetes, fasting glucose ≥100 mg/dl or insulin resistance (fasting insulin in top 25% of nondiabetic population)	Fasting glucose ≥100 mg/dl	Fasting glucose ≥100 mg/dl *or* type 2 diabetes
Central obesity	Waist-to-hip ratio: >0.90 in men >0.85 in women *or* BMI >30 kg/m^2	Waist circumference: >102 cm in men >88 cm in women	Ethnicity-specific waist circumference cut points *or* BMI >30 kg/m^2
Blood pressure	≥140/90 mmHg	≥130/85 mmHg or treatment for hypertension	Systolic ≥130 mm Hg; diastolic ≥85 mm Hg; *or* treatment for hypertension
Triglycerides	≥150 mg/dl *or*	≥150 mg/dl	≥150 mg/dl or specific treatment for this lipid abnormality
HDL	<35 mg/dl in men <39 mg/dl in women	<40 mg/dl in men <50 mg/dl in women	<40 mg/dl in men <50 mg/dl in women *or* specific treatment for this lipid abnormality
Microalbuminuria	Urinary albumin excretion rate >20 μg/min *or* albumin-to-creatinine ratio ≥30 mg/g	Not applicable	Not applicable

BMI, body mass index; *HDL,* high-density lipoprotein; *NCEP,* National Cholesterol Education Panel

In models of obesity-initiated cardiometabolic syndrome, expansion of abdominal adipose tissue drives an interconnected sequence of events, including hepatic gluconeogenesis, reduced skeletal muscle glucose uptake, and pancreatic insulin release, which in turn promote further lipogenesis and contribute to insulin resistance.

10.3 Cardiometabolic Syndrome and CKD Risk

Because hypertension is a core feature of cardiometabolic syndrome and diabetes is a common consequence, there is considerable debate as to whether cardiometabolic syndrome truly represents a novel risk factor for CKD. The following sections review epidemiological data implicating cardiometabolic syndrome as an independent risk factor for microalbuminuria and CKD development and progression.

10.3.1 Microalbuminuria

Most studies evaluating the association of metabolic syndrome with microalbuminuria have been cross-sectional. Using data from the third National Health and Nutrition Examination Survey (NHANES III), several groups reported a two- to fourfold increased odds of microalbuminuria in participants with the cardiometabolic syndrome, though some of these studies included diabetic patients [7, 8]. Using a modified definition of metabolic syndrome, Hoehner et al. reported a twofold increased odds of microalbuminuria among nondiabetic Native Americans [9]. Similarly, Mykkanen et al. reported a strong association between reduced insulin sensitivity or higher fasting insulin concentrations with a higher odds of microalbuminuria among nondiabetic adults [10]. Lucove et al. evaluated the association of metabolic syndrome with the risk of incident microalbuminuria in a cohort of 1,484 Native Americans without baseline diabetes. After a mean of 6.5 years of follow-up, those with the metabolic syndrome had a 30% increased risk for microalbuminuria [11].

10.3.2 CKD

A number of large, prospective studies have evaluated the association of cardiometabolic syndrome with the risk of CKD (Table 10.2). Kurella et al. studied 10,096 nondiabetic individuals with an estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m^2 participating in the Atherosclerosis Risk in Communities (ARIC) study [12]. Incident CKD was defined as eGFR <60 ml/min/1.73m^2 at follow-up.

Table 10.2 Prospective studies of cardiometabolic syndrome and risk of chronic kidney disease (CKD)

Author	Study population	Number of individuals	Average years of follow up	Outcome	Adjusted odds ratio (95% CI)
Ninomiya et al [13]	Japanese adults age ≥40 without CKD	1,440	5	eGFR <60 ml/min/1.73m^2 at follow-up	2.08 (1.23–3.52)
Ryu et al [14]	Korean men ages 30-59 without diabetes, hypertension, proteinuria or CKD	10,685	3.8	eGFR <60 ml/min/1.73m^2 at follow up	1.99 (1.46–2.73)
Rashidi et al [15]	Iranian adults age ≥18 without diabetes or CKD	4607	3	CrCl <60 ml/min/1.73m^2 at follow up	1.88 (1.26–2.80)
Kitiyakara et al [16]	Thai adults ages 35-54 without CKD	2067	12	eGFR <60 ml/min/1.73m^2 at follow up	1.62 (1.00–2.61)
Kurella et al [12]	US adults ages 45-64 without diabetes or CKD	10,096	9	eGFR <60 ml/min/1.73m^2 at follow up	1.43 (1.18–1.73)
Lucove et al [11]	Native Americans ages 45-74 years without CKD	1484	6.5	eGFR <60 ml/min/1.73m^2 at follow up	1.3 (1.0–1.6)
Lea et al. [17]	Non-diabetic African Americans ages 18-70 with hypertension and eGFR 20-65 ml/min/1.73m^2	842	4.1	eGFR decrease by 50% or by 25 ml/min/1.73m^2, or development of ESRD	1.31 (1.03–1.70)
Luk et al [18]	Chinese adults with type 2 diabetes and without CKD	5,829	4.6	eGFR <60 ml/min/1.73m2 at follow up or hospitalization for CKD event	1.31 (1.12–1.54)

CI, confidence interval; *CrCl,* creatinine clearance; *eGFR,* estimated glomerular filtration rate; *ESRD* end-stage renal disease

After 9 years of follow-up, individuals with metabolic syndrome had a significant 43% increased odds of incident CKD after adjustment for age, sex, race, body mass index, cardiovascular disease, and lifestyle factors. Similar findings were noted among individuals without baseline hypertension. When the analyses further accounted for the development of diabetes and hypertension during follow-up, the results were attenuated but remained statistically significant [odds ratio (OR) 1.24, 95% confidence interval (CI) 1.01–1.51]. When individuals were categorized by quintiles of insulin resistance (as measured by the homeostasis model assessment) rather than the presence or absence of cardiometabolic syndrome, more severe insulin resistance was associated with a greater risk for CKD. Ryu et al. evaluated these associations in a study of 10,685 Korean men without diabetes, hypertension, CKD, or albuminuria at baseline [14]. After a mean 3.8 years of follow-up, participants with cardiometabolic syndrome had a substantially higher risk for CKD (OR 1.99, 95% CI 1.46–2.73). Interestingly, the association remained robust even after accounting for measured insulin resistance. These results have been replicated in a number of populations with diverse genetic backgrounds and dietary habits [13, 15, 16, 18], with a few exceptions. In a study of nondiabetic Native Americans, the significant risk of CKD in persons with the cardiometabolic syndrome was explained by the development of diabetes during follow-up [11]. Few large studies have evaluated the association of cardiometabolic syndrome with CKD progression. In the African American Study of Kidney Disease (AASK) conducted in nondiabetic hypertensive African Americans, the association between cardiometabolic syndrome and CKD progression was diminished and no longer significant after controlling for baseline proteinuria [17].

In sum, studies in diverse nondiabetic populations suggest cardiometabolic syndrome is associated with a 30–100% increased risk for CKD development independent of baseline traditional CKD risk factors such as age, race, and hypertension. However, the magnitude of risk varies considerably across different populations after accounting for the development of diabetes and hypertension, raising questions as to whether the risk of CKD is mediated by known (e.g., diabetic or hypertensive nephropathy) or novel pathways associated with aspects of insulin resistance and/or obesity. There is also some evidence linking cardiometabolic syndrome with the development of microalbuminuria, but data are sparse regarding its role in nondiabetic CKD progression.

10.4 Proposed Mechanisms of CKD Risk in Cardiometabolic Syndrome

Several excellent reviews of the mechanisms linking cardiometabolic syndrome with kidney injury and CKD have been published [19, 20]. In the following sections we briefly review some of these mechanisms, focusing on pathways independent of hypertension and diabetes.

10.4.1 Pathologic Findings

Whereas the pathologic findings in diabetic nephropathy and obesity associated glomerulopathy are well known, less is known about kidney pathologic findings observed in cardiometabolic syndrome. A recent study reported a high prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis in patients with cardiometabolic syndrome and normal serum creatinine concentrations compared with matched controls [21]. Interestingly, in contrast to obesity-associated glomerulopathy, glomerular volume was not different between those with and without cardiometabolic syndrome.

10.4.2 Lipotoxicity

Lipotoxicity is the cellular overload of nonesterified free fatty acids (FFA) and triglycerides (TG). Several lines of evidence suggest a role for renal lipotoxicity as a mechanism of injury in CKD associated with cardiometabolic syndrome. For example, in one set of studies, overexpression of the lipid regulatory gene sterol regulatory element binding protein led to glomerulosclerosis, tubulointerstitial injury, and lipid accumulation, whereas mice lacking this gene were protected from these effects. Overload of FFA has been associated with an increase in reactive oxygen species and renal endothelial dysfunction. In other studies, TG-rich lipoproteins have been shown to stimulate mesangial cell proliferation and inflammatory cytokine expression. Data from human studies also support a role for lipid overload and lipotoxicity in CKD pathogenesis. For example, post hoc analyses of several statin trials suggest that statins reduce the rate of CKD progression, though it should be noted that these studies largely excluded individuals with moderate or severe CKD. In a study of 2,150 Japanese individuals with metabolic syndrome, polymorphisms in the apolipoprotein E gene were associated with CKD [22].

10.4.3 Inflammation

Insulin is an anti-inflammatory hormone; thus, resistance to insulin action is thought to promote a state of inflammation. Furthermore, visceral adipose tissue is now recognized as an important source of cytokine production and secretion. In patients with cardiometabolic syndrome, levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP) are elevated, whereas levels of anti-inflammatory cytokines, such as adiponectin, are reduced. Several inflammatory cytokines have been implicated in CKD development or progression. For example, leptin is an adipokine that regulates appetite and energy expenditure and has also been shown to increase insulin sensitivity in various tis-

sues. Leptin receptors are also expressed in the kidney. Administration of recombinant leptin leads to glomerulosclerosis in animal models, and it may also increase sympathetic nerve trafficking and sodium retention, leading to hypertension. TNF-α is a proinflammatory cytokine that has been shown to promote kidney damage in models of glomerulonephritis and acute renal failure but has not yet been studied in obesity- or cardiometabolic-syndrome-associated CKD. Other cytokines, such as IL-6, CRP, and adiponectin, have been implicated in progression of atherosclerosis and may also play a role in promoting kidney injury.

10.4.4 Activation of the Renin–Angiotensin System (RAS) Axis

Activation of the renin–angiotensin system (RAS) axis is a widely studied factor contributing to kidney injury, and an extensive review of these mechanisms is beyond the scope of this article. Increased levels of renin, angiotensinogen, angiotensin-converting enzyme (ACE), and aldosterone in particular have been noted in obese individuals, despite the presence of sodium retention. Insulin resistance and resulting hyperinsulinemia are thought to stimulate the sympathetic nervous system, in turn activating the RAS axis. A direct role of visceral fat is also a suspected trigger, possibly by stimulating synthesis of RAS proteins.

10.4.5 Obesity and Obesity-Related Hemodynamic Factors

Some authors speculate that CKD risk in persons with cardiometabolic syndrome is attributable to obesity rather than directly related to the syndrome itself. Obesity has been associated with hyperfiltration, proteinuria, glomerulomegaly, and – in extreme cases – focal segmental glomerulosclerosis. Furthermore, large epidemiological studies have demonstrated that being overweight and or obese is associated with an increased risk for CKD and end-stage renal disease (ESRD), even after adjustment for diabetes and hypertension. Hyperfiltration from nephron mismatching, either as a consequence of increased body mass and excretory load or as a consequence of intrauterine growth restriction and reduced nephron number, has been suggested as a mechanism of obesity-associated CKD. Other authors postulate that hypofiltration as a consequence of pulmonary hypertension and right ventricular dysfunction may play a role in renal injury in the setting of obesity.

10.4.6 Hyperuricemia

An emerging area of study is that linking increased dietary fructose consumption with an increase in uric acid levels, which, in turn, is speculated to contribute to car-

diometabolic syndrome and CKD development [23]. Epidemiological studies have noted associations between hyperuricemia and CKD in studies of the general population and in hypertensive or diabetic individuals. Furthermore, lowering uric acid levels has been reported to reduce blood pressure and slow CKD progression. These findings are supported by animal data demonstrating that hyperuricemia promotes CKD progression in a remnant kidney model and a model of cyclosporine nephrotoxicity. A high-fructose diet has been linked with microalbuminuria, and oral fructose feeding in kidney transplant recipients induces acute increases in uric acid and serum lipid levels. These intriguing findings need confirmation in additional studies.

10.5 Cardiometabolic Syndrome and CVD Risk

10.5.1 Studies in the General Population

There is strong epidemiological evidence linking cardiometabolic syndrome with an increased risk for CVD events and mortality in the general population. These studies evaluated risk for CVD events in a number of settings, including in middle-aged and elderly populations, in those with and without diabetes, and in those with and without prevalent CVD. For example, a 20-year follow-up study of middle-aged British men without prevalent CVD or diabetes showed that cardiometabolic syndrome (using a modified NCEP ATP III definition) was associated with 60% higher risk of CVD compared with men without cardiometabolic syndrome after adjusting for known CVD risk factors [24]. As in studies of CKD risk, a dose-dependent effect was reported, with higher risk associated with an increasing number of cardiometabolic syndrome components. These findings appear to be consistent across a range of CVD endpoints, including myocardial infarction, peripheral vascular disease events, and stroke.

10.5.2 Studies in CKD Populations

As reviewed in the previous sections, cardiometabolic syndrome contributes to CKD development. Furthermore, some studies suggest that uremia exacerbates insulin resistance, although the mechanisms remain unclear. Thus, individuals with CKD have a substantially higher prevalence of cardiometabolic syndrome compared with individuals in the general population. Certain CKD populations, such as patients on peritoneal dialysis or kidney transplant recipients, may have an especially high prevalence of cardiometabolic syndrome (up to 50%), most likely due to weight gain induced by these therapies. Does the high prevalence of cardiometabolic syndrome in CKD patients explain the increased CVD risk?

An association between cardiometabolic syndrome and CVD risk has been demonstrated in several small studies of persons with advanced CKD. In a study of 183 nondiabetic ESRD patients on hemodialysis, measured insulin resistance was associated with a fourfold increased risk for CVD mortality, even after adjustment for other traditional risk factors, such as age and dyslipidemia [25]. Similar results were seen in a mixed cohort of predialysis participants with stage 4–5 CKD and those on dialysis, as well as in a post kidney transplant population [26, 27].

Studies in populations with milder CKD are conflicting. In 714 ARIC participants with stage 3 CKD, cardiometabolic syndrome was associated with a 40–50% higher risk of CV events and death, similar to results seen in non-CKD populations [28]. In contrast, in a study of 2,696 Danish adults, cardiometabolic syndrome was not associated with an increased risk of all-cause mortality or CVD in participants with a creatinine clearance of < 60 ml/min/1.73m^2 [29]. The Mild and Moderate Kidney Disease Study compared persons with CKD (mean GFR 63 ml/min/1.73m^2) to healthy controls and found that insulin resistance did not predict prevalent or incident CVD [30]. These disparate results may be due to several factors, including small samples, misclassification bias of CKD and insulin resistance, and confounding from malnutrition.

In summary, there is considerable epidemiological data linking cardiometabolic syndrome with CVD events in the general population. Emerging data suggests cardiometabolic syndrome may also be a strong risk factor for CVD events in persons with advanced CKD and ESRD; data are less clear in persons with mild to moderate CKD. Additional prospective studies with larger samples and extended follow-up are needed to clarify these associations.

10.6 Implications for CKD and CVD Risk Prediction and Risk Reduction

10.6.1 Risk Prediction

Whereas many prospective cohort studies demonstrated an association between cardiometabolic syndrome and increased CVD risk, questions remain about how to apply the diagnosis in the clinical setting. One issue is whether cardiometabolic syndrome confers a CVD risk greater than the sum of its individual components. In 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a joint statement on cardiometabolic syndrome, noting: "…there is considerable doubt regarding its value as a CVD risk marker" [31]. Others studies questioned whether cardiometabolic syndrome predicts CVD better than the Framingham Risk Score, noting that the rationale for dichotomizing continuous risk factors is not clear and that the syndrome excludes important CVD risk factors, such as smoking [32, 33]. To our knowledge, no studies have evaluated these issues in CKD or ESRD patients.

10.6.2 Risk Reduction Strategies

Therapeutic implications of diagnosing cardiometabolic syndrome are another area of uncertainty. For example, is the appropriate therapeutic target the putative causes of insulin resistance, such as obesity and physical inactivity; component risk factors, such as hypertension and hyperlipidemia; insulin resistance itself; or an 'all-of-the-above" approach?

Because lifestyle interventions such as weight reduction and increasing physical activity can improve insulin sensitivity and multiple downstream risk factors, these approaches are often recommended as first-line interventions. Multicomponent interventions using lifestyle modification and pharmacologic therapy, such as those used in the Steno-2 trial [34], may be useful models for treating individuals with cardiometabolic syndrome. In the Diabetes Prevention Program, lifestyle modification with diet and exercise was proven effective for reducing diabetes risk, and extrapolation of results suggest they may be very effective for reducing downstream CVD and CKD risk [35]. Recent direct evidence also suggests weight loss may be an effective strategy for reducing CKD and CVD risk. For example, uncontrolled studies report attenuation of hyperfiltration and reduction in albuminuria after bariatric surgery in morbidly obese nondiabetics [36].

Treating hypertension to prevent CVD and CKD is discussed elsewhere in this book and will not be reviewed here. Whereas many guidelines recommend treating hyperlipidemia to prevent CKD progression and CVD events, the optimal agents and appropriate targets remain unclear [37]. Furthermore, whereas data from animal studies and post hoc analyses of cardiovascular trials support a beneficial effect of lipid lowering for preventing CKD and CVD events [38], negative results from two recent statin trials [39, 40] in ESRD patients have called these recommendations into question. Ongoing trials of lipid-lowering agents in patients with CKD may help clarify these questions. Although not a formal criterion for diagnosing cardiometabolic syndrome, a prothrombotic state is noted in individuals with the syndrome. Thus, many authorities recommend low-dose aspirin therapy for middle age or elderly individuals with cardiometabolic syndrome and no other contraindications [3].

Pharmacologic therapy targeting insulin resistance is another potential strategy for treating nondiabetic patients with cardiometabolic syndrome. The effects of thiazolidinedione and/or ACE inhibitor therapy to prevent CVD and CKD events were studied in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, a study of 5,269 nondiabetic individuals with impaired glucose tolerance or impaired fasting glucose and no known CVD or CKD [41]. After a median follow-up of 3 years, rosiglitazone, but not ramipril, reduced the primary outcome of death or incident diabetes. Neither rosiglitazone nor ramipril reduced the secondary composite cardiorenal outcome. Rosiglitazone did reduce the composite renal endpoint by 20% (consisting of progression from normoalbuminuria to either microalbuminuria or proteinuria or from microalbuminuria to proteinuria, a decrease in eGFR of 30%, or renal insufficiency requiring dialysis or transplantation) but also increased the risk of heart failure by sevenfold. Given these findings, the risks and

benefits of thiazolidinediones must be weighed carefully in individual patients before being recommended for CVD and CKD risk reduction.

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Diabetes Mellitus: Is the Presence of Nephropathy Important as a Cardiovascular Risk Factor for Cardiorenal Syndrome?

11

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Abstract Diabetes mellitus is a well established risk factor for cardiovascular diseases (CVD). In addition, a significant proportion of diabetic patients go on to develop nephropathy. Moreover, the presence of nephropathy further increases the risk of CVD in patients with all stages of diabetic nephropathy, including microalbuminuria, macroalbuminuria, and renal failure. The fibrogenic cytokine transforming growth factor beta (TGF-β) and the vascular endothelial growth factor (VEGF) are implicated in the development of cardinal features of diabetic nephropathy, namely, mesangial expansion and albuminuria, respectively. The pathogenesis of CVD in diabetes is multifactorial and can be affected by metabolic factors, such as oxidative stress, glycoxidation, procoagulant states, and inflammation. Furthermore, endothelial dysfunction may lead to simultaneous development and progression of renal and cardiac pathology in diabetes. The risk of microvascular complications can be reduced by intensive glycemic control, whereas cardiovascular benefit is less clear. Intensified intervention involving other vascular risk factors, such as hypertension and dyslipidemia, demonstrated benefits in terms of both macrovascular and microvascular complications. In addition, treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists is associated with a significant reduction in the risk for renal disease progression in diabetes, which parallels the reduced cardiovascular risk. Moreover, changes in microalbuminuria translate into parallel changes in renal and cardiovascular risk. Nephropathy in diabetic patients is, therefore, important in determining the risk for and outcomes from CVD, the improved understanding of the pathogenesis of renal and vascular disease in diabetes, and as a crucial factor in planning a comprehensive treatment approach to reducing CVD morbidity and mortality in diabetic patients.

Keywords: Cardiorenal syndrome • Diabetes mellitus • Cardiovascular risk • Diabetic nephropathy • Microalbuminuria • Proteinuria • Chronic kidney disease • Endothelial dysfunction • Glycemic control • Angiotensin-converting enzyme inhibitors • Angiotensin II receptor antagonists • Transforming growth factor beta • Vascular endothelial growth factor

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Cardiorenal Syndrome. Adel E. Berbari, Giuseppe Mancia (Eds.)

11

11.1 Introduction

Cardiorenal syndrome (CRS) was first defined at the US National Heart, Lung, and Blood Institute Working Group meeting in 2004. Discussion at that meeting focused on accumulated knowledge related to heart–kidney interactions whereby there can exist a clinical situation or "a state in which therapy to relieve congestive heart failure (CHF) symptoms is limited by further worsening renal function." More recently, it was suggested that the definition of CRS should be expanded to better reflect dual heart–kidney interactions [1]. The newly proposed definition was stated as "a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ." To further stress the complicated interactions between these organ systems, a classification was introduced with four types in which the etymology reflects the presumptive primary and secondary abnormality and their chronologies and a fifth subtype that includes systemic conditions that cause both cardiac and renal dysfunction: diabetes mellitus is the typical example of the latter subtype.

11.2 Diabetes Mellitus

The global burden of diabetes continues to increase. According to a recent report by the International Diabetes Federation, diabetes affects 246 million people worldwide, and this number is expected to reach 380 million by 2025. One major contributing factor to the diabetes pandemic is the increasing prevalence of abdominal obesity. This form of obesity is mainly caused by high-energy diets and sedentary lifestyles and is also an identified risk factor for cardiovascular diseases. The high prevalence of diabetes will further burden health care systems by its long-term complications, particularly macrovascular- and microvascular-associated diseases. Macrovascular complications include coronary heart disease, cerebrovascular disease, and peripheral artery disease. Microvascular complications refer to damage within the eye, the kidney, and nerves. In addition to increased morbidity, diabetic patients suffer a high mortality rate, with cardiovascular disease (CVD) being the major cause of death, accounting for some 50% of all diabetes fatalities [2].

11.2.1 Diabetes and the Kidney

Diabetic nephropathy is the most common chronic kidney disease (CKD) and a leading cause of end-stage renal disease (ESRD), accounting for nearly 44% of new cases [3]. Even when diabetes is controlled, the disease can lead to CKD and kidney fail-

ure. Up to 30% of patients with diabetes are believed to develop nephropathy [4]; however, most people with diabetes do not develop CKD severe enough to progress to kidney failure. Nonetheless, the level of proteinuria is a powerful predictor of progression to ESRD [5]. Nephropathy is also an important cause of premature mortality in patients with type 1 or type 2 diabetes mellitus, causing many to die before reaching ESRD.

11.2.2 Diabetes and the Heart

Identification of diabetes as a high-risk condition for macrovascular diseases is based on the fact that there is a high long-term risk for developing CVD. Various studies showed that the risk for cardiovascular events increases two- to fourfold in patients with type 2 diabetes compared with patients without diabetes [6]. In fact, it was shown in a more recent study that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as do nondiabetic patients with previous myocardial infarction [7]. On the other hand, it is widely known that CVD risk in the general population increases with the increasing number of risk factors. This is also true among individuals with diabetes, whereby an accurate assessment of risk was clearly shown to depend on the individual's characteristics [8]. Observational studies showed that the risk for cardiovascular events is increased in the presence of microvascular disease in diabetic patients. Moreover, a recent study showed that microvascular complications significantly increase the risk of first coronary events in patients with type 2 diabetes [9].

11.2.3 Micro- and Macroalbuminuria in Diabetes and CVD Risk

Microalbuminuria is a common complication of diabetes and appears to be a strong predictor of subsequent development of overt nephropathy. Of patients with type 1 diabetes, 50% with childhood onset and 35% with adult onset will develop microalbuminuria in nearly 20 years [10, 11]. In addition, 15% of patients in both groups will have macroalbuminuria by then. In newly diagnosed type 2 diabetes, 28% of patients will develop microalbuminuria and 7% will have macroalbuminuria after 15 years of follow-up [12]. However, microalbuminuria does not only predict future risk of renal injury but is also considered to be associated with increased risk of cardiovascular events and mortality. A cohort study from the Netherlands showed that urinary albumin excretion is a predictor of all-cause mortality in the general population. The excess risk was more attributable to death from cardiovascular causes, independent of the effects of other cardiovascular risk factors [13].

In diabetes, albuminuria appears to further increase the risk of CVD in this high-risk group. A 10-year observational follow-up study demonstrated that type 1 diabetic patients with microalbuminuria or proteinuria have two to ten times faster pro-

gression of cardiac and vascular complications compared with patients with normal albumin excretion [14]. In addition, epidemiological studies in persons with type 2 diabetes have shown that microalbuminuria is an important risk factor for arteriosclerosis, coronary heart disease and other vascular diseases. A recent pooled analysis of type 2 diabetes in 11 cohort studies including more than 2,000 patients with a mean follow-up of 6.4 years showed that microalbuminuria was associated with an adjusted overall odds ratio for all-cause mortality of 2.4 [95% confidence interval (CI) 1.8–3.1] and CVD morbidity and mortality of 2.0 (95% CI 1.4–2.7) [15]. Longitudinal studies also documented that microalbuminuria is an adverse prognostic indicator for clinical CVD outcomes and all-cause mortality in individuals with diabetes. For example, in the Heart Outcomes Prevention Evaluation (HOPE) study that included individuals with vascular disease or diabetes plus another traditional risk factor at baseline, those with microalbuminuria and diabetes had a 1.97-fold (95% CI 1.68–2.31) and 2.15-fold (95% CI 1.78–2.60) increased risk for a composite outcome of myocardial infarction, stroke, or CVD death, as well as all-cause mortality, respectively, compared with individuals with diabetes without microalbuminuria [16]. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, increasing baseline albuminuria was related to increased risk for cardiovascular events, and effective lowering of albuminuria in patients with hypertension and diabetes appeared to be beneficial [17]. Although individuals with microalbuminuria may have a higher prevalence of traditional risk factors than those without microalbuminuria, authors in several clinical studies concluded that microalbuminuria is an independent risk factor for outcome after adjustment for all other CVD risk factors.

11.3 CKD and CVD

Various studies have shown that CVD risk factors, CVD surrogates, and clinical CVD are more prevalent in patients with reduced glomerular filtration rate (GFR). For example, the HOPE study, the Cardiovascular Health Study (CHS), the Hypertension Optimal Treatment (HOT) study, the Framingham and Framingham Offspring studies, and the Atherosclerosis Risk in Communities (ARIC) study, have shown that higher systolic blood pressure and total cholesterol are associated with decreased GFR. In addition, diabetes, left ventricular hypertrophy (LVH), ischemic heart disease, and heart failure are more prevalent in individuals with decreased GFR [18–22]. More recently, it was demonstrated that the level of kidney function is an independent predictor of significant angiographic coronary artery disease [23]. The prevalence of LVH is also inversely related to GFR level. In one study, the prevalence of LVH, as measured by echocardiography, in patients with creatinine clearance <25 ml/min was more than twice that in similar-aged patients in the general population [24].

Studies have also examined the association of different cutoff values of serum creatinine or estimated GFR (eGFR) with the risk of cardiovascular events. Several studies found increased risk of death from any cause, death from cardiovascular causes, and increased cardiovascular events with higher serum creatinine levels [25]. Other studies evaluated eGFR and the risk of outcomes in the general population. The Second National Health and Nutrition Examination Survey (NHANES II) showed that eGFR <70 ml/min per 1.73 m^2 was associated with a 68% increase in the risk of death from any cause and a 51% increase in the risk of death from cardiovascular causes compared with an eGFR of at least 90 ml/min per 1.73 m^2. Similarly, the ARIC study showed that eGFR of 15–59 ml/min per 1.73 m^2 at baseline was associated with a 38% increase in the risk of CVD compared with an eGFR of 90–150 ml/min per 1.73 m^2 [20]. The relationship between GFR and the risk of adverse events was further delineated in a study that found nonlinear relations between GFR and the risks of death, cardiovascular events, and hospitalization, with an increased risk associated with an eGFR <60 ml/min per 1.73 m^2, which further rose sharply when values dropped <45 ml/min per 1.73 m^2. The study found that an eGFR of 15–29 ml/min per 1.73 m^2 and an eGFR <15 ml/min per 1.73 m^2 in the absence of dialysis were associated with strikingly high age-adjusted mortality rates (11.4 and 14.1 per 100 person-years, respectively) [26]. These rates approach the rates among patients with treated ESRD [27].

Patients with diabetes are known to be at increased risk of CVD events. The presence of reduced kidney function in diabetic patients may further enhance the macrovascular risk. For example, studies have shown that type 2 diabetic patients with normal renal function are two to four times more likely to develop CVD than people without diabetes and that CVD event rates in type 2 diabetes with normal renal function are equivalent to those in nondiabetic people with pre-existing CVD [6, 7]. Very recently, it was shown that patients who were 30 years of age with normal renal function and require glucose-lowering therapy exhibit a cardiovascular risk comparable with nondiabetics with a prior myocardial infarction, regardless of gender and diabetes type [28]. The presence of reduced kidney function in diabetic patients can further enhance macrovascular risk. Observational studies have shown that the presence of microvascular complications is significantly associated with an increased risk of CVD morbidity and mortality, and the increased CVD risk associated with microangiopathy has been repeatedly reported in cross-sectional studies or small incident cohorts. The World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes [29] found that heavy proteinuria and retinopathy carried a significant relative risk for CVD mortality. Patients with type 1 diabetes and diminished renal function often develop extensive atherosclerosis. The HOPE study showed that patients with type 2 diabetes with chronic kidney disease due to diabetic nephropathy have a very high risk for myocardial infarction and CVD death, with 40% experiencing a cardiac complication over a 5-year period [19]. A recent large prospective study in type 2 diabetic patients free of CVD assessed the risk of a first cardiovascular event associated with microangiopathy in the context of the full set of

classic risk factors. The results showed evidence that microvascular complications markedly enhance the risk of a subsequent first coronary event in men and women. Microangiopathy retained an independent predictive power, especially in women [9]. Very recently, the prevalence of both LVH and major cardiovascular events was reported to be higher in patients with CKD compared with patients with normal GFR [30]. Reduced GFR is also an independent risk factor for worse outcomes in high-risk populations other than diabetic patients. This was suggested by studies in individuals with hypertension [31], in the elderly [32], and among older patients undergoing general surgery [33].

Progression to ESRD markedly increases CVD morbidity and mortality. Approximately 40% of incident hemodialysis patients have clinical evidence of ischemic heart disease or heart failure. In addition, the prevalence of LVH in incident dialysis patients is high. In the Canadian Prospective Cohort Study of 433 incident dialysis patients, 74% had LVH at baseline [34], and CVD mortality was about 10 to 30 times higher in patients treated by dialysis than in patients in the general population, despite stratification for sex, race, and the presence of diabetes. This mortality rate is likely due to the high prevalence of CVD among these patients. A high case fatality rate in dialysis patients has been observed after acute myocardial infarction and in patients with heart failure. The mortality rate 1 and 2 years after myocardial infarction was 59% and 73%, respectively, in dialysis patients [35]. The observed mortality rate was much higher than after acute myocardial infarction in the general population, even in individuals with comorbid conditions such as diabetes. For example, in the Worcester Heart Attack Study, approximately three fourths of diabetic men and two thirds of diabetic women discharged after an acute myocardial infarction were still alive 2 years later [36].

There may be more than one factor contributing to the observed independent association of reduced GFR and CVD outcomes. A reduced GFR may be associated with an increased level of nontraditional CVD risk factors that frequently are not assessed in many studies. Also, reduced GFR may simply be a marker of undiagnosed vascular disease or, alternatively, a marker for the severity of diagnosed vascular disease, especially in high risk populations such as diabetic individuals. Moreover, recent studies suggest that individuals with reduced GFR are less likely to receive thrombolytic therapy, angiography, and angioplasty as well as medications such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers, β-blockers, or antiplatelet agents during hospitalization than patients with preserved GFR. These medications were shown in conducted trials to benefit patients with reduced GFR similar to patients with preserved GFR [37–39].

In recognition of these significant CVD morbidity and mortality rates associated with CKD, health authorities in several countries are building an infrastructure to facilitate a public health approach to CKD. For example, in the United States, the Centers for Disease Control and Prevention (CDC) recently began a Kidney Disease Initiative that includes conducting surveillance, epidemiology, state-based demonstration projects, and economic studies related to patients with CKD.

11.4 Pathogenesis

The mechanisms by which the diabetic milieu causes kidney injury have been extensively studied. The associated hyperglycemia, glycated proteins, and oxidative stress cause hemodynamic stress and activate metabolic pathways that induce a group of growth factors in the kidney. It is widely believed that the fibrogenic cytokine transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) are implicated in the development of cardinal features of diabetic nephropathy. TGF-β, through its Smad3 signaling pathway, has been shown to be the etiologic agent of renal hypertrophy and accumulation of mesangial extracellular matrix, whereas there is growing experimental evidence that podocyte-derived VEGF is likely directly involved in the development of albuminuria in diabetic patients [40].

On the other hand, CVD pathogenesis in diabetes is multifactorial and can be affected by metabolic and other factors. Increased oxidative stress and glycoxidation, procoagulant states, and activation of inflammatory processes were all shown to be important in CVD pathogenesis in diabetes. Furthermore, it has been suggested that endothelial dysfunction may lead to simultaneous development and progression of renal and cardiac pathology in diabetes. Normally, the endothelial cell (EC) layer functions as a barrier separating circulation in the blood vessel from the vessel intima and media. Another important function of the EC layer is to serve as an anticoagulant and fibrinolytic surface-producing tissue plasminogen activator. In addition, ECs produce nitric oxide (NO), a vasodilator that also limits smooth muscle cell (SMC) migration and proliferation. Metabolic derangements associated with diabetes mellitus that can cause endothelial injury include hyperglycemia and its metabolic byproducts, early and advanced glycation end products (AGEs), increased levels of free fatty acids, and lipoprotein abnormalities. Hyperglycemia, along with elevated levels of oxidized low-density lipoprotein (LDL), results in increased expression of adhesion molecules and fibronectin, infiltration of macrophages into the subendothelium, and predisposition to development of atherosclerotic plaque [41]. Hyperglycemia also reduces bioavailability of NO [42] and increases the rate of endothelial apoptosis that can result in impaired vasorelaxation [43]. With the progression of vascular damage, further endothelial dysfunction leads to paradoxical peripheral and coronary vasoconstriction and an increase in blood pressure levels, which may precipitate tissue ischemia.

In addition, a close association has been firmly established between systemic endothelial dysfunction and microalbuminuria in diabetic patients. Alterations of glomerular endothelial cells, disturbances of endothelial cell–podocyte cross-talk, and disruption of endothelial glycocalyx were shown to be the most important determinants of diabetic microalbuminuria [44]. In type 1 and type 2 diabetes, markers of endothelial dysfunction increase in association with the appearance of microalbuminuria and progress further at the stages of proteinuria and chronic renal insufficiency [45, 46]. Moreover, vascular endothelium dysfunction was suggested to be a link between albuminuria and atherosclerotic CVD in type 2 diabetes [47]. Also, a recent

study in patients with type 1diabetes showed that biomarkers of endothelial dysfunction are significantly associated with all-cause mortality and CVD morbidity and mortality in the presence of nephropathy [48]. However, the important function of ECs in vasodilation, as tested in flow-mediated dilatation of brachial artery, was shown to be preserved in microalbuminuria, decreased in the proteinuria stage, and totally lost in the chronic renal failure stage. This suggests that attenuation of factors affecting the endothelium at the microalbuminuria level may lead to slowing the progression of renal dysfunction and reducing the incidence of CVD in patients with diabetes.

11.5 Treatment

Both microvascular and macrovascular complications contribute to increased morbidity in diabetes. Although microvascular complications predispose to premature mortality, CVD is the leading cause of death in diabetes. In addition to the defined role of hyperglycemia, other modifiable risk factors for late complications in patients with diabetes, including hypertension and dyslipidemia, increase the risk of a poor outcome.

Results from randomized controlled trials demonstrated conclusively that the risk of microvascular complications can be reduced by intensive glycemic control in patients with type 1 and type 2 diabetes mellitus. In the Diabetes Control and Complications Trial (DCCT) [49], intensified treatment of hyperglycemia to a mean HbA1c of 7% resulted in 60% reduction in diabetic retinopathy, nephropathy, and neuropathy compared with a standard group with a mean HbA1c of 9%. Similarly, in the UK Prospective Diabetes Study (UKPDS) [50], intensive control of hyperglycemia to a mean HbA1c of 7% versus conventional treatment to a HbA1c of 7.9% led to a 25% reduction of overall microvascular complications. Evidence related to microvascular risk reduction with intensive glycemic control obtained from these two large controlled trials, along with smaller studies and multiple epidemiologic reports, led the American Diabetes Association (ADA) to recommend an HbA1c goal of 7% for most adults with diabetes [51].

Many epidemiologic studies and meta-analyses have clearly shown a direct relationship between HbA1c and macrovascular/CVD [52]. However, the potential of intensive glycemic control to reduce CVD events has only recently been investigated by three long-term trials. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [53] and the Veterans Affairs Diabetes Trial (VADT) [54] were very recently completed and showed no significant reduction in cardiovascular outcomes with intensive glycemic control. The third trial, Action to Control Cardiovascular Risk in Diabetes (ACCORD) [55], terminated its glycemic control study early due to the finding of surprisingly increased mortality in the arm of intensive glycemic control with a target HbA1c of 6%. However, subset analyses in these trials suggest that patients with shorter duration of type 2 diabetes and without established atherosclerosis may still

have cardiovascular benefit from intensive glycemic control. In addition, long-term follow-up of the DCCT and UKPDS cohorts suggests that treatment to HbA1c targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease [56].

Randomized trials that investigated the effect of intensified intervention involving other vascular risk factors in patients with type 2 diabetes demonstrated benefits in terms of both macrovascular and microvascular complications. Intensive treatment of hypertension in patients with newly diagnosed diabetes during an 8-year period, which decreased systolic and diastolic blood pressure by 10 and 5 mmHg, respectively, significantly reduced both the absolute risk of stroke and the absolute combined end point of diabetes-related death, death from vascular causes, and death from renal causes by 5 percentage points[57]. The HOT study, which treated elevations in diastolic blood pressure for an average of 3.7 years, reported similar reductions in the risk of composite end points for macrovascular disease in subgroup analyses of patients with type 2 diabetes [58]. Subgroup analysis showed a large reduction in the absolute risk of cardiovascular events (19%) among diabetic patients with elevated serum total cholesterol concentrations in patients who took statins for 5.4 years for secondary cardiovascular prevention [59].

Finally, as renal disease is the strongest risk factor for CVD morbidity and mortality, strategies able to reduce renal disease progression are expected to translate into a decreased incidence of cardiovascular events. Several large, randomized studies have convincingly shown that treatments with ACEIs or angiotensin II receptor antagonists are associated with a significant reduction in the risk for renal disease progression, which was paralleled by reduced cardiovascular risk in diabetic and nondiabetic patients with chronic kidney disease [60]. Moreover, a recent observational follow-up study over 8 years in 216 type 2 diabetic patients with microalbuminuria has shown that changes in microalbuminuria translate into changes in renal and cardiovascular risk [61]. A 50% reduction of microalbuminuria was associated with a significant risk reduction of events. However, a significant proportion of patients with chronic nephropathies still progress to end-stage renal failure or die from cardiovascular events. Therefore, a more complex strategy of intervention may be needed. A recent study showed that a comprehensive approach of intensive treatment – with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria – along with secondary prevention of CVD with aspirin in patients with type 2 diabetes and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50 percent [62].

11.6 Conclusions

Nephropathy in diabetic patients appears to be a significant independent contributing factor in the tally of overall risks for and outcomes from vascular complications and related mortality. As such, it is also important in understanding the pathogenesis

of the accelerated course of CVD in affected patients that may be related to a common underlying mechanism in renal and cardiovascular systems. Finally, and depending on the level of renal dysfunction, the presence of nephropathy is important in planning a comprehensive treatment approach in the high-risk patient with complicated diabetes in an attempt to favorably alter disease outcome.

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Section IV
Spectrum of Cardiovascular Disease in Chronic Kidney Disease

Cardiovascular Disease: Coronary Artery Disease and Coronary Artery Calcification

12

S. Beddhu

Abstract Coronary artery disease is common in chronic kidney disease (CKD) and dialysis patients. There is strong evidence that kidney disease is an independent risk factor for atherosclerosis. In addition, traditional risk factors such as obesity, hypertension and diabetes, as well as nontraditional factors such as inflammation and oxidative stress, likely contribute to the excess risk of atherosclerosis in CKD. It remains to be determined whether low serum vitamin D levels and elevated fibroblast growth factor-23 (FGF-23) also play a role in atherosclerosis in CKD. There is some evidence to suggest that statins are useful in moderate CKD, but two large trials in dialysis patients showed no benefit of statin therapy. However, uremic dyslipidemia is characterized by low high-density-lipoprotein (HDL) cholesterol levels and increased triglyceride levels; statins are not effective in treating these lipid abnormalities. Beta blockers, aspirin and angiotensin-converting (ACE) inhibitors are likely effective therapies for treating coronary artery disease (CAD), but these remain very much underutilized. Similarly, despite evidence that coronary revascularization is useful in CKD and dialysis patients, these interventions are also underutilized in these populations.

Keywords: Coronary artery disease • Atherosclerosis • Coronary calcification • Chronic kidney disease • Dialysis

12.1 Introduction

There are more than 13 million people with chronic kidney disease (CKD) in the United States [1]. The 5-year survival of end-stage renal disease (ESRD) patients on dialysis is only 39%. This is lower than that of stage IIIB breast cancer (54% 5-year survival). Furthermore, the age-specific cardiovascular disease (CVD) mortality rates of dialysis patients is 10–100 times greater than those of the general population [2]. Even in early stages of CKD, the risk of death and cardiovascular events increase as glomerular filtration rate (GFR) declines. In an analysis of Kaiser-Permanente

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database [3], among 1,120,295 adults, after adjustment, the risk of death increased as the GFR decreased <60 ml/min/1.73 m^2: the adjusted hazard ratio (HR) for death with an estimated GFR (eGFR) of 45–59, 30–44, 15–29 and <15 ml/min/1.73 m^2 was 1.2[95% confidence interval (CI) 1.1–1.2], 1.8 (95% CI 1.7–1.9), 3.2 (95% CI 3.1–3.4), and 5.9 (95% CI 5.4–6.5), respectively. The adjusted HR for cardiovascular events also increased inversely with eGFR: 1.4 (95% CI 1.4–1.5), 2.0 (95% CI 1.9–2.1), 2.8 (95% CI 2.6–2.9), and 3.4 (95% CI 3.1–3.8), respectively.

Compared with the general population, CKD and ESRD populations have a greater burden of atherosclerosis, vascular calcification, hypertension, valvular calcification, left ventricular hypertrophy (LVH) and cardiomyopathy. The relative contributions of these individual CVD processes to the above-mentioned excess risk of cardiovascular events in CKD and dialysis patients remain controversial. This chapter addresses CAD and coronary calcification; other disease processes are described in other chapters.

12.2 Coronary Artery Disease in Chronic Kidney Disease

The following discussion summarizes the current literature on pathogenesis, clinical presentation, diagnosis and therapy of CAD in CKD.

12.2.1 Etiology and Pathogenesis of CAD in CKD

In 1974, Lindner et al. first proposed the concept of accelerated atherosclerosis in ESRD based upon observed high incidences of myocardial infarction in hemodialysis patients [4]. A high prevalence of atherosclerotic lesions in dialysis patients was also noted in an autopsy series [5]. Sixty-two percent of hemodialysis patients undergoing kidney transplant surgery had atherosclerosis of the internal iliac artery [6]. In another autopsy study, the frequency of advanced atherosclerotic lesions increased gradually as eGFR decreased [7]. Although these studies show that there is a greater prevalence of atherosclerosis in CKD and dialysis populations, they do not prove that CKD by itself leads to a progression of atherosclerosis. It is possible that comorbidities, such as diabetes, that are commonly associated with CKD might be responsible for the increased prevalence of atherosclerosis noted in this population. Furthermore, in pediatric dialysis patients, atherosclerosis is not a major source of morbidity or mortality. Therefore, it has been argued by some that uremia per se is not an atherogenic milieu.

Nonetheless, there is strong evidence to support the notion that CKD is a risk factor for atherosclerosis. It has been shown that lower GFR is associated with increased risk of subsequent myocardial infarction or death, independent of diabetes and other factors [8, 9]. In addition to the above-mentioned epidemiological data,

the following animal studies substantiate this claim. Ponda et al. transplanted atheromatous aortic segments generated from apolipoprotein E knock-out (apoE-/-) mice into either control or moderately uraemic, normolipidemic, wild-type mice [10]. In nonuraemic mice, lesions regressed 55%, whereas lesions in uremic mice increased in size by 17% ($p < 0.01$ for control vs. uraemic). In another study, atherosclerotic lesions in thoracic aorta were significantly larger in uraemic apoE(-/-) mice that underwent uninephrectomy than in nonuraemic controls that underwent a sham operation [11].

12.2.2 Potential Mechanisms of Accelerated Atherosclerosis in CKD

Figure 12.1 summarizes the likely candidates that lead to accelerated atherosclerosis in the CKD population.

12.2.2.1 Visceral Adiposity and Atherosclerosis in CKD

There is controversy regarding the role of adiposity on outcomes in the CKD and dialysis population. In contrast to the general population, higher body mass index (BMI) is associated with better survival in the hemodialysis population [12, 13]. This obviously raises the question that, if adiposity leads to increased mortality in the gen-

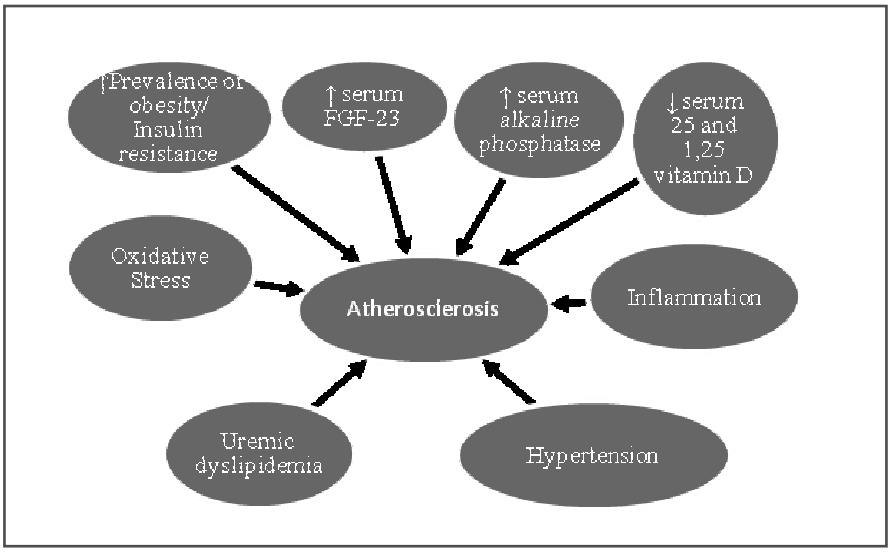

Fig. 12.1 Putative mechanisms of accelerated atherosclerosis in chronic kidney disease

eral population through its metabolic effects of inflammation, insulin resistance and oxidative stress, what are the metabolic effects of adiposity in uremia?

Adipokines are protein hormones produced by adipocytes. These include tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), leptin, angiotensinogen and adiponectin, and they serve as signals for the effects of adipocytes on insulin resistance, dyslipidemia, hypertension, inflammation and atherosclerosis. In obesity, the production of TNF- α, IL-6, PAI-1, leptin and angiotensinogen increases, whereas the production of adiponectin decreases. Increased expression of proinflammatory TNF- α and IL-6 and decreased expression of anti-inflammatory adiponectin by adipocytes might result in insulin resistance, inflammation and oxidative stress. In, CKD and dialysis patients, adiposity is still associated with elevated levels of markers of inflammation and insulin resistance, as well as altered levels of adipokines. Therefore, the metabolic effects of adiposity in the CKD and dialysis population appear similar to those seen in the non-CKD population.

12.2.2.2
Serum Vitamin D, Fibroblast Growth Factor-23 and Alkaline Phosphatase

Serum 25-hydroxyvitamin D levels are lower in the CKD population compared with the general population. The conversion of 25-hydroxyvitamin D to the more active form, 1, 25-hydroxyvitamin D, is also decreased in CKD. Low levels of 25-hydroxyvitamin D was predictive of subsequent risk for myocardial infarction over a 10-year follow-up in the Health Professionals Follow-up Study [14].

Fibroblast growth factor-23 (FGF-23) is a phosphaturic hormone that plays a critical role in phosphorus homeostasis in CKD. Serum levels of FGF-23 are commonly elevated in CKD [15] and dialysis patients [16]. Higher serum levels of FGF-23 predict progression of CKD [15] and cardiovascular events and mortality in dialysis patients [16]. Recently, it was also shown in a cross-sectional study that higher serum FGF-23 levels were associated with magnetic resonance angiographic (MRA) evidence of atherosclerosis [17].

Alkaline phosphatase is secreted by osteoblasts and is commonly elevated in CKD. For a long time, alkaline phosphatase has been considered an innocent bystander and only a marker of bone turnover. In hemodialysis patients, elevated serum alkaline phosphatase has been independently associated with cardiovascular events, CVD mortality and all-cause mortality [18]. In the African American Study of Kidney Disease (AASK) cohort, a strong independent association of serum alkaline phosphatase level with mortality in CKD was demonstrated [19]. Furthermore, higher serum alkaline phosphatase levels were associated with progression of vascular calcification in hemodialysis patients [20].

Thus, these data raise the intriguing possibility that low serum vitamin D levels or elevated serum FGF-23 might play a role in faster progression of atherosclerosis in CKD. Therefore, interventions such as vitamin D supplementation or phosphorus

binders that might reduce FGF-23 levels [21] might retard atherosclerosis in the CKD population. Similarly, cinacalcet, which reduces serum alkaline phosphatase levels [22], might decrease atheroma calcification in CKD.

12.2.2.3 Hypertension

Port et al. found that higher predialysis systolic blood pressure (150–180 mmHg) was not associated with a higher mortality risk than the reference group (120–149 mmHg), whereas relative mortality risk increased as systolic pressures fell below 110 mmHg [23]. Zager et al. found a U–shaped relationship between systolic blood pressure and CVD mortality in chronic hemodialysis patients [24]. Even though the association of blood pressure with mortality in dialysis patients appears to differ from that in the general population, the association of hypertension with atherosclerosis in dialysis patients might be similar to that seen in the general population. In the Hemodialysis (HEMO) Study, hypertension was independently associated with clinical evidence of atherosclerosis in hemodialysis patients. Hypertension was positively correlated with carotid intima media thickness (IMT) in CKD patients**.** Foley et al. showed that hypertension was independently associated with concentric LVH on echocardiography, de novo cardiac failure and de novo ischaemic heart disease in dialysis patients [25]. Further, pulse pressure, a measure of arterial compliance and atherosclerosis, is a strong predictor of death in hemodialysis patients. Thus, it is possible that even in CKD, hypertension is associated with atherosclerosis.

12.2.2.4 Dyslipidemia

The dyslipidemia that is commonly seen in CKD and dialysis population is characterized by elevated serum triglycerides and low high-density lipoprotein (HDL)-cholesterol levels rather than increased low-density lipoprotein (LDL) cholesterol levels [26]. As discussed below, statins are generally ineffective in decreasing serum triglycerides or increasing serum HDL-cholesterol levels; this may partially explain the ineffectiveness of statins in decreasing clinical events in dialysis patients.

12.2.2.5 Inflammation and Oxidative Stress

Elevated levels of inflammation and oxidative stress markers are associated with lower kidney function and predict cardiovascular outcomes and mortality in CKD and dialysis patients [27, 28].

12.2.3 Clinical Presentation and Diagnosis of CAD in CKD

The most typical presentation of CAD is chest pain, but many patients with diabetes and ESRD present with silent or atypical angina. For example, the sensitivity of clinical symptoms for myocardial infarction was only 43% in patients with diabetes and ESRD. On the other hand, up to one quarter of patients with angina pectoris in ESRD have no coronary artery stenosis but have symptoms that are attributed to microvascular disease [29].

12.2.3.1 Laboratory Diagnosis of Acute Coronary Syndromes

Electrocardiographic (ECG) evidence of acute coronary syndrome such as ST- and T-wave changes are typically seen, but LVH and other baseline nonspecific ECG changes could make the interpretation of these findings difficult. Furthermore, even in the absence of acute coronary syndromes, creatinine kinase found in muscle and brain tissue (CK-MB fraction) could be elevated in CKD. Elevation of troponin I is a sensitive (80–90%) and specific (100%) marker for acute myocardial infarction in patients with ESRD.

12.2.3.2 Stress Tests for Diagnosis of Chronic Myocardial Ischemia

Most people with CKD are deconditioned and are unable to reach the target heart rate with physical exercise. In addition, the nonspecific ECG changes at baseline make interpretation of ECG difficult. Therefore, stress ECG is of limited value in CKD. Pharmacological stress agent and an imaging modality are recommended to diagnose chronic myocardial ischemia. Pharmacological stress agents that are typically used are adenosine, dipyridamole, or dobutamine and imaging techniques are echocardiography or a radionucleotide study (such as sestamibi or thallium). The imaging modality used should reflect the expertise available at the local institution. However, if cardiology expertise is available, dobutamine stress echocardiography might be preferable, as this is safe, highly sensitive and specific, and provides additional information on LV function and valvular disease.

12.2.3.3 Electron Beam Computed Tomography

This is discussed in the section on coronary calcification.

12.3 Therapy for CAD in CKD

Appropriate medical or surgical therapy is often underutilized in CKD patients with CAD because of perceived lack of efficacy of therapy or high risk of complications or both in this population. This therapeutic nihilism results from a flawed perspective. While it is true that patients with CKD are at higher risk of mortality after any procedure, the outcomes of CKD patients without appropriate therapy is likely to be worse than those CKD patients who receive appropriate therapy. Therefore, withholding therapy from CKD patients because they are at higher risk of complications could further worsen the outcomes in this population. The following discussion summarizes the current literature on medical and surgical therapy for CAD in CKD.

12.3.1 Antiplatelet Agents

The reduction in 30-day mortality rates postmyocardial infarction with aspirin therapy was similar in ESRD patients and nondialysis controls [30]. However, in the same study, the proportion of dialysis patients treated with aspirin after myocardial infarction was much lower. This is because of the perceived risk of gastrointestinal bleeding in ESRD. Indeed, in CKD patients, 100 mg/day of aspirin vs. placebo was associated with a threefold increase in minor bleed but without a significant increase in major bleed [31]. Therefore, the risk of minor bleed with aspirin is likely outweighed by the reduction in postmyocardial infarction mortality rates, but controlled studies are warranted to provide definitive answers.

Parenteral glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa) provide effective antiplatelet therapy for acute coronary syndrome, but these agents are also underutilized in the CKD patients. Retrospective studies suggest that whereas these agents might increase the risk of bleeding somewhat, they decrease the risk of subsequent cardiovascular events and need for revascularization procedures [32].

12.3.2 Beta Blockers

Beta blockers decrease mortality rates after myocardial infarction in dialysis patients [30]. These agents were associated with a lower risk of new heart failure and cardiac death in a retrospective study of dialysis patients [33]. In a double–blinded, placebo-controlled, randomized trial of dialysis patients with dilated cardiomyopathy, carvedilol resulted in improved ejection fraction and New York Heart Association (NYHA) functional class [34]. Even though beta blockers are part of standard of care after myocardial infarction in the general population, only about half of those with

CKD after myocardial infarction receive these agents despite the lack of increased risk of adverse effects of beta blockers in this population.

Sudden cardiac death accounts for about 50% of deaths caused by CVD in dialysis patients. In hemodialysis patients, elevated norepinephrine levels were associated with increased death from CVD [35]; in CKD patients, higher resting heart rate is associated with increased mortality rates [36]. Therefore, it is possible that primary prevention with beta blockers might be of benefit, but interventional studies are needed to test these hypotheses.

12.3.3 Angiotensinogen-converting Enzyme (ACE) Inhibitors/Angiotensin Receptor Blockers (ARB)

In the Heart Outcomes Prevention Evaluation (HOPE) trial, in the subgroup of 980 patients with mild renal insufficiency (baseline serum creatinine >1.4 mg/dl but <2.3 mg/dl), ramipril reduced the cumulative incidence of death from CVD, myocardial infarction, or stroke [37]. In a smaller study of dialysis patients, those treated with an ACE inhibitor had a 52% relative risk (RR) reduction for mortality over 5 years [38]. However, another underpowered trial in dialysis patients showed a trend but no statistically significant improvement in survival after fosinopril treatment [39]. Overall, these data suggest a survival benefit for ACE inhibitors in CKD patients. On the other hand, in trials of patients with diabetic nephropathy, ARBs showed no cardiovascular benefit [40]. Therefore, ACE inhibitors might be preferable over ARBs in CKD and dialysis patients.

12.3.4 Lipid-Lowering Therapy

In the general population, the efficacy of statins as primary and secondary prevention strategies for CAD is well established. Post hoc analyses of randomized controlled trials that also included those with less severe CKD (eGFR 50–60 ml ml/min/1.73 m^2) suggest benefits of statins in that population [41]. In contrast, statins did not reduce cardiovascular events or mortality rates in the dialysis population in two large randomized controlled trials [42, 43]. In the Randomized Controlled Trial on the Efficacy and Safety of Atorvastatin in Patients with Type 2 Diabetes on Hemodialysis (4-D) study, atorvastatin had no significant impact on the primary end point, which was a composite of death from cardiac causes, nonfatal myocardial infarction and stroke [43] in diabetic dialysis patients. In the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [42] study, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in dialysis patients.

These data have been interpreted as indicating that atherosclerosis is not the cause for the increased cardiovascular events and mortality rates observed in the CKD and dialysis populations [44]. In addition, it has been argued that the above notion is further supported by the following: Sudden cardiac death is common in CKD and dialysis patients and might be due to arrhythmias secondary to cardiomyopathy or electrolyte imbalances, such as hyperkalemia, rather than myocardial ischemia or infarction. Furthermore, even the increased risk of myocardial infarction in this population might be related to nonatherosclerotic processes [45], such as decreased oxygen supply due to anaemia or increased oxygen demand secondary to LVH as a consequence of fluid overload, hypertension and increased arterial stiffness (due to vascular calcification).

On the other hand, carotid intima-media thickness (IMT) is associated with increased all-cause and cardiovascular mortality in hemodialysis patients [46], suggesting that atherosclerosis is indeed associated with increased mortality. Furthermore, dyslipidemia commonly seen in CKD and dialysis patients is characterized by elevated serum triglycerides and low HDL cholesterol levels rather than increased LDL cholesterol levels [26]. It should be noted that statins are generally ineffective in decreasing serum triglycerides or increasing serum HDL cholesterol levels; this may also partially explain the ineffectiveness of statins in decreasing clinical events in dialysis patients.

12.4 Coronary Revascularization in CKD

Compared with the non-CKD population, CKD and dialysis patients undergoing percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) have a higher risk of complications and death. They are also more likely to have a higher prevalence of coronary anatomies unsuitable for coronary revascularization (diffuse vessel disease). These factors have contributed to a general perception that patients with advanced CKD are not candidates for coronary revascularization. This is evident from a study of Cooperative Cardiovascular Project (CCP) in which 81% of CKD patients on medical therapy and who had recurrent pain within the first 24 h after acute myocardial infarction were not treated with revascularization.

The critical question in patients with advanced CKD is not whether they are at higher risk compared with non-CKD patients for the revascularization procedures, but when revascularization is indicated, does coronary revascularization improve or worsen outcomes in the CKD population? Analyses of the United States Renal Data System (USRDS), a national registry of US dialysis patients, as well as single-centre studies consistently show that CABG is better than PCI, which in turn is better than medical therapy alone [47, 48]. A small, randomized trial of 26 asymptomatic or mildly symptomatic patients with diabetes and significant CAD documented pre-transplant angiography patients on medical therapy (aspirin plus calcium-channel blocker) versus revascularization (CABG or angioplasty). In the medical therapy

arm, 77% reached a cardiovascular endpoint, and 38% died within a median follow-up of 8 months. In contrast, in the revascularization group, only 15% reached a cardiovascular endpoint and 8% died [49]. Therefore, revascularization might be superior to medical therapy alone in advanced CKD, and this important therapeutic option should not be denied to this population.

Furthermore, evidence suggests that CABG with internal mammary artery may be the preferred revascularization procedure in patients on dialysis. Advances in coronary artery stents may make stenting the procedure of choice in the future.

12.5 Coronary Calcification in CKD

It is a well established fact that coronary calcification is more prevalent and more prominent in CKD and dialysis patients compared with the general population. Several potential mechanisms for this fact have been proposed, and they are discussed in detail elsewhere in this book. The following brief discussion focuses on the clinical significance and diagnosis of coronary calcification in CKD.

Electron-beam computed tomography (EBCT) or multidetector computed tomography (MDCT) are useful instruments to measure coronary calcification, but these techniques cannot differentiate between intima or media calcification. Hence, there is much controversy as to whether coronary calcification in CKD is due to arteriosclerosis or atherosclerosis. In arteriosclerosis, there is medial hyperplasia and calcification of the media of the arterial wall. This lesion does not result in obstruction of coronary flow. On the other hand, in atherosclerosis, there are lipid-rich plaques in the intima, which might become calcified. Atherosclerotic plaques could rupture, resulting in myocardial infarction. In autopsy studies of CKD and dialysis patients who were known to have CAD [50], intimal plaque calcification was most frequent and severe in dialysis patients and less so in the early CKD stages. Medial calcification was seen in a small number of CKD and dialysis patients. Therefore, it appears that calcification of atherosclerotic plaques rather than medial calcification is the predominant cause of coronary calcification in CKD.

As EBCT and MDCT are rapid, noninvasive tests that do not require an exercise stress test or pharmacologic stress agent to evaluate the presence of CAD, it has been suggested that these techniques could supplant stress tests. However, the sensitivity and specificity of coronary calcification for coronary artery stenosis is only about 80–85%. Therefore, these techniques cannot be used at this time in routine clinical practice to diagnose CAD.

In summary, CAD is very common in CKD. Uremia by itself might be an atherosclerotic risk factor. Both traditional and nontraditional factors contribute to the increased risk of atherosclerosis in CKD. Medical and revascularization therapies are underutilized in the treatment of CAD in CKD and dialysis patients.

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Cardiomyopathy in Chronic Kidney Disease and in End-stage Renal Disease

13

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Abstract Cardiovascular disease contributes to about 50% of overall mortality in end-stage renal disease (ESRD) patients. Alterations in left ventricular mass (LVM) and geometry and LV dysfunction are commonly prevalent and represent the strongest death predictors in this high-risk population. Although more refined techniques based on magnetic resonance imaging (MRI) are available, quantitative echocardiography is the most frequently used means of evaluating abnormalities in LVM and function. Echocardiography allows detailed examination of the pericardium, valvular apparatus, atria and ventricles, as well as reasonably reliable quantification of LVM and function. This technique also provides information on LV geometry, i.e., it identifies the pattern of cardiac remodelling (eccentric or concentric) and allows estimation of LV function during systolic and diastolic phases of the cardiac cycle. The vast majority of studies on cardiomyopathy in ESRD are observational in nature, and the number of controlled clinical trial in these patients is very small. Beta blockers (carvedilol) and angiotensin receptors blockers improve LV performance and reduce mortality in ESRD patients with LV dysfunction. Conversion to nocturnal dialysis and perhaps to short, daily dialysis produces a marked improvement in LV hypertrophy (LVH) in ESRD patients. Nocturnal dialysis appears recommendable in dialysis patients with asymptomatic or symptomatic LV disorders wherever the needed organizational and financial resources exist.

Keywords: LVH • LV systolic dysfunction • LV diastolic dysfunction • EF • Midwall fractional shortening • Hypertension • ESRD • CKD • Cardiovascular risk

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13

13.1 Introduction

Chronic kidney disease (CKD) is a well-recognized, solid predictor of all-cause mortality and cardiovascular disease (CVD). Patients who enter into the most advanced phase of this condition, i.e., end-stage renal disease (ESRD), show an exceptionally high risk. Although the proportion of patients dying because of CVD in this population does not differ from the corresponding proportion in the general population, the absolute risk for all-cause and CVD death in ESRD is so high that the probability of these outcomes in ESRD patients is about 100 times higher than that in age- and sex-matched individuals in the general population [1]. The clinical diagnosis of congestive heart failure (CHF), a condition most often preceded by left ventricular hypertrophy (LVH), in the ESRD population indicates an extremely high risk, with 3-year survival being only 17% in these patients [2]. Prospective studies consistently demonstrate that LVH is common (about 40–50%) in the predialyses stage of CKD [3, 4] and that this alteration is extremely frequent (70–80%) in ESRD patients [5].

Partial regression of LVH may occur after long-term control of arterial hypertension or severe uremic anemia as been achieved. However, careful studies by magnetic resonance imaging (MRI) have recently shown that restoring renal function by renal transplantation does not regresses LVH in dialysis patients [6].

13.2 Left Ventricular Mass and Function in Stages 3–5 Chronic Kidney Disease Patients and Dialysis Patients

13.2.1 Problem of Appropriate Indexing

LVM is proportional to body size. Therefore, this parameter should be appropriately indexed to body surface area (BSA) or height (either crude height or height to the power of 2.71 [7]). Indexing is problematic in patients with ESRD and those with CKD because weight, a basic parameter for calculating BSA, decreases in malnourished patient [8]. Weight loss determines an overestimation of LVM when it is indexed to BSA. On the other hand, because fluids accumulation is accompanied by an increase in body weight in volume-expanded patients, LVM will be underestimated by the same indexing. Thus, measurements of LVM in CKD and ESRD patients can be distorted in an unpredictable way and in opposite directions by malnutrition and extracellular volume expansion when BSA indexing is used.

The decision on whether to index LVM by BSA or by height$^{2.71}$ can influence estimates of the prevalence of LVH in ESRD, and, more importantly, its capacity to predict cardiac risk. Data from patients with ESRD indicate that the height$^{2.71}$-based method is superior to the BSA-based method for predicting death and CV events [8].

Furthermore, the prognostic value of subcategorizing patients according to whether cardiac remodelling is concentric (as in 50% of cases) or eccentric (as in the other 50% of cases) becomes apparent only when LVM is indexed to height$^{2.71}$ [8]. Although no study has specifically investigated the prognostic value of the relationships between LVM and malnutrition/extracellular volume expansion in patients with stage 3–4 CKD, similar associations can be expected in this population. Thus, it can be recommended that renal physicians ask cardiologists and echocardiography (EChoG) technicians to index LVM by height$^{2.71}$ in EChoG reports for patients with ESRD, and perhaps also for patients with CKD.

13.2.2 Cardiomyopathy in Stages 3–5 Chronic Kidney Disease Patients

Cardiomyopathy has been less intensively investigated in patients with stages 3–5 CKD than in ESRD patients. Hypertension is the most frequent cause of CKD and LVH. It is therefore important to examine these links in patients with primary hypertension. Studies in hypertensive patients with apparently normal renal function demonstrate that age-dependent decline in renal function is associated with concentric LVH or concentric remodeling [9]. However, other observations indicate that in essential hypertension, hyperfiltration rather than hypofiltration is associated with LVH [10]. In analyzing these links, it should be considered that the association between LVM and renal function in hypertensive patients, LVH should not be held as the sole or dominant effect of high blood pressure (BP) per se. In fact, other risk factors commonly associated with hypertension – such as endothelial dysfunction, insulin resistance, inflammation, and hyperuricemia – also represent well-established functional correlates of LVM and renal function.

Studies in the 1990s revealed that BP per se does not completely account for the increased LVM in these patients [11]. Age, gender, race, body weight, salt intake, sympathetic nervous system (SNS) overactivity, angiotensin II, aldosterone, insulin, insulin growth factor and other growth factors, endothelial dysfunction, C-reactive protein (CRP) and uric acid, as well as genetic factors [12] all play a role in LVH in primary hypertension. Notwithstanding substantial progress in this area, the pathophysiological links underpinning LV structural abnormalities in essential hypertension are still incompletely understood. Five reasonably large surveys testing the association between LVM and the glomerular filtration rate (GFR) have been performed in untreated nondiabetic individuals with uncomplicated hypertension. In the first study, creatinine clearance was directly and strongly related with LVM, indicating that glomerular hyperfiltration, rather than hypofiltration, is linked to early hypertensive cardiac structural changes [10]. A direct association between creatinine clearance, estimated by the Cockcroft-Gault equation, and LVM was also reported in a subgroup of hypertensive patients with high-normal albumin excretion rate [13]. In contrast, studies performed in untreated patients with established hypertension showed that age-dependent GFR decline is more pronounced in individuals with concentric LVH than in hypertensives with normal LVM [9], which accords with find-

ings in a small series of Japanese patients [14]. These associations are in keeping with notion that both LVH and carotid intima-media thickness underlie a higher prevalence of mild renal dysfunction in essential hypertension [15]. The two largest studies performed so far in patients with untreated, uncomplicated, essential hypertension [9, 16] coherently demonstrated a strong inverse relationship between GFR and LVM. Importantly, the second study [16] showed that this link (Fig. 13.1) is largely independent of a series of emerging risk factors, such as endothelial dysfunction, inflammation, insulin resistance, and uric acid. The reason that minor degrees of renal function loss predict adverse clinical outcomes and LVH in individuals with otherwise uncomplicated hypertension remains largely unknown. A likely explanation is that in hypertensive patients, creatinine and other GFR indicators represent integrated measures of organ damage that, in association studies, may capture the information loss attributable to the imprecision of BP measurements (residual confounding). In keeping with this possibility, in the study mentioned above [16], clinic-measured BP was only weakly related with LVM. On the other hand, it can be hypothesized that impaired renal function is a surrogate of other known and unknown factors. In this respect, sodium retention and attendant alterations in the renin–aldosterone system and SNS overactivity are important causative mechanisms of LVH, which are potently activated in renal insufficiency. Sympathetic activity, in particular, is very strongly associated with LVM in hypertensive patients [17]. Intriguingly, renal function loss and insulin resistance interacts in determining the severity of LVH in essential hypertensives. Indeed, LVM was higher in insulin-resistant patients with moderate CKD than in those with identical renal impairment but preserved insulin sensitivity [16]. A role of insulin resistance and attending metabolic sequels, including hyperinsulinemia and insulin-like growth factor-1 on cardiac mass in patients with essential hypertension, was reported [18]. Interaction between moderate renal

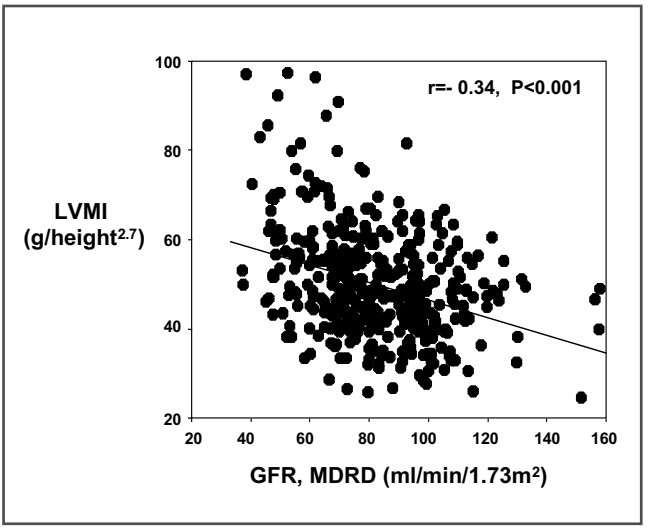

Fig. 13.1 Relationship between glomerular filtration rate (GFR) and left-ventricular mass (LVM) index in essential hypertensive patients with various degrees of renal function; *MDRD,* Modification of Diet in Renal Disease study (modified from [16])

insufficiency and insulin resistance would imply that hypertensive patients displaying both risk factors deserve closer clinical attention and appropriate interventions to limit progression of renal insufficiency and improve insulin sensitivity.

Impaired diastolic function is often the first detectable abnormality in many cardiac diseases and represents a frequent alteration in unselected patients with moderate to severe CKD. In fact, 65% of the latter display alterations in indices of diastolic function [i.e., velocity of early diastolic transmitral flow (E) and late (A) diastolic transmitral flow, E/A ratio, pulmonary vein flow velocities, and isovolumetric relaxation time], as determined by conventional echocardiographic methods, and as many as 82% show diastolic dysfunction upon tissue velocity imaging [19]. In CKD patients, there is a continuous, inverse relationship between LVM and GFR [20]. Such a link is not confined to patients with established renal diseases because coherent associations between echocardiographic LVM and renal function were reported in community studies in the elderly [21] and because similar associations between echocardiographically-detected LVH and renal function were also reported in a study at the community level [22].

A detailed analysis of the prevalence, dynamics, and prognostic implications of abnormalities in LVM in CKD patients without overt heart failure has been performed in the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study cohort [4]. In this study, which is the largest so far in predialysis stage 3–4 CKD patients, the prevalence of LVH at baseline was 47%, i.e., similar to that found in a previous study in 244 nondiabetic stages 3–5 CKD patients [3]. In CREATE, eccentric LVH was more frequent than concentric LVH (about 20% and 27%, respectively. On extended (4-year) longitudinal observation, CV event-free survival was worse in the presence of concentric LVH and eccentric LVH compared with the absence of LVH. Treatment to the higher hemoglobin (Hb) target (13 g/dl) was associated with reduced event-free survival in the subgroup with eccentric LVH at baseline. CREATE findings confirm that LVH is common in predialysis patients and that it predicts poor clinical outcomes and poses a strong warning against complete anemia correction in this population because a high Hb target (13 g/dl) aggravates the adverse prognosis of eccentric LVH.

13.2.3 Cardiomyopathy in End-stage Renal Disease Patients

LVH by EChoG is highly prevalent in ESRD, affecting 70–80% of the dialysis population. As previously alluded to, MRI is a better method for measuring LVM and function than is EChoG. MRI allows direct measurement of LVM and is free of the mathematical constraints intrinsic to the geometric assumptions needed when LVM is estimated by standard EChoG. MRI is a well-validated technique that reliably estimates LVM in patients with essential hypertension, with these estimates being uniformly lower than those provided by EChoG [23].

A thorough analysis of determinant of LVM by MRI was recently performed in a large dialysis (246 hemodialysis patients) population in Scotland [24]. In that study,

63.8% of patients had LVH on MRI, and this alteration was more common in patients with higher predialysis systolic BP, predialysis pulse pressure, and calcium-phosphate product. Furthermore, LVH was significantly associated with higher end-diastolic and end-systolic volumes and lower ejection fraction (EF). The independent predictors of LVH were end-diastolic volume, predialysis systolic BP, and calcium per phosphate product. In essence, this study substantially confirms previous observations made with EChoG and indicates that the discrepancy in the estimates of LVH by MRI and EChoG in ESRD (63.8% vs 70–80%, respectively) are less pronounced than initially envisaged, particularly taking into account that the population in this study was composed of individuals at relatively low risk (candidates to renal transplantation) who were on average 10–15 years younger than unselected ESRD patients enrolled in the studies by Parfrey et al. [25] and Zoccali et al. [8].

Alterations in LV function are classically distinguished into two broad categories: diastolic and systolic dysfunction. Approximately 40% of patients with CHF have predominantly diastolic LV dysfunction. Even though the E/A ratio predicted mortality in a Japanese study [26], because of the difficulty of grading diastolic function and the extremely high frequency of diastolic dysfunction in ESRD, this alteration per se is unlikely to provide additional information beyond that given by LVM for risk stratification in this population.

LV systolic function can be estimated by EChoG based on measurements made at the endocardial level, i.e., by standard fractional shortening or EF (the most popular index of systolic function). As these methods can overestimate cardiac contractility in patients with concentric LVH, a new (geometry-independent) index of myocardial contractile efficiency – midwall fractional shortening – was introduced in the early 1990s [27].

More than one third of patients starting dialysis have clinical evidence of heart failure, and the underlying cardiomyopathy is not halted by chronic dialysis. Because reversal of cardiomyopathy in ESRD is difficult to achieve, it is fundamental to focus on patients when they are at an asymptomatic phase. No study has, however, tested the prognostic value of systolic function indicators in asymptomatic patients with CKD. In the asymptomatic ESRD population, the proportion of patients with systolic dysfunction is at least seven times higher than in coeval cohorts in the community [28]. Of note, fractional shortening at midwall identifies a much greater proportion of ESRD patients with abnormal systolic function than does standard EF (48% vs 22%) (Fig. 13.2). This phenomenon can be attributed to the high prevalence of concentric LVH (35–40%) in the dialysis population. As noted in studies of individuals with essential hypertension, at comparable levels of midwall fractional shortening, both EF and fractional shortening at endocardial level systematically overestimate systolic function in patients with concentric hypertrophy or remodeling. Importantly, LV systolic dysfunction, measured either by midwall fractional shortening or by standard EF, is a strong and independent predictor of incident CV complications in patients with ESRD [28]. Furthermore, the simultaneous presence of raised LVH and compromised LV systolic function entails a higher risk in this population than that portended by these alterations separately (Fig. 13.3). Collectively, these findings indicate that echocardiographic assessment of myocardial contractility may prove useful in secondary prevention strategies for patients with ESRD.

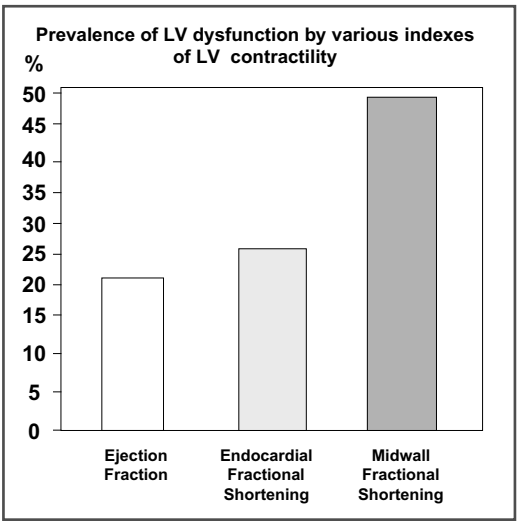

Fig. 13.2 Prevalence of left-ventricular (LV) systolic dysfunction by various indicators of cardiac contractility in end-stage renal disease (ESRD) patients (modified from [28])

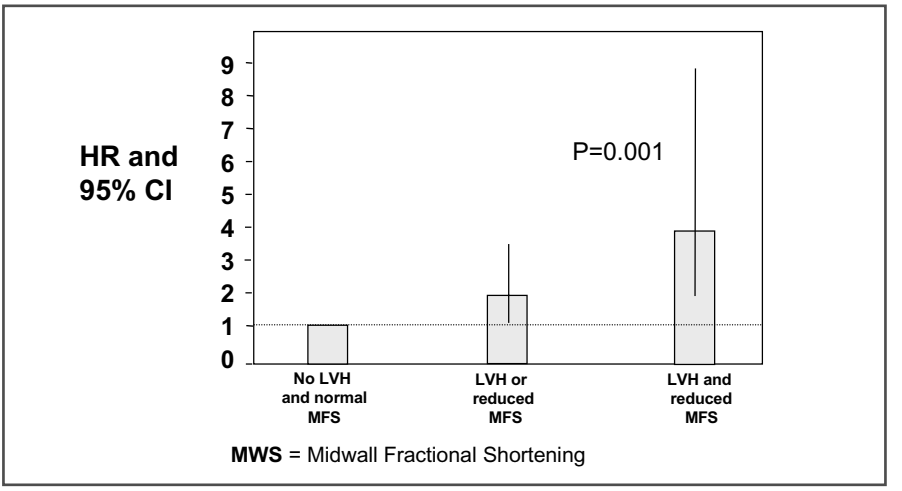

Fig. 13.3 Interaction between left-ventricular hypertrophy (LVH) and LV systolic dysfunction [as defined on the basis of midwall fractional shortening (MWFS)] in the risk of incident cardiovascular events in end-stage renal disease (ESRD) patients (modified from [28]). Patients are divided into three groups: the first patients with normal LV mass (LVM) and MWFS, the second with either LVH or abnormal MWFS, and the third with both alterations. *HR*, hazard ratio; *CI*, confidence interval

Secondary prevention strategies demand that cardiac alterations with the potential to evolve into more severe disease not only be screened or detected but also monitored periodically using well-validated clinical indicators. Recent evidence indicates that both LVH progression and worsening systolic dysfunction predict CV events in

ESRD independently of baseline values and traditional and emerging risk factors. Kidney Disease Quality Outcomes Initiative (KDOQI) guidelines recommend that EChoG be repeated at 3-year intervals. Recent data indicate that studies performed at intervals of 15 months can provide relevant prognostic information and that therefore, EChoG repeated at this interval may be useful [29]. Standard EChoG studies, therefore, have the potential to improve the quality of follow-up in CKD and ESRD patients. Future studies will establish whether treatment policies guided by indicators of LVM and LV function actually produce better outcomes in this high-risk population. Prevention strategies are fundamental in CKD because LV systolic dysfunction confers a highly adverse prognosis in ESRD. Systolic dysfunction is the strongest predictor of recurring heart failure in dialysis patients. Furthermore, the mean time to death in patients with this disturbance is just 38 months [25].

13.3 Drug Treatment of Left-Ventricular Disorders in Chronic Kidney Disease and End-stage Renal Disease Patients

Because LVH is a risk factor for death and CV complications independently of BP, and because at comparable BP reductions, angiotensin-converting enzyme inhibitors (ACEIs) are superior to other drugs for regressing LVH in ESRD patients, an ACEI is the first rational choice in these patients. A per-protocol analysis of a recent randomized trial, Fosinopril in Dialysis (FOSDIAL) in ESRD patients with EChoG-confirmed LVH showed a 21% decrease in the risk of major CV events [30], which is in line with previous retrospective analyses of ACEI treatment in observational databases. Of note, in the FOSDIAL study, fosinopril produced a –5/–3 mmHg BP fall compared with placebo in hypertensive patients but did not modify arterial pressure in normotensive patients. ACEIs are unlikely to induce favorable effects on LVM when administered to normotensive dialysis patients. Indeed, ramipril had no influence on this outcome measure in a randomized placebo-controlled study in dialysis patients with LVH and optimal BP control (average BP 125/69 mmHg) [31].

The great majority of dialysis patients presents with LV dilatation and dysfunction, i.e., alterations frequently associated with a history of myocardial infarction (MI) and cardiac ischemia. ESRD patients with LV dysfunction are at high risk of death, even when asymptomatic [28]. In the Survival and Ventricular Enlargement (SAVE) trial in asymptomatic patients with LV EF 40% after MI, captopril prompted a 19% reduction in all-cause mortality and a 37% decrease in the risk of progressing to heart failure[32]. Importantly, these beneficial effects were registered in all patient groups, including those with moderate kidney failure and those with adjunctive therapies, such as thrombolysis, aspirin, and/or beta blockers. Similar benefits were elicited by perindopril in the Trandolapril Cardiac Evaluation (TRACE) trial [33]. Although detailed data on LV function in patients enrolled in the FOSDIAL study [30] were not reported, it is possible that part of the beneficial effects of fosinopril in ESRD with LVH derived from the prevention of LV dysfunction progression. Available analyses

of another placebo-controlled, randomized study with telmisartan in ESRD patients with heart failure [New York Heart Association (NYHA) II–IV] and LV EF <40% shows that this drug reverses LV remodelling and ameliorates LV function in this population [34].

Beta-blocker prescription is formally recommended in patients who suffered MI because these drugs reduce the rate of sudden death and recurrent MI. A post hoc analysis of the SAVE trial suggested that β-blockers may also retard ventricular disease progression because the use of these drugs was associated with a 30% reduction in the risk of CVD death and with a 21% reduced risk of heart failure. This retrospective analysis is fully in line with results of the CArvedilol Post infaRction survIval COntRol in left ventricular dysfunction (CAPRICORN) study [35], which prospectively tested the effect of carvedilol in patients with EF 40% who were being treated with an ACEI. That β-blockade may be particularly relevant in ESRD patients with LV dysfunction is suggested by the fact that SNS activity assessed by plasma norepinephrine appears to be raised in proportion to EF decline in these patients [36]. Furthermore, the beneficial effect of carvedilol in the ESRD population is directly supported by a small, randomized, placebo-controlled trial that showed consistent improvement in LV volumes, LV function, cardiac arrhythmia [37], and survival in these patients [38]. It is important to emphasize that in the above-mentioned Telmisartan -based study in ESRD [34], the benefit of angiotensin II blockade was additive to that of ACEIs and β-blockers. This protective effect may depend on the peculiarly favorable effect of this sartan on parasympathetic–sympathetic nervous system balance. Indeed, telmisartan significantly increases parasympathetic nervous system activity while leaving SNS activity unmodified in patients with essential hypertension.

Tailoring interventions aimed at countering hypertension, LVH, and systolic dysfunction in ESRD extreme care should be aimed at maintaining BP at the best-tolerated level. Reaching and maintaining a normal BP goal in patients with dilated cardiomyopathy with a regimen including a β-blocker (carvedilol) may improve the hemodynamic profile and prolong survival even in this high-risk category of ESRD patients.

13.4 Dialysis Treatment Modalities, Implantable Cardioverters, and Cardiac Resynchronization in End-stage Renal Disease Patients with Left-ventricular Systolic Dysfunction

There is no randomized controlled trial comparing peritoneal dialysis to hemodialysis in the management of LV dysfunction and heart failure. United States Renal Data System (USRDS)-based analyses consisting of >100,000 incident ESRD patients suggest that mortality rates are actually higher in peritoneal dialysis patients with CHF and gets worse with increasing duration of follow-up [39]. Subclinical overhydration is more common in peritoneal than in hemodialysis patients [40]. Subtle volume expansion is associated with hypertension and LVH, both of which trigger LV systolic dysfunction.

The most relevant advancement in treating LVH and LV disorders in ESRD patients is the demonstration by Culleton et al. that nocturnal dialysis reverses LVH [41]. These authors, in a randomized, controlled trial in 51 patients, compared the effects of nocturnal hemodialysis (five or six 6-h, dialysis sessions per week) to conventional thrice-weekly hemodialysis over 6 months. Remarkably, nocturnal hemodialysis significantly reduced LVM. This change went along with reduced systolic BP, prompting a decrease or discontinuation of antihypertensive medications in about 60% of patients. This study, which echoes clinical observations made in a large dialysis program in Tassin in the 1980s [42], emphasizes the impact of volume and hypertension control for improving the discouraging results of recent intervention studies aimed at reducing CV risk in ESRD patients.

The American College of Cardiology recommends that implantable cardiac defibrillators (ICDs) should be used in patients with an EF <30%, mild to moderate symptoms of heart failure, and a life expectancy >1 year. Some dialysis patients with severely reduced EF can be expected to survive >1 year. In the trial by Cice et al, discussed in the previous section [38], the 2-year mortality for patients with an average EF of 26% on carvedilol was 52%. ICD use appears to be beneficial in ESRD because a 42% relative risk reduction [RR 0.58 (95% confidence interval {CI} 0.50–0.66)] with ICD implantation was registered in hemodialysis patients [43]. The use of ICD in dialysis patients is quite limited because a mere 8% of eligible patients receive an ICD as secondary prevention. The fact that to date there are still no randomized studies looking at the benefit of ICD implantation for primary or secondary prevention in these patients is probably the reason renal physicians and cardiologist do not apply ICDs in ESRD patients with LV dysfunction.

Cardiac resynchronization (CRT) with or without ICD implantation is increasingly applied to treat heart failure in selected patients. This device consists of a specialized pacemaker that synchronizes pumping activity of the left and right ventricles. Indications for CRT implantation include EF <35%, a QRS interval >130 ms, and the presence of heart failure symptoms. A post hoc analysis of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [44] reported that CKD is associated with a 69% excess risk for sudden death, but no such data exist for ESRD populations. CRT may be a valid treatment option in suitable hemodialysis patients. However, we still lack studies based on clinical end points comparing various dialysis strategies.

13.5 Conclusions

In conclusion, alterations in left ventricular mass and function are much frequent in patients with CKD and almost universal in those with ESRD. While the negative prognostic value of these alterations is well established we still have a very scarce number of intervention studies testing the effect of drugs and other interventions on LVH and LV function disorders in these patients. Beta blockers and angiotensin

antagonists improve LV performance and reduce mortality in ESRD patients with LV dysfunction. On the other hand more frequent and longer dialysis schedules determine a substantial regression of LVH in these patients. Given the extremely high risk of cardiomyopathy in ESRD, secondary prevention strategies in the early phases of CKD appear of paramount importance.

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Pathophysiological Mechanisms and Prognostic Significance of Renal Functional Impairment in Cardiac Patients

14

M. Volpe, M. Testa

Abstract Heart and kidney dysfunction are often associated, the primary disorder of one of these two organs being the cause of secondary involvement of the other. These interactions represent the pathophysiological basis of cardiorenal syndrome. Renal dysfunction is very common in heart failure patients, with a highly variable prevalence according to the subgroup of patients considered. The complex pathophysiologic interactions between heart and kidney are far from being completely understood. Several "cardiorenal connectors," which represent the major players of the neurohumoral response in heart failure, have been identified. They act both through and independently from extracellular fluid volume control. Another mechanism, more recently taken into great consideration, is that of increased central venous pressure. Anemia, very frequent in both heart and renal failure, is most probably the third condition of this deadly syndrome, sometimes also called cardiorenal-anemia syndrome. In patients with heart failure, renal function has a powerful prognostic significance. This is true both in chronic heart failure over a long follow-up and in acutely decompensated heart failure for in-hospital mortality. In patients with advanced heart failure, baseline glomerular filtration rate has been reported to be even more powerful than left ventricular ejection fraction in predicting mortality. The prognostic meaning of worsening renal failure during hospitalization for acute decompensated heart failure is, on the contrary, less clear.

Keywords: Heart failure • Cardiorenal syndrome • Renal impairment • Extracellular fluid volume • Neurohumoral response • Renin–angiotensin–aldosterone system • Central venous pressure • Anemia • Prevalence • Prognosis • Pathophysiology

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Cardiorenal Syndrome. Adel E. Berbari, Giuseppe Mancia (Eds.)

14

14.1 Definition of Cardiorenal Syndrome

Various degrees of heart and kidney dysfunction are very often associated, with the primary disorder of one of these two organs being the cause of secondary involvement of the other. These interactions represent the pathophysiological basis of very relevant clinical entities collectively defined as cardiorenal syndrome (CRS). What really needs to be stressed is the bidirectional nature of the pathophysiological relationship between the kidney and the heart. According to a recent definition, five subtypes of CRS can be identified [1]:

- Type 1 CRS: Also called acute CRS, this subtype is characterized by acute kidney injury secondary to acute heart failure (HF), both de novo acute HF and acutely decompensated chronic HF (ADHF). Type 1 CRS can occur either in HF with systolic left ventricular (LV) dysfunction or in HF with preserved LV systolic function, with different prognostic impact.
- Type 2 CRS: Also called chronic CRS, this subtype is characterized by progressive chronic kidney disease (CKD) secondary to chronic HF.

These two subtypes of CRS, characterized by renal involvement in patients primarily affected by cardiac diseases, are the main focus of this chapter.

- Types 3 and 4 CRS: Also called acute and chronic renocardiac syndrome, these two subtypes, on the contrary, refer to cardiac dysfunction secondary to primary kidney disease. They will not be the main topic of this chapter.
- Type 5 CRS: This subtype is a less well-defined entity characterized by combined cardiac and renal dysfunction due to acute or chronic systemic disorders.

This classification, which focused on the aspects of duration (acute vs. chronic disease) and sequence of events (kidney failure first vs. HF first) seem to be useful for clinical purposes although questionable from a strictly pathophysiological point of view [2], and has been recognized as a work in progress by working groups of nephrology societies.

14.2 Prevalence of Renal Functional Impairment in HF

Renal dysfunction is common in HF patients, and a precise estimate of its prevalence is greatly dependent on definitions of renal dysfunction; equations used to estimate creatinine clearance (CrCl), i.e., Cockroft–Gault formula, or glomerular filtration rate (GFR), i.e., the more recent and widely used Modification of Diet in Renal Disease (MDRD) equation; and from subsets of HF patients. About a half the patients with chronic HF develop CKD when it is defined as serum creatinine level ≥1.5 mg/dl or a CrCl <60 ml/min.

In a recent meta-analysis of published literature that included a community-based clinical trial and hospitalized HF patients, Smith and co-workers [3] reported that

63% of HF patients had some degree of renal impairment (defined as creatinine >1.0 mg/dl, CrCl or estimated GFR (eGFR)<90 ml/min, cystatin-C >1.03 mg/dl) and that 29% of patients had moderate to severe impairment (defined as creatinine ≥1.5 mg/dl, CrCl or eGFR<53 ml/min, cystatin-C ≥1.56 mg/dl). The same authors also reported that the prevalence of renal impairment may largely vary according to the subgroup of patients considered, going from 51% to 69% of patients with any degree of impairment and from to 10% to 32% of patients with moderate to severe impairment when considering outpatients and hospitalized patients, respectively.

The prevalence of renal dysfunction is even higher when considering patients with ADHF. Only 28.7 patients enrolled in the Acute Decompensated Heart Failure National Registry (ADHERE) had creatinine level <1.0 mg/dl at the initial evaluation, and even fewer patients (9%) had a completely normal renal function when evaluated according to the estimated CrCl calculated using the Cockcroft–Gault equation adjusted for ideal body weight and gender [4]. Patients in the ADHERE database had a median age of approximately 75 years and were 10–15 years older than those typically enrolled in clinical trials. Another peculiar feature of the ADHERE database is that women were slightly more highly represented than men [5].

Taking advantage of the differences in characteristics of patients enrolled in the three trials of the Candesartan in Heart Failure–Assessment of Mortality and Morbidity (CHARM) program, Hillege and co-workers reported that the proportion of patients with an eGFR<60 ml/min was comparable among patients with LV ejection fraction (LVEF) >40% (CHARM preserved) and <40% (CHARM added), being 34.7% and 33%, respectively [6]. The prevalence of patients with eGFR <60 ml/min, however, was substantially higher (42.6%) in the subgroup of patients with LVEF <40% and intolerant to angiotensin-converting enzyme inhibitors (ACEIs), who were enrolled in the CHARM alternative trial. A similar prevalence of patients with serum creatinine >1.7 mg/dl (22.2% vs 18.9%) was reported from Bhatia and co-workers among patients with preserved LVEF (>50%, mean 62.4%, n = 880) and reduced LVEF (< 40%, mean 25.9%, n = 1,570), respectively, admitted during a 2-year period to 103 hospitals in the province of Ontario, Canada [7].

Among the 14,527 patients enrolled in the Valsartan In Acute Myocardial Infarction (VALIANT) trial with acute myocardial infarction complicated by clinical or radiologic signs of HF, LV dysfunction, or both, and a documented serum creatinine measurement, 33.6 % had CKD (as reflected by an eGFR < 60 ml/min per 1.73m^2 of body surface area). The real prevalence of CKD after acute myocardial infarction was even higher, considering that patients with creatinine > 2.5 mg/dl were excluded from the trial [8].

14.3 Pathophysiological Mechanisms

The complex pathophysiologic interactions between heart and kidney are far from being completely understood. In 1990, Guyton extensively described normal physio-

logical interactions between extracellular fluid volume (ECFV) control by the kidney and systemic circulation by the heart [9]. The kidney has a key role in Guyton's as the central regulator of ECFV and the renin–angiotensin–aldosterone system (RAAS). The model is sufficient to explain changes in ECFV, blood pressure, and cardiac output in combined heart and renal failure.

More recently, in their fundamental article that highlights a number of important mechanisms perpetuating and amplifying structural and functional CRS derangements, Bongartz and co-workers [10], in the search for common denominators in heart and renal failure, proposed four potential cardiorenal "connectors" (CRC): inflammation, nitric oxide (NO)/reactive oxygen species (ROS) balance, the sympathetic nervous system (SNS), and the RAAS. The four CRCs represent the major players of neurohumoral response in HF and are generally adaptive in the short term and maladaptive over the long term, hence establishing and exacerbating the vicious cycle that contributes to acceleration of both morbidity and mortality in patients with HF. These CRCs strictly interplay among them and have effects on both ECFV regulation and beyond ECFV regulation, although this distinction may actually be arbitrary.

The neurohumoral response that aids the body in adjusting to challenges that impair circulation, particularly underfilling of the systemic arterial bed or a decrease in blood pressure – also referred to as the *hemodynamic defense reaction* – is the most important among the different homeostatic mechanisms. This is virtually the same physiologic response to exercise and hemorrhage that becomes maladaptive in HF because of its long duration and progressive intensification. The three major components of the hemodynamic defense reaction – salt and water retention, vasoconstriction, and cardiac stimulation – are each mediated by signalling cascades controlled by several extracellular messengers that act not only on the heart but also on vessels and kidneys. These include biologically active peptides such as angiotensin II (Ang II), vasopressin, atrial natriuretic peptide (ANP), endothelin and cytokines, catecholamines, aldosterone, NO, prostaglandins, and erythropoietin. A single extracellular messenger can cause different, and even opposite, responses by activating different receptor subtypes. Many mediators share actions on the kidneys, i.e., fluid retention; on blood vessels, i.e., vasoconstriction; and on the heart, i.e., enhanced contractility.

One typical key feature of the hemodynamic defence response is represented by the paradoxical response of the kidney and its related signalling-mediator peptides, which in the presence of fluid retention and systemic vasoconstrictors react to underfilling of the arterial system as perceiving fluid depletion and hypotension. This response causes further water and sodium retention and vasoconstriction.

14.3.1 Complex Mechanisms Involved in ECFV (Dys)regulation in HF

Edema and dyspnea are the major clinical manifestations of HF and are partially due to sodium and water retention by the kidneys. Several mechanisms interplay to deter-

mine expansion of ECFV in HF. HF is characterized by a decrease in cardiac index and in intra-arterial blood volume. Arterial hypovolemia inactivates the high pressure baroreceptors in the aortic arch and coronary sinus, attenuates tonic inhibition of afferent parasympathetic signals [11] to the central nervous system, and enhances sympathetic efferent tone with subsequent activation of the RAAS. Also, hypoperfusion of the juxtaglomerular apparatus contributes to this response.

Angiotensin and renal nerve stimulation both activate receptors on the proximal tubule epithelium, which enhances sodium reabsorption [12, 13]. Furthermore, the resultant decreased sodium delivery to the distal nephron impairs the normal escape mechanism from the sodium-retaining effect of aldosterone. Renal vasoconstriction of the glomerular efferent arteriole by Ang II in HF also alters net Starling forces in the peritubular capillary (decreased hydrostatic and increased oncotic pressure) in a direction that enhances sodium reabsorption [14]. Thus, angiotensin and alpha-adrenergic stimulation increase sodium reabsorption in the proximal tubule by activating sodium bicarbonate cotransporters and apical sodium–hydrogen exchangers [15]. Finally, Ang II promotes aldosterone secretion, which boosts sodium reabsorption at the distal nephron level [16]. Importantly, increased proximal sodium reabsorption decreases distal sodium and water delivery, stimulating macula densa cells to increase synthesis of renin that further amplifies neurohormonal activation [17]. SNS activation leads also to nonosmotic release of arginine vasopressin (AVP) [16].

Enhanced renal sodium and water reabsorption predominantly fills the compliant venous circulation, increasing central venous and atrial pressures. Normally, an increase in atrial pressure suppresses AVP release and enhances water diuresis, decreases renal sympathetic nerve tone [18], and augments natriuretic peptide secretion. However, in patients with HF, cardiac mechanoreceptor activity is blunted, and thus this "servomechanism" is impaired [19, 20]. Atrial natriuretic peptide, in view of its natriuretic, vasorelaxant, and renin-inhibitor properties, has been regarded as an ideal counterregulatory mechanism to the activation of vasoconstrictors and sodium-retaining hormones in HF [21]. Unfortunately, in patients with HF, these atrial–renal reflexes are overwhelmed by neurohormonal activation. Moreover, in contrast to healthy individuals, plasma levels of atrial natriuretic hormone were found not to increase further during a saline load in patients with dilated cardiomyopathy and mild HF, and the natriuretic response was also blunted [22].

Another important mediator in renal control of ECFV is NO, which causes vasodilatation, natriuresis, and desensitization of tubuloglomerular feedback [23], whereas ROS have the opposite effects [24].

14.3.2 CRC: Mechanisms Beyond ECFV Regulation

The four CRCs proposed by Bongartz and co-workers [10] are all fundamental and interconnected mechanisms involved in regulating ECFV, but their roles are also crucial in determining other structural and functional derangements at the level of both heart and kidney.

14.3.2.1 RAAS

One of the most deleterious actions of the RAAS is activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by Ang II, resulting in formation of ROS, documented in several cell types, including renal cells [25] and cardiomyocytes. At the level of the heart of patients with HF, an increase in NADPH-oxidase activity that results in induction of hypertrophy has been demonstrated [26, 27]. Changes in the cellular redox state are also implicated in vascular inflammation via nuclear factor kappa B (NF-κB) pathway [28]. Furthermore, the RAAS interacts with the SNS by complex mechanisms [29] that can be blocked by ACEIs.

14.3.2.2 Balance Between NO and ROS

In the CRS, the balance between NO and ROS is altered because of an increased production of ROS, a low antioxidant status, and lower availability of NO. In renal failure, a relative NO-deficiency is caused by both reaction of NO with oxygen radicals and by high concentrations of circulating asymmetric dimethyl arginine (ADMA), an endogenous NO synthase inhibitor [30], which has also been demonstrated in patients with HF. Oxidative stress by hydrogen peroxide (H_2O_2) has been shown to increase activity of preganglionic sympathetic neurons in vivo and in vitro in rats, raising mean arterial pressure and heart rate [31].

14.3.2.3 Inflammation

There is abundant literature on inflammation in both HF and renal failure. Testa and co-workers [32] studied a wide panel of cytokines and their receptors in patients with mild to severe HF due to different etiologies and reported a correlation between cytokine levels and symptom severity. In renal failure, circulating levels of C-reactive protein (CRP) and several proinflammatory cytokines are predictors of atherosclerosis [33]. This low-grade inflammation state can cause ROS production and RAAS and SNS activation.

14. 3.2.4 SNS

The SNS affects the other CRCs, contributing to RAAS activation, ROS production, and immune system activation. SNS activation induces release of neuropeptide Y, which is involved in prolonged vasoconstriction and altered immune function [34].

14.3.3 Importance of Central Venous Pressure

Another mechanism, more recently taken into great consideration, is that of increased central venous pressure (CVP) [35], and in this context, the expression "congestive kidney failure" has been proposed. Mullens and co-workers [36] studied 145 patients admitted with ADHF treated with intensive medical therapy guided by pulmonary artery catheter and reported that worsening renal function (WRF), defined as an increase of serum creatinine ≥0.3 mg/dl during hospitalization, is best predicted by high values of CVP at admission and after intensive medical therapy. More than 75% of patients presenting with a CVP in the higher quartile (>24 mmHg) developed WRF that was not related to baseline cardiac index. On the contrary, a weak but statistically significant correlation was observed between baseline serum creatinine and cardiac index, whereas no correlation could be found between baseline CVP and baseline renal function. The same authors [37] previously demonstrated that elevated intra-abdominal pressure (≥8 mmHg) – from ascites and visceral edema, known to be associated with intra-abdominal organ dysfunction – is prevalent in patients with ADHF and is associated with impaired renal function. In the setting of intensive medical therapy for ADHF, changes in intra-abdominal pressure were better correlated with changes in renal function than any other hemodynamic variable.

Damman and co-workers [38] studied the relationship between CVP, renal function, and mortality in 2,557 patients with a broad spectrum of CVDs, mostly aortic and mitral valve disorders and HF, who underwent right heart catheterization. They found a curvilinear relationship between CVP and eGFR (estimated according to the MDRD equation): eGFR showed a small increase when CVP increased, remaining within the physiologic range from 1 to 6 mmHg, and a steep decrease when CVP increased to values >6 mmHg. Beside CVP, age and cardiac index were also associated with eGFR. In their study population, increased CVP was also independently related to all-cause mortality.

Data to support the concept that venous congestion, being transmitted to the renal veins and kidneys, leads to renal dysfunction became available in the 1930s when Winton [39], working on isolated mammalian kidney, showed that increased renal venous pressure was associated with reduced renal blood flow, urine flow, and urinary sodium chloride excretion – abnormalities that were reversed by lowering renal venous pressure. In the late 1980s, Firth and co-workers demonstrated that an increase in renal venous pressure can cause sodium retention by direct action on the kidney and initiate a vicious circle characterized by expansion of plasma volume and further increase in venous pressure [40]. Studies in animals have shown that increasing renal venous pressure leads to reduced GFR, sodium excretion, and renal blood flow [41–44]. Increased CVP also causes an increase in renal interstitial pressure in dogs [45], and small increases in CVP decrease the sensitivity of integrated baroreflex control of SNS activity in healthy humans [46].

14

14.3.4 Anemia: The Third Condition of a Deadly Triad?

The prevalence of anemia in studies on HF patients is highly variable – from 4% to 61% according to the different definitions of anemia used – with the majority of studies indicating a prevalence>20% [47, 48]. The prevalence of anemia is higher in patients with more advanced HF and increases even further if renal disease coexists, and with aging. Among the 3,029 patients in the New York Heart Association (NYHA) functional classes II–IV and LVEF <35% enrolled in the Carvedilol or Metoprolol European Trial (COMET) study [49], the prevalence of severe anemia (defined as hemoglobin level <11.5 g/dl for men and <10.5 g/dl for women) was 3.6% in men and 2% in women. Among the 59,772 HF patients, with a mean age of 72 years, enrolled in the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) study [50] from northern California, USA, 42.6 % were anemic at baseline according to World Health Organization (WHO) criteria. Anemic patients also had a higher mean serum creatinine level when compared with nonanemic patients (1.3 ± 0.8 vs. 1.1 ± 0.4 mg/dl, respectively, p <0.001). In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, which contained information on 48,612 patients hospitalized for HF in 259 U.S. hospitals with the aim of developing a clinical model predictive of in-hospital mortality rate, 51.2% of the cohort had hemoglobin levels of <12.1 g/dl and 25% were moderately to severely anemic (hemoglobin levels of 5–10.7 g/dl) [51]. In addition, the prevalence of anemia increases significantly with disease severity.

Evaluation of pathophysiological mechanisms of anemia in the setting of CRS is of great importance, particularly in order to determine the best therapeutic approach. To this end, Opasich and co-workers [52] evaluated stable patients with anemia and HF in NYHA functional class, mostly men, with ischemic or primary dilated cardiomyopathy in 80% of them, and mean EF of about 30%. Mean creatinine was at the high limit of normal, and 30% of patients had CKD. Almost all patients were treated with drugs inhibiting the RAS and diuretics. In their population, anemia was most commonly due to chronic disease (60%), less commonly to kidney disease (25%), and only rarely to iron deficiency. Several authors [53–57] agree that the most relevant pathophysiological mechanism responsible for anemia in HF is unresponsiveness to erythropoietin, due, at least in part, to chronic inflammation. Erythropoietin plasma levels, in turn, increase progressively with deteriorating cardiac function in patients with HF, possibly because of a slight partial pressure of oxygen (PO_2) reduction and relative renal ischemia [58].

Drugs commonly used in HF patients may also be involved. Among them, we could separate drugs with a potential inhibitory action at the level of bone marrow (i.e., ACEIs and angiotensin receptor blockers) from those that could be responsible for acute or chronic/occult blood loss, such as antiplatelet drugs and anticoagulants, which are ever-increasingly used in association in patients with HF due to ischemic heart disease.

Anemia is a frequent, well-recognized, and well-studied complication of CKD,

occurring early during the course of the disease and worsening as kidney function declines. Although decreased erythropoietin production is the most important mechanism of anemia in patients with advanced CKD, other mechanisms may be relevant, as resistance to erythropoietin, reduced expression of erythropoietin receptors and alteration of downstream signal transduction, bone marrow alteration, iron and vitamin deficiency, inflammatory states, occult blood loss, and drugs [59]. Nevertheless the negative or neutral results of many trials on anemia correction in both HF and renal patients [60–68] emphasize our limited understanding of the complex relationship between anemia, HF, and CKD.

14.4 Prognostic Significance

In patients with HF, renal function has a powerful prognostic significance. This is true both in chronic HF over a long follow-up and in ADHF for in-hospital mortality when evaluated by both serum creatinine level and GFR and, in most cases, both for single measurement and WRF.

14.4.1 Chronic HF

Data from the Studies of Left Ventricular Dysfunction (SOLVD) trial [69], which enrolled patients with LVEF ≤ 35%, both asymptomatic (SOLVD prevention, 4,228 patients) and with symptoms of HF (SOLVD treatment, 2,569 patients) suggest that even moderate impairment in renal function (patients with creatinine >2 mg/dl were excluded from enrollment) is independently associated with all-cause mortality. In particular, a CrCl <60 ml/min (as estimated from the Cockroft–Gault equation) carried a relative risk =1.41 both in the SOLVD prevention (95% CI 1.15–1.74) and SOLVD treatment trials (95% CI 1.20–1.65).

In a subgroup of 372 patients from the population of the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME II), mostly men (80.4%), with advanced HF (NYHA class III or IV), and with a mean age of 64.7 ± 9.5 years, baseline GFR, calculated by the Cockroft–Gault equation predicted mortality, over a median follow-up of 277 days, better than did LVEF [70]. Patients in the lowest quartile of GFR values (<44 ml/min) had almost three times the mortality risk (relative risk 2.85; $p<0.001$) of patients in the highest quartile (>76 ml/min).

In the 585 participants of the 6-min walk substudy of the Digitalis Investigation Group (DIG) trial, with 85% of them in NYHA classes II and III, with a mean age of 65 ±12 years, and a mean LVEF of 35 ± 13%), estimated CrCl predicted mortality, over a median follow-up of 2.6 years, independently of functional capacity measured by 6-min walk distance [71]. Furthermore, this study demonstrated a continuous relationship between CrCl and survival, and the probability of survival was reduced by

even minor reductions in CrCl, levels at which serum creatinine might still be normal.

In the meta-analysis by Smith and co-workers [3], adjusted all-cause mortality was increased for patients with any impairment of renal function (HR =1.56; 95% CI 1.53–1.60) and moderate to severe impairment (HR =2.31; 95% CI 2.18–2.44). Mortality worsened incrementally across the range of renal function, with 15% (95% CI 14–17) increased risk for every 0.5 mg/dl increase in creatinine and 7% (95% CI 4–10) increased risk for every 10 ml/min decrease in eGFR.

In the whole CHARM population, including those with reduced as well as preserved LV systolic function, eGFR was a significant and independent predictor of worse outcome during the follow-up (median = 34.4 months) after adjustment for major confounding baseline clinical characteristics. The risk for cardiovascular death or hospitalization for worsening CHF as well as the risk for all-cause mortality increased significantly below an eGFR of 60 ml/min^{-1} per 1.73 m^2, which is relatively common in patients with HF [6].

Anemia, too, has a meaningful prognostic value in the setting of chronic HF. In the ANCHOR study [50], a J-shaped curve for hemoglobin level and risks of death and hospitalization for HF – independently from underlying kidney dysfunction, major comorbidities, and longitudinal use of HF therapies – was demonstrated. Investigators found that very high (≥17.0 g/dl) and reduced (<13.0 g/dl) hemoglobin levels, as well as reduced kidney function (GFR <60 ml/min^{-1} per 1.73 m^2) were strong predictors of death and hospitalization among adults with HF, with or without reduced LVEF.

The unfavorable prognostic significance of anemia has been recently confirmed by data from the OPTIMIZE-HF registry [51]. Anemic patients had significantly higher in-hospital mortality [4.8% vs 3.0%, lowest (hemoglobin <10.7 g/dl) vs. highest (>13.5 g/dl) quartile], longer hospital length of stay (6.5 vs. 5.3 days), and more readmissions by 90 days (33.1% vs. 24.2%). They were also less likely to receive ACEIs and β-blockers at discharge. Lower hemoglobin levels remained an independent predictor for adverse outcomes after extensive covariate adjustments.

14.4.2 Acute HF

Data from the ADHERE database [5] shows that as renal function worsens, prognosis deteriorates as well. The mortality rate for all patients in ADHERE was 4.0%, whereas patients with severe renal dysfunction (serum creatinine level ≥3.0 mg/dl) not yet receiving dialysis had an in-hospital average mortality rate of 9.4%. Patients already on chronic dialysis had a mortality rate of 4.5%, only slightly higher than that of the general population of ADHERE. Not surprisingly, renal dysfunction also impacts hospital length of stay. The median length of stay for all patients in ADHERE was 4.1 days, but this increased to 5.7 days for patients receiving dialysis at the time of admission and to >7 days when serum creatinine level at admis-

sion was ≥3.0 mg/dl. By using only three parameters – serum creatinine, blood urea nitrogen, and systolic blood pressure – it is possible to identify a subgroup of patients with very high in-hospital mortality rate: if blood urea nitrogen was ≥43 mg/dl, systolic blood pressure <115 mmHg, and serum creatinine ≥2.75 mg/dl, then the mortality rate was 19.5%.

Forman and co-workers [72], retrospectively studying 1,004 patients admitted to hospital with a primary diagnosis of HF, showed that WRF developed in 27% of patients, most often within 3 days from admission. Parameters independently associated with WRF were history of diabetes mellitus, admission creatinine ≥1.5 mg/dl, and systolic blood pressure >160 mmHg. The adjusted risk ratio for hospital mortality rate was 7.5 (95% IC 2.9–19.3) for patients with WRF vs. patients without WRF.

Interesting data derives from analysis of OPTIMIZE-HF [73]. Patient characteristics that were most strongly predictive of in-hospital mortality rate included admission serum creatinine and systolic blood pressure and patient age. In-hospital mortality rate increased 18% for every 0.3 mg/dl increase in serum creatinine up to approximately 3.5 mg/dl; increases >3.5 mg/dl were not associated with incremental risk. The 1,834 patients that died during their hospital stay had at admission a serum creatinine of 2.2 ± 1.6 mg/dl, whereas the 46,778 survivors had a serum creatinine of 1.7 ± 1.6 mg/dl. The highest mortality rate, 16.3%, was observed among the subgroup of patients with serum creatinine ≥2.0 mg/dl and systolic blood pressure ≤100 mmHg at admission.

Data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial [74], designed to prospectively compare the strategy of pulmonary artery catheter-guided therapy with treatment based on clinical assessment alone with regard to short-term and 6-month outcomes in patients hospitalized with advanced HF, has been reported. These data confirm the prognostic value of renal function at baseline (evaluated as both serum creatinine and eGFR), but this parameter did not predict WRF from baseline to discharge and, at variance with previous reports, WRF was not associated with increased risk of death, or the composite end-point of death or rehospitalization, at 6 months. Thus, baseline renal function appeared to be more predictive of long-term outcomes than of WRF during hospitalization. There are a number of potential explanations for these results. First, a change in serum creatinine from 1.5 to 1.8 mg/dl represents a greater absolute loss of renal function than a change from 3.0 to 3.3 mg/dl. Therefore, the impact of a ≥0.3 mg/dl increase in serum creatinine may differ based on baseline renal function. Secondly, elevations in serum creatinine may have different prognostic implications, depending on the patient population and therapies used. In patients with HF, aggressive use of diuretics and RAAS inhibitors, which may improve both symptoms and possibly outcomes, is likely to result in increases in serum creatinine, but this increase may have a different prognostic meaning than a spontaneous one [75].

The significance of "iatrogenic" decline in renal function during hospitalization for ADHF is of great clinical importance and deserves further investigation.

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Stroke

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Abstract Stroke is a devastating co-morbidity in chronic kidney disease that is several -fold more common than in the general population. Although traditional cardiovascular risk factors account for much of the stroke risk in CKD, some risk factors like anemia and dyslipidemia are challenging to address in view of recent clinical trial data that do not seem to provide the full degree of expected benefit from risk factor correction as reviewed herein. Others such as hypertension and proteinuria reduction remain mainstays in stroke prevention.

Keywords: Hypertension • Stroke • Proteinuria • Dyslipidemia • Anemia • CKD • ESRD

15.1 Introduction

Each year in the United States, about 800,000 people experience a stroke, with one person dying from stroke every 3–4 min [1]. Recent data collected by the United States Renal Data System (USRDS) provided information on the prevalence of stroke in chronic kidney disease (CKD) and in patients who reach end-stage renal disease (ESRD) [2]. This annual data report indicates that about 9% of patients with CKD [generally defined as having an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2] and about 16% of those reaching ESRD had a stroke in 2004 compared with a prevalence of about 4% in those without CKD [2]. Stroke remains one of the most feared medical complications because of the dependency on other people it may cause. In this chapter we review the epidemiology of stroke in CKD, discuss mechanisms that are thought important in stroke occurrence, highlight those aspects of CKD that seem to enhance incident stroke rates, and conclude with a review of therapies recommended for stroke deterrence, including those for both primary and secondary stroke prevention.

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15.2 Epidemiology

15.2.1 Gauging Stroke Risk in CKD

A recent review summarized epidemiologic data showing the association of CKD and stroke risk [3]. Evaluating stroke risk in CKD involves processes similar to those used in other populations, as similar risk factors apply (Table 15.1). Patients are typically assessed for the presence and severity of factors listed in Table 15.1, type of renal disease, and estimated glomerular filtration rate (eGFR). Traditional risk factors account for much of the stroke propensity in CKD. However, an elevated risk of stroke in CKD persists even after adjusting for such factors [4]. Although the relative contributions of traditional and CKD-specific risk factors to stroke are unclear, modifiable risk factors should be identified and addressed when possible.

One noteworthy CKD-stroke relationship is that of subarachnoid hemorrhage in patients with autosomal dominant polycystic kidney disease. The risk of intracranial aneurysm is about 10% at age 50, and the presence of an aneurysm can be evaluated through noninvasive imaging. Counseling patients in advance about the implications of aneurysm detection on driver's licensing, life insurance, and other issues is advisable [5]. One final point is that CKD increases the mortality associated with acute stroke, particularly in those with the greatest degree of renal function impairment [6].

15.3 Mechanisms of Stroke Occurrence in CKD

15.3.1 Blood Pressure

One of the clearest lessons from treating high blood pressure (BP) with drug therapy has been the reduction in stroke occurrence. BP control seems to be the most important factor in stroke prevention, irrespective of the antihypertensive agent used [7]. Timely BP control, reaching goal values within weeks rather than months, is an important factor in risk reduction, especially in patients at high cardiovascular disease (CVD) risk. There are several mechanisms by which increased BP contributes to stroke risk: it enhances the rate of atherosclerosis and contributes to formation of small aneurysms in the cerebral circulation [8].

15.3.2 Dyslipidemia

It has been difficult to clearly associate increased cholesterol levels with stroke risk. The large meta-analysis of 45 prospective studies with >450,000 individuals followed for 5–30 years failed to show a relationship between cholesterol and stroke [9]. However, the large statin trials of the 1990s demonstrated in patients with coronary artery disease, appropriate treatment lowered the relative risk for stroke by 21% [10]. It appears that the benefits obtained with statin therapy are largely related to low-density-lipoprotein (LDL) cholesterol reduction, despite LDL being a weak stroke predictor in epidemiologic studies. Moreover, low levels of LDL are associated with increased risk of hemorrhagic stroke [11]. Outside of epidemiologic associations, little is known of the pathophysiologic role of LDL or any other cholesterol particle in cerebrovascular disease.

15.3.3 Anemia

Anemia is a common occurrence in CKD patients and substantially increases the risk of death in CVD [12] and stroke associated with CKD [13]. For example, in their study of 13,716 participants in the Atherosclerosis Risk in Communities (ARIC) Study, Abramson et al. analyzed the joint effect of CKD (creatinine clearance of <60 ml/min) and anemia (hemoglobin levels of <13 g/dl for men or <12 g/dl for women) on the risk of incident stroke during a 9-year follow-up period [14]. They noted that CKD was associated with an increased stroke risk after adjustment for other factors [hazard ratio (HR) 1.81; 95% confidence interval (CI) 1.26–2.02]. They noted further that this association was modified substantially by anemia, in which there was a higher risk of stroke compared with no CKD (HR 5.43; 95% CI 2.04–14.41). Thus, the combination of CKD and anemia carried substantial stroke risk independently of other known risk factors. Anemia increases cardiac output. A chronic increase in cardiac output can lead to vascular remodeling of elastic arteries, such as aorta and carotids. Such remodeling in turn results in arterial enlargement and compensatory arterial intima-media thickening, or arteriosclerosis. Both processes participate in vascular target-organ damage [15].

15.3.4 Proteinuria

Proteinuria increases stroke risk by 50–70% [16]. Data in support of a causal role for proteinuria in stroke patients are derived from post hoc analyses of large-scale clinical trials that suggest that reducing the level of albuminuria is associated with a concurrent decrease in cardiovascular risk. For example, in the Reduction in Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist

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Losartan (RENAAL) study involving 1,513 patients with type 2 diabetes mellitus and nephropathy, a 50% decrease in albuminuria was associated with a significant 18% decrease in risk of CVD [17]. Similarly, in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study of older people with hypertension and left ventricular hypertrophy, participants who achieved a lower level of albuminuria using losartan- or atenolol-based regimens had a significantly lower risk of subsequent fatal or nonfatal stroke than those with persistent albuminuria [18]. Although these associations do not necessarily imply causality and potentially are confounded by parallel changes in BP, they suggest that decreases in urinary protein excretion may result in a decreased risk of subsequent cardiovascular events. The presence of proteinuria may signal a greater thromboembolic tendency as a mechanism contributing to stroke risk. Alternatively, proteinuria may also reflect higher BP, and it is difficult to uncouple the benefit of BP reduction from an antiproteinuric effect in assessing the role of proteinuria reduction in stroke benefit [17]. Figure 15.1 shows some of the complex interactive factors in the predisposition to stroke in CKD. A number of other chapters in this book deal with specific CKD issues that enhance vascular risk, such as stiffness and calcification, and are not further covered in this chapter.

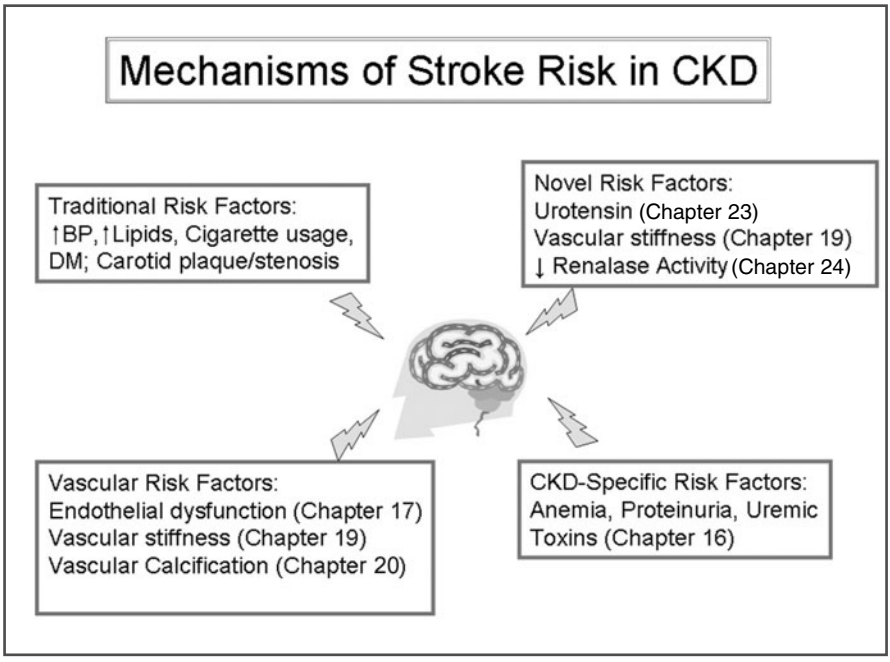

Fig. 15.1 Relationship between various risk factors and stroke. *CKD,* chronic kidney disease; *BP,* blood pressure; *DM,* diabetes mellitus

15.4 Management of Stroke Risk in CKD

15.4.1 Hypertension

Virtually all guidelines suggest antihypertensive therapy will reduce stroke risk [19, 20]. In the past 5 years, the only antihypertensive agent from which stroke benefit does not appear as robust as with comparators is atenolol [21]. Some data suggest an advantage for angiotensin receptor blocking (ARB) drugs based upon animal studies and limited human data. Stimulation of angiotensin II receptor subtype 2 (AT_2) could protect cerebrovascular function by recruiting collateral vessels and enhancing resistance of neurons to anoxia [22]. A recent meta-analysis compared ARB to angiotensin-converting enzyme inhibitor (ACEI) therapy covering about 36,000 patients in clinical trials, including the recently reported Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [23]. Results showed a statistically insignificant reduction in stroke risk with ARB (717/18,245) compared with the ACEI [768/18,292; OR 0.93 (95% CI 0.84–1.03)]. ARB therapy typically increased circulating angiotensin II levels that, though blocked from stimulating angiotensin II receptor subtype 1 (AT_1), stimulate other unblocked angiotensin-II receptors, such as AT_2. The subtle benefit of ARB on stroke risk has been thought to derive from AT_2 stimulation, because animal models using ARB in acute stroke show that these benefits are prevented by coadministration of AT_2 blockers [22]. Other proposed explanations for an ARB-related stroke benefit include reductions in platelet aggregation, reduced risk for new-onset type 2 diabetes mellitus, lower serum levels of uric acid [unique to the ARB losartan), and a benefit on atrial-fibrillation-related stroke risk (24]. Most authorities agree that BP reduction irrespective of the pathway chosen will reduce primary stroke occurrence.

Concern was recently expressed about the possibility of increasing stroke risk in those with stage 3–4 CKD (eGFR 15–60 ml/min/1.73m^2) [25]. Publication of the results of BP lowering treatment in patients with a prior stroke and current CKD in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial showed that BP reduction was beneficial and not attended by a J-curve effect at the lower level of achieved BP [26].

A recent review of BP-lowering therapies in patients with CKD [who were generally a subset of a larger trial, with the exception of the African American Study of Kidney Disease (AASK)] is summarized in Table 15.1 [27]. The authors echo the concern of many about the paucity of randomized clinical trial data in treating CKD patients and make the important point that stroke (and the related vascular morbidity dementia) is more common in CKD patients than is ESRD, arguing that cerebrovascular protection should be an even greater priority than nephroprotection [27]. Note that Table 15.1 does not include the PROGRESS trial data, which were published later than the period incorporated in the review.

Table 15.1 Stroke risk in cardiovascular disease patients: active vs. active antihypertensive drugs. Reproduced from [27], with permission from Journal of Nephrology, Wichtig Editore, Milano, Italy

Study	Drugs	Population	Δ BP, mm Hg	Stroke risk		
				RR	95% confidence interval	P Value
ALLHAT	Amlodipine vs. chlorthalidone	n=4,129; GFR <60 ml/min per 1.73 m^2	+0.4/-1.4	1.12	0.87-1.44	0.38
	Lisinopril vs. chlorthalidone	n=4,146; GFR <60 ml/min per 1.73 m^2	+0.9/+0.1	1.10	0.86-1.42	0.45
AASK	Ramipril vs. metoprolol vs. amlodipine	n=1,094; African-Americans; HTN renal disease (GFR. 20-65 ml/min per 1.73 m^2)		Strokes/patient-year=1.3% vs. 1.2% vs. 1.0%		NS
LIFE	Losartan vs. atenolol	n=1,063; DM + HTN + LVH	-2/0	0.60	0.23-1.25	0.17
IDNT	Irbesartan vs. amlodipine	n=1.146; DM; proteinuria >0.9 g/day and SCr=1.0(1.2)-3.0 mg/dL	-1/0	1.55	0.84-2.87	0.16
E-COST-R	Candesartan vs. conventional (mainly BBs and CCBs)	n=141; non-DM, age 60- 75 years; SCr = 1.2-2.0 mg/dL	+1.2/-1.4	*	*	NS

BBs, beta-blockers; *CCBs*, calcium channel blockers; *DM*, diabetes mellitus; *GFR*, glomerular filtration rate; *HTN*, hypertension; *LVH*, left ventricular hypertrophy; *NS*, nonsignificant; *SCr*, serum creatinine
*No data available

15.4.2 Dyslipidemia

Reduction of LDL cholesterol may be beneficial in secondary prevention of CVD in general, though not apparently for stroke, among persons with reduced kidney function. In patients with a creatinine clearance ≤75 ml/min in the Cholesterol and Recurrent Events (CARE) trial, pravastatin therapy was associated with a lower incidence of the combined primary outcome [death from coronary artery disease or symptomatic nonfatal myocardial infarction (MI)] compared with placebo after a median follow-up of nearly 5 years (adjusted HR 0.72; 95% CI 0.55–0.95; $P = 0.02$) [28]. However, stroke reduction, a secondary end point in the trial, did not quite reach significance (adjusted HR 0.62; 95% CI 0.39–1.00; $P = 0.051$).

Treatment with atorvastatin in the 4D trial undertaken in diabetic German dialysis patients also failed to show a stroke risk benefit [29]. In that study, the diabetic patients had about twice as many stroke-related deaths on the statin compared with those on placebo. Similarly, the recently reported Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), which assigned statin therapy to 1,389 dialysis patients and placebo to 1,384 dialysis patients had a slight but statistically insignificant increase in nonfatal stroke endpoints (53 in the rosuvastatin group versus 45 in the placebo group) [30].

Although much epidemiologic evidence points to increased LDL as a risk factor for stroke, the significant stroke risks reductions noted in individuals with normal kidney function just have not been seen in CKD. The most recent data from the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study in patients with an eGFR < 60 ml/min/1.73m^2 found 11 stroke events in 286 patients assigned to atorvastatin therapy (3.8%) compared with 12 strokes among 292 control individuals (4.1%) [31]. The 4D study cited earlier studied patients with ESRD and also showed no stroke-risk benefit [29]. Similar findings occurred in the AURORA trial. Thus, although the ALLIANCE trial did show an 8.6% reduction in all CVD, the benefit in CKD was principally noted in nonfatal MI and cardiac-related death.

The recent editorial by Wanner et al. on the ALLIANCE data summarized well the state of dyslipidemia treatment in CKD [32]. The authors indicated that the CKD subgroups of large statin trials demonstrate that statin treatment is both safe and effective in patients with a mean GFR of approximately 50 ml/min/1.73 m^2. However, as they also noted, little is known about the efficacy of statins in those with CKD stage 4. Future studies such as the ongoing Study of Heart and Renal Protection (SHARP), including roughly 9,000 participants with CKD and evaluating the effects of simvastatin plus ezetimibe, should provide more information about lipid reduction and prevention of vascular events in kidney disease [33].

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15.4.3 Anemia

Recombinant erythropoietin, an erythropoiesis stimulating agent (ESA), is indicated to correct anemia in persons with CKD (Amgen® prescribing Package Insert). A 2006 update of National Kidney Foundation guidelines defined target hemoglobin as ≥11.0 g/dl and advised caution when using an ESA to intentionally maintain hemoglobin at >13.0 g/dl [34]. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) investigators concluded that a hemoglobin target of 13.5 g/dl was associated with significantly greater risk of the primary composite outcome (death, MI, hospitalization for congestive heart failure without renal replacement therapy, or stroke) compared with a lower target of 11.3 g/dl (HR 1.34; 95% CI 1.03–1.74; $P = 0.03$), with no difference noted in quality of life between the groups [35]. A recent multinational randomized clinical trial [Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)] using darbepoetin alpha to manage anemia (hemoglobin target of 13 g/dl) in type 2 diabetes mellitus and CKD (not on dialysis), showed no beneficial effect on the studied primary outcomes (death; cardiovascular and renal events). On the other hand, fatal or nonfatal stroke was much more common in patients assigned to darbepoetin (HR 1.92) [36]. It could be that the small BP increase noted with ESAs, the lessened bleeding tendency when hematocrit is raised (thus a greater thrombosis potential), the increase in blood viscosity when hematocrit is higher, and the potential oxidative stress induced by greater iron administration may have contributed to these findings. The recommended hemoglobin target is between 11.0 and 12.0 g/dl in patients with CKD.

15.4.4 Other Targets

Several nontraditional risk factors are emerging as studies continue to unfold some of the mysteries of how CKD seems to accelerate atherosclerosis. An intriguing investigation by Bhuriya et al. indicates that higher levels of parathyroid hormone are associated with increased CVD [37]. Vascular calcification and stiffness also seem clearly connected to stroke and CVD in general, particularly in the dialysis populations, in whom they are best characterized [38]. The remarkable lack of awareness of the presence of diabetes in people with early CKD (<10% with CKD were aware of it) identified by the Kidney Early Evaluation Program (KEEP) represents an additional opportunity for educational endeavors in the area of public health [39].

With respect to antiplatelet approaches to stroke prevention, there are no data upon which to base a recommendation for the use of aspirin for primary prevention of stroke in CKD, as covered in a very comprehensive recent review [40]. There are also no data on secondary prevention in CKD using aspirin, but it is likely to be beneficial based on the aggregate experience in many populations and the known safety profile. In a secondary prevention trial known as the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, clopidogrel did not appear to

reduce recurrent stroke in the main trial [41]. Again, this did not include CKD patients, but the experience with using aspirin and clopidogrel to maintain graft patency showing an increased risk of serious hemorrhagic events in dialysis patients would urge caution in its use in CKD [42]. Limited data on dipyridamole from the European Stroke Prevention Study (ESPS) suggests that in combination with aspirin, it is useful in reducing secondary stroke rates, but no information was provided about kidney disease, which was not listed as a significant comorbidity in the study [43]. A decision to use an antiplatelet agent in CKD needs to be made principally on clinical judgment at this time.

15.5 Conclusions

CKD is associated with increased stroke risk. Stroke prevention requires aggressive management of traditional risk factors, particularly hypertension. Some of the excess stroke risk in persons with CKD appears to derive from consequences of renal impairment. Procoagulant and inflammatory pathways also are abnormally affected in mild to moderate CKD independently of other coexisting illnesses and vascular risk factors, as are alterations in arterial compliance.

Multiple classes of antihypertensive agents reduce stroke risk. Some physiologic evidence points to a basis for stroke risk reduction with ARB therapy, perhaps attributable to more than just BP lowering alone. Nonetheless, a recent large meta-analysis suggests strongly that stroke reduction benefit is principally derived from BP reduction [7]. Management of lipid levels is less certain and represents a fruitful area for future investigation. Anemia management appears helpful as long as the target hemoglobin achieved is not excessive, at least per US guidelines. Further clarification of antiproteinuric therapy benefits on stroke reduction are yet another area of active interest.

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Section V
Mechanisms of Cardiovascular Complications

Uremic Toxins

16

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Abstract A major complication of chronic kidney disease (CKD) is concomitant cardiovascular damage. Although patients suffering from CKD are frequently affected by a number of other conditions and/or comorbidities that enhance the cardiovascular risk, such as hypertension, insulin resistance, fluid overload, anemia, diabetes mellitus, and dyslipidaemia, the weight of these factors per se is insufficient to explain the entire uremic cardiovascular problem; therefore, it has been suggested that factors specific to CKD, such as the uremic milieu, must play a central role. In this chapter, we review current knowledge on uremic toxins with a potential cardiovascular impact, emphasizing their specific effects on the major cell types involved in this process, such as leukocytes, endothelial cells, vascular smooth muscle cells, and platelets.

Keywords: Chronic kidney disease • Uremic toxins • Cardiovascular impact

16.1 Introduction

Chronic kidney disease (CKD), the gradual loss of kidney function, provokes uremic syndrome, a complex of biological and biochemical alterations resulting in malfunction of various organs. Uremic syndrome originates from retention of solutes that under normal conditions are cleared by the kidneys into the normal urine. These compounds are called uremic retention solutes; if they are biologically/biochemically active, they are called uremic toxins. Even if they are not toxic, some uremic retention solutes may be useful markers of retention and/or toxicity.

Although the link between clinical deterioration and uremia was recognized decades ago, and although the number of newly identified pathophysiologic elements in this area has risen exponentially over recent years, knowledge about the responsible factors remains far from complete.

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16.2 Cardiovascular Implications

Up to 13% of the general population is affected with CKD stages 3–5 (≥ 50% loss of kidney function). Mortality increases from CKD stage 3 on, or even earlier [1], and survival on dialysis is shorter than that after diagnosis of most cancers.

Cardiovascular disease (CVD) accounts for > 50% of this mortality, and the process leading to cardiovascular events occurs early in the progression of CKD; CVD also develops in a dramatically shorter time compared with in the general population [1].

It is notable that the quality of vessels is to a large extent different in the uremic population compared with the population with normal kidney function, irrespective of stenotic or thrombotic lesions. The arterial system undergoes a specific remodelling process characterized by increased wall stiffness in parallel with the decline in renal function [2]. This results in decreased dampening of pressure and flow oscillations and progressive disturbance of normal ventricular–vascular coupling. The ejection of the same blood volume in a stiffer central arterial system generates a high-pressure wave, which propagates faster toward the periphery (increased pulse wave velocity) and the reflection of which returns earlier during the cardiac cycle than in healthy individuals (wave reflection). The resulting mismatch between the higher systolic workload and decreased diastolic perfusion leads to a lower coronary reserve, irrespective of stenotic or thrombotic lesions. To some extent, arterial stiffness can be attributed to medial wall calcification, or "elastocalcinosis," a specific feature of the overall increased propensity of patients with kidney disease to develop calcifications.

Atherosclerosis, the process leading to CVD, is causally related to conventional risk factors (hypertension, dyslipidemia, glucose intolerance) that, however insufficiently, explain the high CVD risk in CKD. Nontraditional risk factors for CVD, such as malnutrition, oxidative stress, and inflammation, play an at least as important role. Atherosclerosis, originally considered degenerative, is to a large extent linked to inflammation, and CKD and uremia are microinflammatory conditions [3]. Reviewing current research on the causes of inflammation in CKD reveals that some factors at play are known (e.g., cytokines), but substantial gaps remain in our knowledge, and many culprits remain unidentified.

Knowledge about uremic solute retention and their clinical and biological effects are reviewed in the following, emphasizing uremic toxins affecting the four major cell types involved in vascular damage: leukocytes (monocytes and granulocytes), smooth muscle cells, endothelial cells, and platelets (Table 16.1).

16.3 Classification of Uremic Retention Solutes

The classification system applied is essentially based on physicochemical characteristics of molecules that influence solute removal by dialysis or related strategies [4].

Table 16.1 Uremic toxins with potential vascular impact

Uremic toxin	Classification	Leukocytes	Endothelial cells	Smooth muscle cells	Thrombocytes
AGE	MM/PB	x	x	x	
AOPP	MM/PB	x	x		
AGE-β_2-microglobulin	MM	x			
Angiogenin-DIP-I	MM	x	x		
AII variants	MM			x	
β_2-microglobulin	MM	x	x	x	
Complement factor D	MM	x			
Cytokines	MM/PB	x	x	x	x
Guanidines	SWS	x			
Homocysteine	PB	x	x	x	
Ig-light chain	MM	x			
Indoxyl sulphate	SWS/PB		x	x	
Leptin	MM/PB	x	x		x
NpxN	MM/PB	x			x
Oxalic acid	SWS	x	x		x
p-Cresyl sulphate	PB	x			
Phenylacetic acid	PB		x		
Resistin	MM/PB	x	x		

AII variants, structural variants of angiotensin II; *AGE,* advanced glycation end products; *AOPP,* advanced oxidation protein products; *DIP-I,* degranulation-inhibiting protein I; *MM,* middle molecule; *Np_xN,* dinucleoside polyphosphates; *PB,* protein-bound solute; *SWS,* small water-soluble compound; *X,* biological effect was described that interferes with the corresponding cell system with the potential to induce vascular damage

Three major groups can be identified:

1. Small water-soluble compounds (SWS): Molecular weight (MW) of these compounds is arbitrarily defined as 500 Da maximally. The prototypes are urea and creatinine, which are easily removed by any dialysis strategy. Compounds in this group do not necessarily have a marked toxic activity.
2. The middle molecules (MM): MW is arbitrarily set at being > 500 Da. The prototype is β_2-microglobulin. These molecules can only be removed by dialysis strategies that employ dialyzer membranes containing pores large enough to allow these molecules to cross [either peritoneal dialysis or high-flux hemodialysis (HD)]. Shifting the dialysis approach from diffusion, whereby solutes are moved passively from one compartment to another (mostly but not exclusively from plasma water to dialysate) to convection, whereby solutes are actively dragged out of the plasma by imposing water shifts through the membrane there-

by inducing substantial amounts of ultrafiltration (hemofiltration–hemodiafiltration), usually facilitates their removal. Many compounds in this group are peptides that affect a host of organ systems. Some of the larger middle molecules have a MW > 15,000 Da and are sometimes called low-MW proteins, although all peptides, even those much smaller than 15,000 Da, semantically and chemically comply with this qualification as low-MW proteins.

3. Protein-bound compounds (PB): Most solutes in this group have a low MW, but some have middle molecule characteristics (e.g., leptin, cytokines). Prototypes are phenols and indoles. These compounds are difficult to remove by most of the available dialysis strategies, including high-flux dialysis; many compounds in this group have toxic activity.

16.3.1 Advanced Glycation End Products

Advanced glycation end products (AGEs) are glycation adducts formed in the later stages of protein glycation reactions. Protein glycation was originally considered a posttranslational modification situated mostly on extracellular proteins. It is now known that AGE residues are also formed on short-lived cellular and extracellular proteins. Cellular proteolysis forms AGE free adducts from these proteins, which normally have high renal clearance, but this declines markedly in CKD, leading to profound increases in plasma AGE free adducts [5], inducing an increase in leukocyte oxidative stress [6]. For many years, the biologic effect of AGE was studied mainly with artificially prepared AGE, which might not be representative of AGE compounds actually present in uremia, such as fructose lysine, N-α-carboxymethyllysine, pyrraline, or pentosidine. Glorieux et al. demonstrated the proinflammatory effect of several AGE compounds that are retained in uremia: Arg I (arginine modified with glyoxal), carboxyethyllysine, and carboxymethyllysine, demonstrating increased production of free radicals by monocytic cells [7]. It is interesting that one AGE studied, arginine II (Arg II), had no effect on leukocytes, showing that the behavior of a number of compounds belonging to a specific group cannot automatically be extrapolated to all solutes of that group.

Binding of AGE compounds to its receptor, RAGE, extracting them from the circulation and/or inducing biological responses, has recently been questioned. Other RAGE ligands have been reported, such as the extracellular newly identified RAGE-binding protein (EN-RAGE), S100A12 [8]. This S100A12 protein is expressed abundantly in the esophageal epithelium, neutrophils, and monocytes/macrophages in humans[8]. Recently, mean plasma S100A12 levels were shown to be twice as high in HD patients compared with healthy controls; they correlated with carotid intima media thickness (IMT) in HD patients [9]. Engagement of RAGE by S100A12 induces: (1) activation of nuclear factor-κB (NF- κB), a central transcription factor for inflammatory events, (2) upregulation of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) in vascular endothelial cells, and (3) enhanced migration and activation of mono-

cytes/macrophages, suggesting the potential contribution of S100A12 to the development of atherosclerosis [8]. The link AGE/RAGE might be found in the following: activation of RAGE by S100A12 decreases glyoxalase 1 (Glo1) expression; Glo1 downregulation increases local concentrations of methylglyoxal (MG) and glyoxal and related AGE residue formation. Recently, MG modification of vascular type IV collagen was shown to cause endothelial detachment, anoikis, and inhibition of angiogenesis [10]. Increased numbers of circulating endothelial cells are indicative of endothelial damage and prognostic for CVD in renal failure [11].

16.3.2 Advanced Oxidation Protein Products

Oxidative stress, defined as a disruption of the equilibrium between generation of oxidants and activity of antioxidant systems, plays a significant role in the development of inflammatory syndrome associated with chronic renal failure (CRF) and HD. In addition to glycation, the vulnerability of proteins to reactive oxygen species (ROS) is well documented. Oxidation of amino acid residues, such as tyrosine, which leads to formation of dityrosine, protein aggregation, cross-linking, and fragmentation, is but one example of ROS-mediated protein damage in vitro. Dityrosine-containing protein cross-linking products in the plasma of dialysis patients were reported and were addressed as advanced oxidation protein products (AOPP). Increased levels of AOPP are already observed at an early stage of CRF, and increase with uremia progression. Human serum albumin (HSA)-AOPP can trigger the oxidative burst in neutrophils and monocytes. Interestingly, the intensity of the respiratory burst is dependent on the level of protein oxidation. HSA-AOPP can also trigger the synthesis of inflammatory cytokines in monocytes, such as tumor necrosis factor alpha (TNF-α). AOPPs may play a role in the development of cardiovascular complications, as a significant association of plasma AOPP levels with common carotid artery intima media thickness (CCA-IMT) and CCA wall-to-lumen ratio was observed in uremic patients. Finally, caution is recommended with the classical methods for measuring AOPP concentration [12], as they can be biased by an unpredictable background noise created to a large extent by triglycerides and coagulation factors [13].

16.3.3 Angiogenin – Degranulation-inhibiting Protein I

Peptides constitute a heterogeneous group of molecules. In general, peptides can be considered as typical middle molecules. A degranulation-inhibiting protein (DIP; 24 kDa), identical to angiogenin, was isolated from plasma ultrafiltrate of uremic patients. The structure responsible for inhibition of degranulation is different from the sites responsible for angiogenic or ribonucleic activity of angiogenin. Next to the immune modulatory effects, which suppress polymorphonuclear leukocytes, angiogenin has been implicated as a mitogen for vascular endothelial cells, an activator of

certain protease cascades such as matrix metalloproteases and plasminogen-activated plasmin pathways, and as an adhesion molecule [14].

16.3.4 Angiotensin II Variants

Next to genuine angiotensin, structural variants, such as angiotensin A, characterized by decarboxylation of the asparagine molecule in the peptide, have been described [15]. Also, these structural variants have vasoconstrictive properties, be they less prominent than those of genuine angiotensin II. Their concentration is increased in CKD compared with individuals with normal kidney function. It is conceivable that other variants of angiotensin are retained in CKD, which could play a pathophysiologic role in renal-failure-related vascular dysfunction.

16.3.5 Complement Factor D

Plasmatic concentrations of complement factor D increase in uremia, essentially because of alterations in renal removal [16]. Complement factor D exerts specific protease activity on its natural substrate, complement factor B, which results in activation of the alternative complement pathway. This effect could in part be responsible for the baseline inflammatory status observed in chronic renal disease. Furthermore, complement factor D adversely affects stimulated polymorphonuclear leukocyte (PMNL) functions. Some dialysis membranes remove complement factor D, and this is at least in part attributed to adsorption [16].

16.3.6 p-Cresyl Sulphate

The amino acids tyrosine and phenylalanine, generated from nutritional proteins, are metabolized by intestinal flora into 4-hydroxyphenylacetic acid, which is decarboxylated to p-cresol. However, unconjugated p-cresol is not detectable in normal and uremic plasma, whereas during its passage through the intestinal mucosa, a cytosolic sulfotransferase metabolizes p-cresol into p-cresyl sulphate, its main conjugate. Nevertheless, most pioneering research on phenolic uremic retention compounds focused on the concentration and toxicity of the mother compound, p-cresol. This was due to the fact that previously measured p-cresol values were the result of p-cresyl sulphate hydrolysis as a consequence of sample deproteinization by acidification. In this way, serum levels of p-cresol in uremic patients increase about tenfold, and those of the free non-protein-bound p-cresol are even more substantially increased. p-Cresol, per se, was demonstrated to affect the inflammatory response by decreasing the reaction of activated polymorphonuclears and decreasing endothelial cell

response to inflammatory cytokines in vitro [17], whereas p-cresyl sulphate has a proinflammatory effect on unstimulated leukocytes in vitro, suggesting its contribution to the propensity for vascular damage in renal disease patients [18]. Nevertheless, previously held conclusions about protein binding and relationship with clinical outcome parameters of p-cresol [19] probably are still valid, as there is very likely a correlation between former p-cresol estimations and current p-cresyl sulphate measurements.

16.3.7 Cytokines

Under normal circumstances, cytokines are not detectable in body fluids or tissue. In CKD, and especially in stage 5, mean concentrations of most cytokines are several-fold higher due to both increased production and decreased renal clearance. In addition, the dialysis procedure itself may further stimulate cytokine production. However, as the half-life of most cytokines is short, local tissue cytokine inactivation may be the most important pathway of cytokine degradation. In general, cytokines are classified according to their pro- [TNF-α, IL-1, IL-6, IL-18, interferon-gamma (IFN-γ)] or anti-inflammatory [IL-4, IL-10, IL-13, transforming growth factor beta (TGF)-β] properties. From that point of view, the balance between opposing cytokines may be more important than the absolute amounts of a single cytokine. Because of the strong associations between atherosclerosis, malnutrition, and inflammation [3], it may be speculated that factors associated with malnutrition and inflammation, such as cytokines, contribute to the excess prevalence of CVD, as well. IL-6 exhibits both pro- and anti-inflammatory effects and promotes inflammatory events mainly through lymphocyte activation and proliferation B-cell differentiation, and leukocyte recruitment. IL-6 has been linked to progression of carotid atherosclerosis in CKD stage 5 patients [20]. Accumulation of TNF-α may contribute to the development of neurologic and hematologic complications in uremia. More research is needed to determine the relative importance of the kidneys in cytokine clearance.

16.3.8 Dinucleoside Polyphosphates

Dinucleoside polyphosphates (NpxN) are a group of substances involved in regulation of vascular tone as well as in proliferation of vascular smooth muscle cells (VSMCs) [21] and mesangial cells. Specific members of this group, the diadenosine polyphosphates, were detected in hepatocytes, human plasma, and platelets. In addition, concentrations of diadenosine polyphosphates are increased in platelets from HD patients. Recently, uridine adenosine tetraphosphate (Up4A) was identified as a novel endothelium-derived vasoconstrictive factor released from renal tubular cells upon stimulation, whereby it acted as a strong vasoconstrictive mediator on afferent arterioles, suggesting a functional role of Up4A as an autocrine hormone for

glomerular perfusion [22]. Plasma Up4A concentrations were increased in juvenile hypertensive patients compared with juvenile normotensive individuals; it also correlated with left ventricular mass and IMT, which could be attributed to its proliferative effect on VSMCs [23]. Its vasoconstrictive effects, its plasma concentration, and its release upon stimulation strongly suggest that Up4A has a functional vasoregulatory role. Dinucleoside polyphosphates also activate leukocytes defined by their capacity to induce free radical production, which in turn might contribute to the chronic inflammatory status of uremic patients (unpublished data).

16.3.9 Guanidines

Guanidines are small, water-soluble uremic retention solutes and structural metabolites of arginine. Among them are well-known uremic retention solutes such as creatinine and guanidine and more recently detected moieties such as asymmetric and symmetric dimethylarginine (ADMA and SDMA). Guanidine levels have been determined in serum, urine, cerebrospinal fluid, and brains of uremic patients [24]. Guanidino compounds have mainly been implicated in neurotoxicity [25]. Potential cardiovascular impact was, until recently, mainly attributed to ADMA, which inhibits inducible nitric oxide synthase (iNOS), an endothelial-protective enzyme [26]; Nevertheless, a mixture of guanidino compounds was shown to suppress natural killer cell response to IL-2 and free-radical production by neutrophils [27]. In more recent studies, guanidino compounds have been shown to enhance baseline immune function related to vascular damage, and methyl guanidine and guanidino acetic acid were shown to significantly enhance lipopolysaccharide (LPS)-stimulated production of TNF-α by normal monocytes [28]. In addition, they have been related to decreased protein binding of homocysteine, another compound with vessel-damaging potential [29]. Schepers et al. demonstrated that SDMA, considered the inert counterpart of ADMA, stimulates free-radical production by monocytes by acting on calcium (Ca^{2+}) entry via store-operated channels [30]. This proinflammatory effect may trigger vascular pathology and may be involved in altering the prevalence of CVD in CKD.

16.3.10 Homocysteine

Homocysteine (Hcy), a sulphur-containing amino acid, is produced by demethylation of dietary methionine. Moderate hyperhomocysteinemia is an independent risk factor for CVD in the general population. Patients with CRF have serum Hcy levels two- to fourfold above normal. Hcy increases proliferation of VSMCs, one of the most prominent hallmarks of atherosclerosis [31]. Moderate hyperhomocysteinemia may induce endothelial dysfunction and generate oxidative oxygen species. Hcy-induced superoxide anion generation is responsible for NF-κB activation and subsequent monocyte chemoattractant protein-1 (MCP-1) expression in macrophages [32],

inducing inflammatory responses. Administration of excessive quantities of the Hcy precursor methionine to rats induces atherosclerosis-like alterations in the aorta. Hcy also disrupts several anticoagulant functions in the vessel wall, which results in enhanced thrombogenicity. Studies of the potential of folic acid or 5-methyltetrahydrophosphate (MTHF) to decrease Hcy levels emanated in contradictory results. Touam et al. reduced total Hcy to normal in > 50% of the studied population by administering folinic acid, a precursor of MTHF [33]. Van Guldener et al., on the other hand, showed that even when it was possible to decrease Hcy levels therapeutically, carotid artery stiffness was not altered [34]. More recently, several interventional trials with folic acid have been finalized. Next to being negative, these trials had several shortcomings [35]. For example, the placebo group in the Homocysteinemia in Kidney and End Stage Renal Disease Trial (HOST), a randomized, double-blind trial performed in about 2,000 patients with CKD and 700 patients on dialysis with a follow-up of 3 years, cannot be considered a pure placebo group, as they were allowed to take folic acid supplements at their discretion. In addition, only one third of patients had their homocysteine levels normalized.

16.3.11 Immunoglobulin Light Chains

Immunoglobulin light chains (IgLCs) are part of intact immunoglobulins and contribute to antigen recognition. IgLCs are synthesized by B cells and metabolized primarily by the kidneys. Polyclonal free IgLCs accumulate in the serum of patients with CKD, and their concentration progressively increases with CKD stage [36]. In parallel, polyclonal IgLCs appear in the urine [36]. Free IgLCs exert biological effects on immune cells, such as neutrophil and mast cells. It was demonstrated that neutrophil migration toward the chemotactic tripeptide formyl-methionyl-leucyl-phenylalanine (fMLP) was significantly inhibited in the presence of IgLCs of both κ and λ type. IgLCs also reduced glucose uptake by fMLP-stimulated neutrophils. On the other hand, IgLCs did not inhibit phagocytosis of opsonized *Escherichia coli,* and intracellular killing was not affected, either. However, considering that IgLCs interfere with essential neutrophil functions and that their levels are increased in patients with CKD, they are potential uremic toxins contributing to diminished immune defense in uremia. Of note, as baseline levels of glucose uptake are increased by IgLCs, free IgLCs may contribute to neutrophil priming, which is characteristic for the chronic state of inflammation described in uremia [37].

16.3.12 Indoxyl Sulphate

Indoles are a group of protein-bound compounds generated by chemical transformation processes such as conjugation. Indoxyl sulphate, the most abundant indolic compound in the body of uremic patients, has been linked to endothelial damage, inhibition of

endothelial regeneration and repair, and endothelial and human aortic smooth muscle cells free-radical production [38]. Induction of oxidative stress by indoxyl sulphate promotes proliferation of human aortic smooth muscle cells [39] and been related to renal fibrosis and progression of renal failure. The adsorbent AST-120 (Kremezin^{R}) decreases serum and urine concentration of indoxyl sulphate in rats. A large prospective clinical study in humans with AST-120 demonstrated decreased plasma concentration of indoxyl sulphate, but showed no clinical benefit. However, more recently, AST-120 has been associated with postponement of the start of dialysis and, if applied before the start of dialysis, with better outcomes once dialysis is initiated [40].

16.3.13 Leptin

Leptin, a 16-kDa plasma protein decreases the appetite of uremic patients. Increase in serum leptin is mostly attributed to decreased renal elimination and is almost entirely limited to the free fraction. Napoleone et al. demonstrated that leptin induces tissue factor expression by mononuclear cells [41]. Tissue factor is a pivotal agonist in the clotting cascade and contributes to atherosclerosis by playing a key role in thrombosis and inflammation. When either a leptin antibody or leptin receptor antibody was added in these experiments, before leptin exposure, the observed effect was inhibited. Increased leptin is associated with low protein intake and loss of lean tissue in CKD. An inverted correlation between leptin and nutritional status and a direct correlation with C-reactive protein (CRP) was suggested. In continuous ambulatory peritoneal dialysis (CAPD) patients, serum leptin showed a progressive rise only in patients with body weight loss [42]. Erythropoietin treatment results in a decline of leptinemia and improvement of nutritional status [42]. Leptin-receptor-deficient mice resist uremic cachexia [43]. However, leptin levels are also elevated in obese individuals and are hence not necessarily related to reduced appetite. Body fat and serum leptin also correlate with uremia. Female gender and obesity are important factors that affect serum leptin in CKD stage 5 patients, in whom Don et al. suggest that leptin may be depressed during inflammation and may actually act as a negative acute-phase reactant [44]. Therefore, the biochemical role of leptin in renal failure remains inadequately defined. Low serum leptin concentration is an independent predictor of cardiovascular and infectious mortality in patients with CKD stage 5 on HD therapy [45].

16.3.14 β_2 Microglobulin and AGE-modified β_2 Microglobulin

$\beta_2$microglobulin (β_2M) (MW 11,800 Da) is a component of the major histocompatibility antigen. Uremia-related amyloid is to a large extent composed of β_2M and is essentially found in the osteoarticular system and the carpal tunnel, although deposition can be systemic as well. Uremia-related amyloidosis most often becomes clinically apparent after several years of CKD and/or in the aged, although its prevalence

tends to decrease, probably due to modifications in dialysis strategies and improvements in dialysis water quality. AGE-modified β_2M has been identified in amyloid of hemodialyzed patients [46] and enhances monocytic migration and cytokine secretion [47], suggesting that foci containing AGE-β_2M may initiate inflammatory response, leading to bone and joint destruction. Possibly AGE transformation plays a more important role in the inflammation surrounding β_2M-amyloid than in its generation. AGE-modified β_2M was also shown to increase TNF-α messenger ribonucleic acid (mRNA) expression and production and to decrease eNOS mRNA and protein expression by human umbilical cord vein endothelial cells (HUVECs) [48]. Reduced nitric oxide (NO) production due to eNOS inhibition may reinforce vascular damage. Both native β_2M and AGE-modified β_2M have been shown to enhance bone resorption in neonatal mice and net calcium efflux from mouse calvariae. These actions are attributed to stimulation of osteoclastogenesis, probably via upregulation of TNF-β and IL-1 β expression [49]. Several devices with strong adsorptive capacity for β_2M have been developed. In a subanalysis of the Hemodialysis (HEMO) study, serum β_2M levels were directly related to patient outcome and infectious mortality [50]. In a proteomic analysis for arteriosclerosis biomarkers in the general population without renal dysfunction, β_2M was selected as the most appropriate index molecule [51]. In another report, serum β_2M was found to be associated with arterial stiffness in the general population [52].

16.3.15 Oxalic Acid

Increased plasma oxalic acid synthesis in CKD results from diminished excretion of precursors of oxalic acid, glycolic acid, and ascorbic acid. In addition, glycolic acid conversion to glycine is probably increased in uremia. Ascorbic acid administration after hemodialysis causes a striking increase in plasma oxalic acid levels as a consequence of increased metabolism of accumulated vitamin. Increased plasma oxalic acid levels seem to be an important factor for calcium oxalate deposits in uremia. Boogaerts et al. demonstrated that calcium oxalate crystals present in vessel walls may trigger polymorphonuclear cells and platelets to damage endothelium, both in vitro and in vivo [53]. These findings may have relevance to understanding accelerated atherogenesis of hyperuricemia and fulminant vasculitis of oxalosis or ethylene glycol poisoning. Elevated plasma oxalate levels may also exert atherogenic effects by elevating intracellular calcium in endothelial cells, inhibiting proliferation and thus preventing re-endothelialization [54].

16.3.16 Phenylacetic Acid

Phenylacetic acid (PAA) is a degradation product of the amino acid phenylalanine. Plasma concentrations of PAA in patients with CKD stage 5 strongly exceed those in

healthy controls. PAA was shown to inhibit iNOS expression and consequently, NO production [55], was identified as an inhibitor of Ca^{2+} adenosine triphosphatase (ATPase) activity in CKD stage 5. PAA was recently shown to increase formation of ROS in VSMCs [56] and to have inhibitory effects on macrophage-killing function [57]. In a study by Scholze et al., an association between plasma PAA levels and arterial vascular properties in patients with CKD stage 5 was demonstrated [58].

16.3.17 Resistin

Resistin is a 12.5-kDa protein that, in humans, is mainly produced by macrophages and released predominantly by human visceral white adipose tissue macrophages. Serum concentrations of resistin are markedly increased in CKD patients with both advanced or mild to moderate renal function impairment compared with controls [59]. In patients with CKD, resistin levels correlate with CRP and TNF-α and even with body mass index (BMI) as a covariate, suggesting it may play a role in the subclinical inflammation associated with CKD [60]. Resistin significantly attenuates neutrophil chemotaxis toward the chemotactic peptide fMLP at concentrations measured in serum samples of uremic patients. In addition, it decreases *E. coli* and phorbol-12-myristate-13-acetate (PMA)-activated oxidative burst by neutrophils. From this point of view, resistin can contribute to the disturbed immune response in uremic patients, playing a role in uremic inflammation. Furthermore, resistin was shown to be present in human atherosclerotic lesions and therefore has a potential role in atherogenesis [61]. Pathophysiologically relevant concentrations of resistin increase endothelial cell adhesion molecule expression, possibly contributing to increased atherosclerosis risk [62]. Plasma resistin positively correlates with leukocyte counts, high sensitivity CRP, and endothelin-1 after adjustment for age, sex, and BMI [63]. Therefore, resistin may be involved in the development of coronary artery disease by influencing systemic inflammation and endothelial activation.

16.4 Conclusions

Many compounds accumulated in CKD have the capacity to interfere with the metabolic systems in the body, creating cardiovascular damage. If we translate this information into physicochemical characteristics affecting removal by dialysis, which is still the most important method of eliminating these molecules and their effects, it is clear that the majority of these compounds are molecules that are difficult to remove by standard hemodialysis, such as middle molecules and/or protein-bound molecules (Table 16.1). Eliminating them more efficiently necessitates more complex methods, such as high-flux dialysis or convective strategies [64], and/or modification of standard conditions, e.g., prolonging dialysis time and/or frequency [65]. Even small

water-soluble compounds, such as guanidines, have markedly different kinetic characteristics compared with the current marker molecule, urea [66]. Hence, it should be realized that in uremic retention in general, as well as in uremic retention related to cardiovascular risk, there is more than urea alone. In addition, in uremic toxin removal, it may also be useful to pursue more than urea removal alone. Present and future research should lead to a classification of uremic compounds based on severity of their effect, and it should focus on detecting new responsible compounds and/or mechanisms, resulting in the development of more effective removal methods and pharmacological strategies to block responsible pathways, ultimately improving patients' condition and outcome.

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Endothelial Dysfunction, Nitric Oxide Bioavailability, and Asymmetric Dimethyl Arginine

17

C. Zoccali

Abstract Endothelial dysfunction is common to various pathophysiological conditions and disease states. This dysfunction encompasses alterations in various processes that are modulated by the endothelium, including thrombosis, inflammation, control of vascular tone, and vessel growth and remodelling. Although this term has been used commonly to refer to an impairment of endothelium-dependent vasorelaxation secondary to reduced nitric oxide (NO) bioactivity, the clinical and scientific relevance of endothelial dysfunction rests on its global impact on the integrity of the arterial system and on its fundamental role in cardiovascular and renal diseases. Low NO availability is indeed a critical factor in hypertension, hypercholesterolemia, aging, diabetes, and heart failure and represents the basic mechanism whereby some environmental factors, such as smoking and small particulate matter, cause cardiovascular disease. A decline in NO bioavailability may be caused by decreased expression of endothelial NO synthase (eNOS), reduced substrate or cofactors for this enzyme, alterations of cellular signalling, eNOS inhibition by asymmetric dimethyl arginine (ADMA), and accelerated NO degradation by reactive oxygen species.

Keywords: NO • Endothelial dysfunction • ADMA • CKD • ESRD • Cardiovascular risk

17.1 Introduction

Over the past three decades, our conception of the endothelium has evolved from being seen as a purely structural layer covering the luminal side of the vascular system into being considered as a functionally complex system at the crossroad of the regulation of several fundamental mechanisms for health and survival, including arterial pressure control, hemostasis regulation, inflammation, and vascular genera-

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tion and repair. These disparate mechanisms operate in a tightly integrated manner, but depending on environmental stressors, disease states, and genetic factors, alterations in a given function may occur, whereas other aspects of endothelial function remain relatively unaltered. Atherosclerosis is perhaps the disease that best epitomizes the central role of endothelium in human health. From an experimental and epidemiological standpoint, a variety of risk factors, including nonmodifiable factors such as age and sex, and modifiable factors such as hypertension, hypercholesterolemia, diabetes, and obesity, have been solidly linked to cardiovascular and renal disease. However, not rarely in clinical practice we see individuals harboring one or more of these factors who are spared the disease and, conversely, risk-factors-free individuals who develop atherosclerotic complications. Such apparently contradictory observations suggest that endothelial factors may modify (either reduce or amplify) the effect of noxious factors. In other words, it is the interaction between the endothelium and risk factors rather than the individual or combined effects of risk factors per se that ultimately determines vascular damage. Because of their biological properties and their peculiar location, endothelial cells represent a critical element for the maintenance of vascular function. Among the above-mentioned properties of the endothelium, the capacity to induce vascular relaxation by nitric oxide (NO) is the first to be altered. Beyond vasodilatation, this gasotransmitter is also an important regulator of hemostasis because it inhibits platelet aggregation, leukocyte adhesion to endothelium and vessel-wall infiltration by these cells, and smooth-muscle-cell hypertrophy and hyperplasia – all alterations conducive to plaque formation and vascular remodelling. Furthermore, NO bioavailability is central to renal function regulation.

17.2 Basic Biochemistry of the NO System

NO is a free radical. As mentioned, synthesis of this gaseous compound depends on NO activity, the main regulator of NO bioavailability [1]. This enzyme exists in three structurally similar isoforms: Inducible nitric oxide synthase (iNOS) is typically produced by macrophages in response to proinflammatory stimuli; the second form, neuronal NOS (nNOS), is highly represented in the nervous system; the third, endothelial NOS (eNOS) in endothelial cells. In the presence of oxygen (O_2), eNOS oxidizes L-arginine by the transfer of five electrons (e), which gives rise to an intermediate compound NG-hydroxy-L-arginine, a compound finally transformed into NO and citrulline [2]. Tetrahydrobiopterin (tBH4), flavine adenine mononucleotide (FMN), flavine adenine dinucleotide (FAD), and reduced nicotinamide adenine dinucleotide phosphate (NADPH, i.e. a source of e-) are all necessary cofactors in this reaction.

17.3 Endothelial Dysfunction: Molecular Mechanisms

Various factors contribute to the regulation of eNOS, either increasing or decreasing the expression of this enzyme at the cellular level. Among factors that downregulate eNOS, tumor necrosis factor-α (TNF-α) is one of the best characterized. This cytokine makes eNOS messenger RNA (mRNA) unstable and therefore compromises the ability of this mRNA to produce to a fully active enzyme. Such a mechanism appears also responsible for reduced eNOS activity brought about by bacterial lipopolysaccharide, by oxidized low-density lipoprotein (LDL), and by hypoxia. Endothelial NOS is a Janus enzyme. Indeed, apart from generating NO, because endowed with an oxidant site, it also acts as an amplifier of oxidative stress. In conditions characterized by low levels of L-arginine (as in malnutrition states) and/or low tBH4 (as in smokers, in type-2 diabetics, in patients with severe hypercholesterolemia, and patients with inflammation), eNOS can generate superoxide anion, thus amplifying reactive oxygen species (ROS) generation [3].

17.4 Endothelial NOS Activity Modulation and Factors Affecting NO Bioavailability

The very location of eNOS in the cell appears to be relevant to its enzymatic activity. Caveolae are invaginations of the plasma membrane composed of cholesterol, glycosphingolipids, and a structural protein called caveolin. Endothelial NOS in caveolae is modulated by a variety of extracellular stimuli that affect the caveolin-eNOS link [4]. High levels of oxidized LDL reduce cholesterol in caveolae, which favors translocation of the caveolin–eNOS complex to the cytoplasm, i.e., at a site where eNOS activity is blocked. In addition to this mechanism, oxidized LDL and other lipids may also interfere with signal transduction by receptors that activate eNOS (e.g., acetylcholine, serotonin, and other receptors).

Apart from its location, eNOS modulation is regulated by several factors that may either enhance or decrease its activity. As mentioned, the parasympathetic neurotransmitters acetylcholine and serotonin are strong eNOS activators. Bradykinin and histamine represent additional, important eNOS enhancers. On the other hand, its downregulation depends on cell concentration of endogenous eNOS inhibitors. Vallance and coworkers were the first to envision the potential role of asymmetric dimethyl arginine (ADMA) as an endogenous NOS inhibitor, with far-reaching implications for human health [5]. Methyl arginine is synthesized in endothelial cells from arginine by enzymes of the arginine protein methyl transferase (PRMT) family. Studies in the early 1990s by Cooke et al. [6] showed that L-arginine restores response to acetylcholine (an endogenous eNOS stimulant) in the thoracic aorta of hypercholesterolemic rats. Subsequently, in vivo studies by Böger and coworkers [7] showed that L-arginine supplementation improves endothelium-dependent vasodi-

latation in rabbits with hypercholesterolemia and atherosclerosis, an effect that is associated with reduced platelet aggregation and monocyte adhesion as well as with diminished vascular smooth-muscle proliferation. These intriguing findings that point to L-arginine as a potential treatment for endothelial dysfunction contrast with experimental in vitro observations negating L-arginine-induced vasodilatation in arterial rings. Other in vitro studies pointed out that eNOS is saturated at physiological L-arginine concentrations and emphasized that L-arginine administration fails to increase eNOS activity. It was hypothesized that the discrepancy between in vitro and in vivo experiments, the "L-arginine paradox," depends on the presence at the intracellular level of endogenous competitive inhibitors of L-arginine, such as ADMA and monomethyl arginine (MMA) [8]. Thus, administration of L-arginine at high doses in vivo may displace ADMA from the eNOS catalytic site and by this mechanism may restore NO production to physiological levels in intact experimental models and humans. Even though doubts still exist on the actual ADMA concentration at the cell level, available data demonstrate that intracellular ADMA is one factor higher than the simultaneous concentration of this amino acid in extracellular fluids [9].

The metabolic pathways regulating plasma ADMA are summarized in Fig. 17.1. In endothelial cells, the key enzyme that regulates ADMA synthesis, PRMT-1,

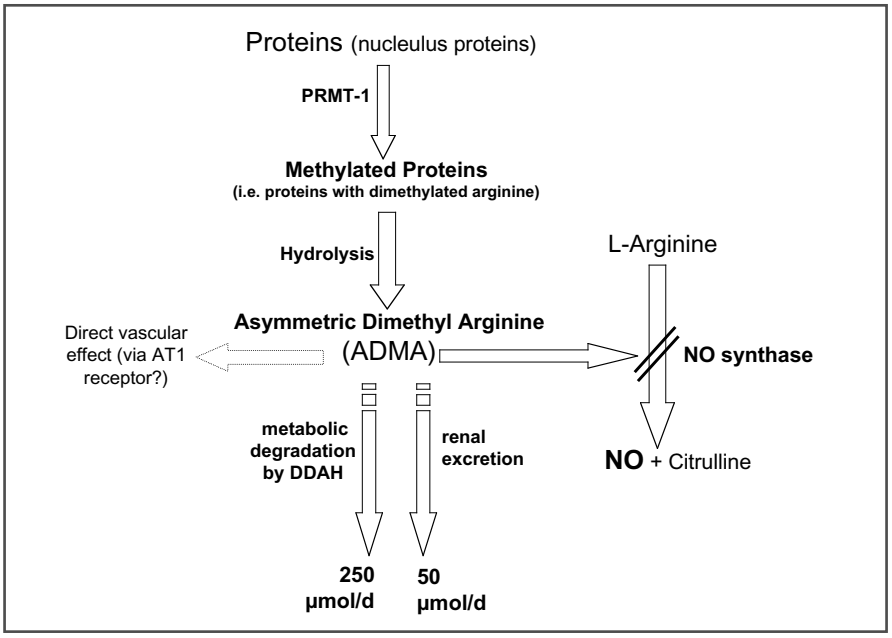

Fig. 17.1 Asymmetric dimethyl arginine (ADMA) metabolism and interference with nitric oxide (NO) synthesis. *PRMT-I* protein methyltransferase type I, which is activated by shear stress and oxidized lipoproteins and gives rise to proteins with methylated amino acids, including dimethyl arginine. *DDAH* dimethyl arginine dimethyl amino hydrolase, which is inhibited by hyperglycemia, hyperlipidemia, smoking, and hyperhomocysteinemia and activated by interleukin-1β and estrogens

depends on a variety of stimuli. Both LDL and shear stress increase expression of this enzyme. In contrast, kappa beta inhibitor kinases (κβ-IK) [i.e., kinases that phosphorylate a group of proteins designed as kappa beta inhibitors (κβ -I), a process that leads to the transfer of κβ from the cytoplasm to the nucleus where this factor starts the synthesis of inflammatory cytokines] reduce PRMT-1 expression [10]. These effects suggest that ADMA participates in the modulation of blood flow and that the levels of this methyl arginine can be modified by a key factor that regulates the inflammatory process via nuclear factor κβ (NF- κβ). ADMA degradation is mainly controlled by the enzyme dimethylarginine dimethyl aminohydrolase (DDAH), which transforms ADMA into citrulline. This is a key metabolic step because it was found that hypercholesterolemia, hyperglycemia, inflammatory cytokines, and hyperhomocysteinemia all reduce the activity of DDAH, a process that increases ADMA levels and alters endothelial function.

Arginase, the enzyme that breaks down arginine into ornithine and urea, is another critical element in the system that determines NO bioavailability. Arginase-I is expressed in a constitutive manner in endothelial cells, whereas the related enzyme, arginase-II, is typically activated by substances (lipopolysaccharides and interferon-γ) that are liberated during sepsis, an effect that may serve to limit NO synthesis. ROS are also critical to NO availability. Indeed, ROS transform NO into peroxynitrite, a highly reactive substance that alters DNA and various proteins, thus contributing to a variety of diseases including cardiovascular, inflammatory, and neurodegenerative diseases. In essential hypertensives [11] and in diabetics, pharmacological doses (500 mg/min administered intra-arterially) of a strong antioxidant, such as vitamin C, reverses the subnormal response of forearm blood flow to acetylcholine, implying that oxidative stress is a major factor responsible for this alteration. Of note, advanced glycosylation end products (AGES) inactivate eNOS, and this mechanism, which is reversed by AGE inhibitors such as aminoguanidine, is considered as a relevant pathway whereby AGEs engender cardiovascular and renal damage and dysfunction [12].

17.5 Biomarkers of Endothelial Function

In clinical studies, endothelial function may be tested either by measuring the hemodynamic response to substances that stimulate NOS (such as acetylcholine) in easily accessible vascular districts (the forearm) or by measuring the plasma concentration of substances that are made up by the vascular endothelium and released in increased amount into the systemic circulation when the endothelium is exposed to offending factors [13]. The plasma concentration of von Willebrand factor (vWF), the intercellular adhesion molecule (ICAM), the vascular adhesion molecule (VCAM), and the endothelial selectin (E-selectin) are currently considered the most reliable markers of endothelial dysfunction/damage. Hemodynamic and biochemical markers of endothelial function reflect different aspects of endothelium physiology and there-

fore these tests are not expected to be either strongly interrelated or necessarily altered in a parallel fashion in disease states.

Among mechanisms that may impair NO synthesis, increasing attention is presently being focused on an endogenous amino acid, asymmetric dimethyl arginine (ADMA). Overall, ADMA is emerging as a cardiovascular risk marker of primary importance [14] and as a potential target for interventions aimed at reducing atherosclerotic complications [15].

17.6 Endothelial and Renal Dysfunction in Essential Hypertension and in the Aging Kidney

At the renal level, NO dilates both afferent and efferent arterioles and affects renal sodium handling along various tubule segments. Inhibition of NO synthesis in human volunteers by infusion of the endogenous inhibitor of NOS, ADMA, triggers a dose-dependent decrease in renal plasma flow (ERPF) and increases renal vascular resistance without modifying the glomerular filtration rate (GFR) [16], thus engendering an increase in filtration fraction and glomerular hypertension (Fig. 17.2).

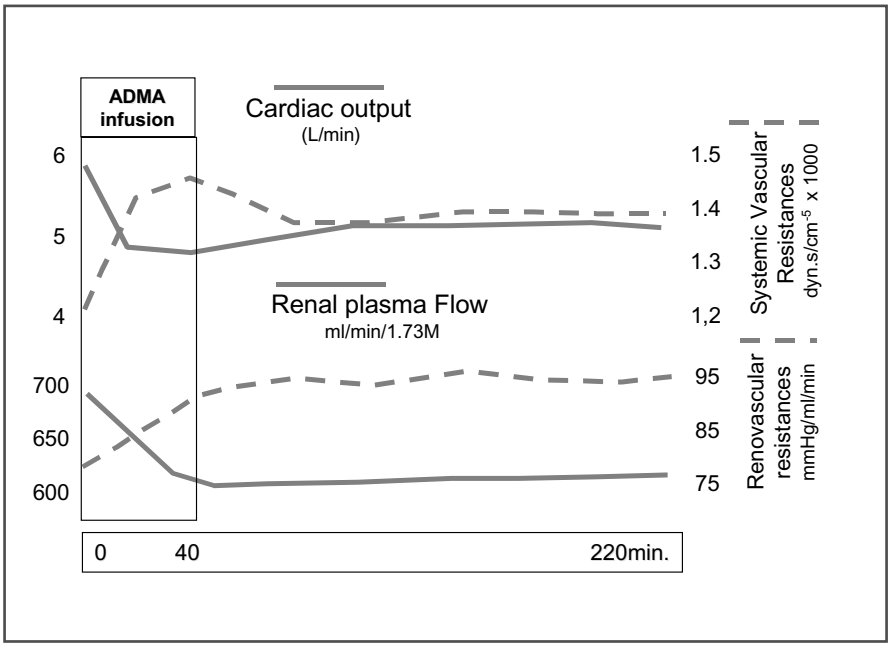

Fig. 17.2 Effect of asymmetric dimethyl arginine (ADMA) infusion on systemic (cardiac output systemic vascular resistances) and renal (renal plasma flow, renovascular resistances) hemodynamics

Arterial hypertension is one of the most prevalent causes of renal insufficiency. In animal models, a defect in renal sodium excretion at normal perfusion pressures occurs at a very early stage (pressure natriuresis). Thus, glomerular hypertension is a required hemodynamic adjustment to excrete a sodium load, which can ultimately lead to glomerular obsolescence (hyperfiltration injury) [17].

In Dahl rats, high salt intake causes acidosis and an increase in NADPH oxidase activity because it augments expression of two critical components of this enzyme (p47 phox and gp91 phox), leading to superoxide production that in turn inhibits NO synthesis. Oral L-arginine supplementation re-establishes normal NADPH oxidase activity in the kidney cortex by reversing p47 phox and gp91 phox expression [18]. This phenomenon suggests that administration of NOS substrate abolishes the imbalance between NO and ROS by increasing NOS-derived NO. Of note, high salt diet in this model also causes a marked increase in urinary excretion of ADMA, reflecting an increased renal synthesis of this NOS inhibitor [19]. It is therefore possible that part of the beneficial effects of L-arginine in this model derives from the fact that high levels of the natural NOS substrate antagonize the effect of ADMA. High salt intake per se increases expression of all NOS isoforms in the renal medulla. Thus, the effects observed in salt-sensitive Dahl rats represent an alteration peculiar to this hypertensive model rather than a physiological response to high salt. Overall, altered NO synthesis secondary to acidosis, superoxide, and ADMA is much more important in this strain because Dahl rats given a high-salt diet develop renal lesions that are virtually identical to those in human hypertensive nephrosclerosis [20]. High plasma ADMA concentrations have been found in essential hypertension [21–24], particularly in salt-sensitive individuals [25], and a link between ADMA and endothelial function was documented in hypertensive patients [26]. Plasma ADMA is sensitive to extracellular volume expansion [25], and such an increase is closely associated with a measurable decrease in plasma NO. Likewise, changes in plasma ADMA are associated with the pressor response to high salt intake in postmenopausal, normotensive women and explain as much as 16% of salt-induced changes in arterial pressure in these individuals [27].

Salt sensitivity is an age-dependent phenomenon in humans, and there is evidence that this phenomenon is intimately connected with disturbed NO regulation. Reduced NO bioavailability plays a major role in functional and structural adaptations of the aging kidney. Indeed endothelial dysfunction, a hallmark of the aging of the cardiovascular system, is extended to the renal circulation. Furthermore, NOS inhibition produces a stronger vasoconstriction in aging than in young renal vessels [28, 29], which indicates that endogenous NO production is of particular relevance in the control of renal circulation in aging animals. Importantly, total body NO generation is reduced in aging rats [28, 30], a phenomenon accompanied by high ADMA levels [30], a marked increase in proteinuria [31], and declining renal plasma flow [28]. Plasma ADMA was specifically associated with reduced renal plasma flow in apparently healthy older individuals [32], suggesting that ADMA accumulation may have a prominent role in the decline of renal perfusion in the elderly. Finally, high ADMA shortens telomeres [33], which is an additional, highly relevant pathway that may cause renal function loss associated with aging.

17.7 Endogenous Inhibitors of the Nitric Oxide System, CKD, and Cardiorenal Risk

In patients with chronic kidney disease (CKD), ADMA accumulates as renal function deteriorates [34]. The risk of death and of progression to ESRD is markedly higher in patients with ADMA, being greater than the median value in those with values below this threshold. Thus, in patients with CKD, ADMA is a risk marker both for renal disease progression and death. These observations, originally made in CKD [34] and ESRD patients [35], have been confirmed very recently in studies in the general population. Data gathered in the Framingham Heart study cohort show that ADMA is a predictor of death at the community level [36] as well as a marker of atherosclerosis [37].

Until now, there have been no clinical trials assessing whether or not the association between ADMA and clinical outcomes and atherosclerosis in the general population and in CKD patients is causal. Such studies are now possible because several existing drugs may modify ADMA levels. Furthermore, compounds accelerating ADMA degradation [i.e., activators of the enzyme that degrades ADMA, namely, dimethylarginine dimethyl aminohydrolase (DDAH)] are being tested in animal models [15].

17.8 ADMA as a Risk Factor for CKD

The hypothesis that ADMA is causally implicated in renal disease progression still needs definitive testing, i.e., a clinical trial demonstrating that ADMA modification curbs the progression rate of renal insufficiency. ADMA may be modified both by supplementing the diet with supraphysiologic quantities of L-arginine or by stimulating the enzyme that degrades ADMA, i.e., DDAH. In this regard, glitazones seem a promising class of drugs because activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ) ligands induces an overexpression of DDAH. Some angiotensin -II antagonists, such as telmisartan, have potent effects on the PPAR-γ receptor, and therefore these compounds, prima facie, would appear ideally suited for cardiovascular and renal protection. However, the disappointing results of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [38] negate that telmisartan is of benefit when added to standard renoprotection by angiotensin-converting enzyme (ACE) inhibitors in patients with moderate CKD and slight or no proteinuria. *DDAH* gene transfer in the remnant kidney model demonstrated that DDAH overexpression not only reduces plasma and urinary levels of ADMA but also prevents progression of renal dysfunction and remodeling of the renal architecture in this model [15]. As previously mentioned, DDAH activators remain an intriguing experimental opportunity for selectively testing the therapeutic potential of lowering ADMA in cardiovascular and renal diseases. These

compounds have complex effects, some of which can be negative for human health [39]. Therefore, before testing DDAH activators in the clinical arena in patients with CKD and high ADMA levels, it is fundamental that their complex interference with pathophysiological mechanisms implicated in human diseases be fully elucidated.

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Pathophysiologic Link between Atherosclerosis and Nephrosclerosis

18

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Abstract The progression of both atherosclerosis and glomerulosclerosis follows similar pathways. An initial injury leads to an enhanced endothelial transcytosis of low-density lipoprotein (LDL) in the subendothelial space. Lipid accumulation by macrophages engenders formation of foam cells. Activated endothelial cells induce inflammation through the release of monocyte chemoattractant protein 1. This stimulates the influx of monocytes to the intima/glomerulus and exacerbates vascular/glomerular injury by releasing chemokines and cytokines. The initial stage of inflammation leads to interactions between infiltrating and resident cells mediated through release of a range of mediators, including chemokines, cytokines, vasoactive peptides, growth factors, and reactive oxygen species (ROS). Further, activation and proliferation of vascular smooth muscle cells (VSMCs) and mesenchymal mesangial cells and their synthesis of the extracellular matrix (ECM) contribute to the fibrotic process. The final fibrotic phase results from an imbalance between ECM synthesis and degradation, leading to irreversible sclerosis.

Keywords: Atherosclerosis • Glomerulosclerosis • Lipids • Macrophages • Inflammation • Mesangial cells • VSMC • Cytokines • Growth factors • ROS • ECM

18.1 Introduction

About two centuries ago, the word "atheromatosis" was coined by the London surgeon Joseph Hodgson to describe the fatty degeneration of atherosclerotic arteries. In 1914, the clinician Franz Vollhard and the pathologist Theodor Fahr suggested a novel classification of renal diseases and the term "nephrosclerosis" [1]. Further research on the pathogenic role of lipids led to the idea that glomerulosclerosis and atherosclerosis feature similarly pathophysiologic mechanisms. This hypothesis was

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developed by Grond et al. [2], El Nahas [3], and Diamond and Karnovsky [4], who highlighted the similarities between the pathogenesis of these diseases.

Atherosclerosis, a chronic systemic disease of the vasculature with an inflammatory component, involves multiple processes, including endothelial dysfunction, inflammation, vascular proliferation, matrix alteration, and thrombosis. Glomerulosclerosis, on the other hand, is known as segmental collapse of glomerular capillaries, with thickened basement membranes and increased mesangial matrix seen sometimes in nephrotic syndrome or mesangial proliferative glomerulonephritis. Numerous factors, including genetic, immunologic, behavioral, and environmental influences have been implicated in the development of both diseases.

It has been speculated that certain histological features accompanying focal and segmental glomerulosclerosis – such as the presence of lipids, segmental glomerular accumulation of serum proteins, and the presence of macrophages – resemble the lesion of atherosclerosis and may indicate a parallel pathogenesis [2]. Diamond and Karnovsky [4] emphasized the similarities between mesangial cells and vascular smooth muscle cells (VSMC): As mesangial cells are similar to VSMC in terms of origin, contractility, myoid chemical, and structural characteristics, they may respond in an analogous fashion, after presentation of excess lipid to them, with proliferation and production of excess matrix substance, both of which are pathologic harbingers of glomerulosclerosis. These cells have been found to have many common properties with VSMC, including receptor subtypes, calcium-dependent contractile response, and proliferative response to several mediators [5]. In the atherosclerotic plaque, the arterial intima expands in size due to VSMC proliferation and increased synthesis of extracellular matrix (ECM), whereas in the glomerulus, mesangial cell numbers increase and the mesangial matrix expands.

Recent findings of novel cellular mechanisms have confirmed and expanded the hypothesis about similarities between the development of fatty streaks in the atherosclerotic vessel wall and progressive glomerular lesion leading to glomerulosclerosis.

18.2 Lipid Accumulation

First data in experimental animal models of both atherosclerosis and glomerulosclerosis have focused on the roles of hypercholesterolemia and the monocyte/macrophage in propagating these lesions. Initially, two main processes are involved in the atherosclerotic cascade: enhanced endothelial transcytosis of low-density lipoproteins (LDLs) in the subendothelial space, and preferential recruitment of blood monocytes to the intima [6]. It has been suggested that glomerular deposition of circulating lipids contributes also to the injury in renal disease. The finding of lipid droplets in glomerular sclerotic lesions in humans and experimental animals, induction of glomerular injury by lipid feeding in rabbits, and reduction of glomerular injury in obese rats after treatment of hyperlipidemia [7] has prompted the

suggestion that the pathogenesis of glomerular sclerosis has features similar to those in the development of atherosclerosis [4].

More recently, the Atherosclerosis Risk in Communities (ARIC) study has demonstrated an association of hyperlipidemia with increased risk of end-stage renal failure [8]. Notably, an interaction among hypertension, diabetes, elevated oxidized LDL (ox-LDL), and low high-density lipoprotein (HDL) has been suggested to accelerate progression of chronic kidney disease to end-stage renal failure [8].

Once lipoproteins gain access to the glomerular mesangium, they could bind to mesangial cells, which can take up native and ox-LDL, leading to formation of foam cells [9]. Under conditions of oxidative stress, mesangial cells can mediate the oxidation of LDL [10], which, in turn, induces further inflammatory changes through the release of monocyte chemoattractant protein 1 (MCP-1). This would stimulate the influx of monocytes to the glomeruli and exacerbate glomerular injury [11].

The presence and the role of monocytes/macrophages in atherosclerosis have long been established. These cells play an important role during all phases of the atherosclerotic process. Monocytes initiate the development of early lesions, as they adhere to the vascular endothelial surface, pass through this barrier, and infiltrate the subendothelial space. They further participate in the subsequent steps of atherogenesis, characterized by lipid-laden macrophages and the elaboration of ECM. Finally, macrophages contribute to the development and remodelling of more mature plaques [6].

Monocytes have also been detected in the glomeruli of rats with a variety of kidney diseases [12]. In these studies, glomerular infiltration by monocytes is associated with mesangial proliferation and release of chemokines, cytokines, complement components, and platelet-activating factors. Monocytes are capable of synthesizing and releasing ECM components, such as fibronectin and collagen [13] in the kidney and vessels. Further, macrophages are likely sources of ECM-regulating enzymes. They can release tissue inhibitor of metalloprotease (TIMP-1), thus contributing to kidney disease. The relevance of monocytes in the progression of glomerulosclerosis has been supported by studies in which their depletion by antibodies, an essential fatty-acid-deficient diet, or diphosphonates have proved to be protective [13].

18.3 Inflammation

Recent studies have confirmed Virchow's early suggestion that atherosclerosis has features consistent with a chronic inflammatory disease [14]. The inflammatory response plays an important role in the development, progression, and activity of atherosclerotic lesions [15]. Chronic renal disease is also considered to be an inflammatory disease because many markers of inflammation have been identified with this condition. Thus, it has been suggested to extend the lipid nephrotoxicity hypothesis of nephrosclerosis and to include the influence of inflammation [16]. Lipid accumulation in intimal macrophages facilitates arterial inflammation, which can trigger

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specific immune responses against antigens in the vascular wall [6]. Similarly, lipoproteins might act as proinflammatory mediators in the kidney. At certain concentrations, LDL and triglyceride-rich lipoprotein [very-low-density lipoprotein; intermediate-density lipoprotein (VLDL; IDL)] enhance the secretion of inflammatory cytokines, such as interleukin-6 (IL-6), platelet-derived growth factor (PDGF), and transforming growth factor beta-1 (TGF-β1) by human mesangial cells, whereas tumor necrosis factor alpha (TNF-α) secretion is stimulated by ox-LDL [17]. Moreover, minimally modified LDL leads to TNF-α induction in rat mesangial cells [16]. On the other hand, systemic or local inflammation could be an additional factor, which influences both intra- and extracellular cholesterol homeostasis through regulation of lipoprotein receptors. For example, inflammatory cytokines induce type A scavenger receptors (Scr) in human mesangial cells and modify cholesterol homeostasis through dysregulation of the LDL receptor. Furthermore, TNF-α and IL-1β accelerate VLDL-induced foam-cell formation [16].

Most inflammatory processes in the vessel wall are mediated by the endothelium. The endothelium normally inhibits leukocyte adhesion, lipid deposition, and VSMC proliferation. In response to injury or cytokines, activated endothelial cells upregulate adhesion molecule expression, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1); and release chemoattractants, such as monocytic chemotactic protein-1 (MCP-1), that facilitate endothelial interactions with leukocytes. Under these pathological conditions, endothelial cells support monocyte recruitment, inflammation, foam-cell formation, metalloprotease activation, and plaque weakening. Glomerular endothelial injury is characterized by swelling, cell-surface protrusions, and detachment from the underlying basement membrane. Functional endothelial changes also include the expression of cell-adhesion molecules and loss of anticoagulant properties, as well as the release of chemotactic, growth-promoting, and fibrinogenic mediators [18].

An important factor in the loss of endothelial anti-inflammatory and anticoagulant properties is the decreased nitric oxide synthase (NOS) activity. Reduced intracellular availability of L-arginine for NOS, altered NOS activity, impaired NO release, and increased inactivation owing to excess vascular generation of ox-LDL or ROS are among several described mechanisms linked to reduced NO bioavailability in both the kidney and vessels.

A prominent role of autocoids, such as angiotensin II (Ang II) and endothelin-1, has been postulated in the pathogenesis of atherosclerosis and glomerulosclerosis. Ang II via its AT1 receptor is involved in neointima formation in atherosclerosis and processes leading to renal scarring [19-21]. Activation of AT1 receptors engenders powerful proinflammatory effects [22]. AT1 receptor stimulation induces nuclear factor kappa B (NF-κB) via production of superoxide and regulates cell adhesion molecules ICAM-1, VCAM-1, and E-selectin, and cytokines IL-6, IL-8, MCP-1, and TNF-α. This, in turn, mediates the adhesion of monocytes, lymphocytes, and leukocytes to the vessel wall, and their migration, T –cell activation, B cell differentiation, etc. Both angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockade have been shown to be protective in atherosclerosis-related diseases and glomerulosclerosis [21, 23].

Endothelin-1, a potent proinflammatory autacoid, increases in hypercholesterolemia and atherosclerosis in humans and experimental animals [24]. The effects of endothelin in the endothelial cells, VSMCs, and macrophages may, at least in part, be mediated through the activation of NF-κB and consequent synthesis and release of cytokines and chemokines. This may take place in glomerular endothelial cells, mediated by the endothelin B (ETB) receptor, as well as in the tubular epithelial cell, mediated by the endothelin A (ETA) receptor [22]. Endothelin blockade inhibits fatty-streak formation and improves vascular function in hypercholesterolemia, hypertension, and heart failure in experimental animals [24]. Endothelin blockade also attenuates kidney scarring in immune and nonimmune models of glomerulosclerosis in experimental animals [25].

18.4 Cellular Proliferation

Vascular proliferation contributes to the pathobiology of atherosclerosis and is linked to other cellular processes, such as inflammation, apoptosis, and matrix alterations. VSMCs migrate, proliferate, and synthesize ECM components on the luminal side of the vessel wall, forming the fibrous cap of the atherosclerotic lesion. Intimal proliferation and matrix accumulation occur under the influence of PDGF, TGF-β1, Ang II, epidermal growth factor and insulin-like growth factor-1 [26].

It has been suggested that cytokines and growth factors stimulate the release of PDGF by mesangial cells, thus initiating their proliferation [27]. Mesangioproliferative glomerulonephritis is associated with up-regulation of glomerular PDGF [28]. Infusion of PDGF into rats or transfection of glomeruli with PDGF induces mesangial proliferation in vivo, whereas pharmacological inhibition of its effects decreases the mesangioproliferative changes observed in glomerulonephritis. In addition, treatment of rats with recombinant PDGF leads to tubulointerstitial cellular proliferation and interstitial fibrosis.

Ang II promotes migration and proliferation of smooth muscle cells (SMC) and ECM production through AT1 receptor activation in a model of vascular injury [29]. Ang II stimulates contraction, hypertrophy, and proliferation of mesangial cells and their ECM synthesis [20]. These effects are directly and indirectly mediated through NF-κB and TGF-β1 activation.

18.5 Extracellular Matrix Turnover

Within the glomeruli, both mesangial and epithelial cells respond to injury by transforming into mesangial phenotype with the expression of cytoskeletal proteins and acquisition of a network of stress fibres [30]. Such a transformation of glomerular

cells may contribute to glomerulosclerosis through the release of interstitial collagens (types I and III) that the glomeruli are unable to clear due to lack of specific collagenases. Similarly, injury of VSMCs leads to their transformation and regression to a myofibroblastic phenotype, contributing to plaque changes in atherosclerosis [31].

Fibroblast/myofibroblast modulation is essentially regulated, in addition to mechanical forces, by TGF-β1 produced locally by macrophages and eventually fibroblastic cells. TGF-β1, the most important fibrogenic growth factor in the pathogenesis of glomerulosclerosis [32], has been shown to be upregulated in the glomeruli and tubules of rats with nephropathies. TGF-β1 induces phenotypic changes in mesangial cells, including their expression of alpha-smooth muscle actin and mediates glomerulosclerosis by stimulating ECM synthesis and inhibiting its breakdown by matrix metalloproteinases (MMPs). A reduction of the natural antagonist of TGF-β1, decorin, in glomeruli appears to promote the development of glomerulosclerosis in experimental animals [33].

Recent studies have produced conflicting results in terms of TGF-β1 and atherosclerosis. TGF-β1 can be both pro- and antiproliferative as well as pro- and anti-inflammatory [34]. In situ localization of TGF-β1 has been reported in fibrofatty lesions as well as in human vascular restenotic lesions. New data suggest that TGF-β1 modulates the growth and stability of the atherosclerotic lesions as well as their inflammatory properties. Major antiatherogenic effects of TGF-β1 are caused by its inhibitory action on T cells. Whether direct effects on SMCs also impact on the development of atherosclerotic lesions remains to be determined.

Changes of the ECM have also been suggested to be at the origin of plaque vulnerability, mainly because of local production of proteolytic enzymes. Matrix degradation, which occurs both in atherosclerosis and glomerulosclerosis, depends on the activity of two collagenolytic systems: MMPs and the plasminogen-plasmin system. Collagen can be degraded by various MMPs that act extracellularly. MMPs require activation and may be inhibited by TIMPs. Exposure to proinflammatory cytokines, such as IL-1α, TNF-α, or CD-40 ligand, can induce VSMCs to express interstitial collagenase and stromelysin. Whereas nonatherosclerotic arteries contain TIMPs-1 and 2 and gelatinase A (MMP-2), in atherosclerotic plaques, SMCs, T cells, and macrophages can express interstitial collagenases, gelatinase B (MMP-9), and stromelysin. Atheromata overexpress all three interstitial collagenases: MMP-1, -8, and -13 [35]. Increased synthesis of ECM components has been described in a wide range of nephropathies in experimental animals [36]. Glomerular ECM is regulated by the synthesis of its components by all glomerular cells as well as its breakdown by MMP-1, -2, and -9. MMPs and TIMPs in the kidney are known to be released by mesangial cells. MMP-9 expression appears to be mainly confined to the glomerulus, and increased TIMP-1 and -2 expression was found to be associated with glomerulosclerosis in humans. In immunoglobulin A (IgA) nephropathy, overexpression of MMP-9 was reported in mesangial lesions. In contrast, sclerotic glomeruli showed an up-regulation of TIMP-1 and down-regulation of MMP-9 [37]. Thus, ECM

turnover seems to be very complex in the kidneys, depending on the primary renal disease.

The second major matrix degradation pathway is the plasminogen-plasmin system. It is inhibited by plasminogen-activator inhibitor 1 (PAI-1), which is up-regulated in various experimental animal models of kidney disease, as well as in atherosclerosis. PAI-1 synthesis, in turn, is increased by fibrotic mediators, such as angiotensin II and TGF-β1 [20]. Thus, both, atherosclerosis and glomerulosclerosis, are characterized by an imbalance between proteases and their inhibitors, which promote changes in the cellular composition and, subsequently, tissue remodelling. Furthermore, advanced atherosclerosis may result in aneurysm formation, and glomerulosclerosis could be accompanied by microaneurysms [38].

18.6 Thrombosis

The endothelium plays an important role in the maintenance of thromboresistance. Endothelial injury or exposure to atherogenic stimuli triggers endothelial cell inflammatory response, which via cytokines alter endothelial cell function toward a prothrombotic phenotype, which is characterized by increased production of PAI-1, tissue-factor expression, and extrinsic coagulation pathway activation. Loss of anticoagulant properties contributes to the adhesion and aggregation of platelets both within the damaged glomeruli and within the vascular wall. Interaction between platelets, monocytes, and mesangial cells within glomeruli may determine the extent of glomerular microthrombosis. It has been suggested that capillary microthrombi contribute to glomerular sclerosis by direct occlusion of capillary lumens and release of platelet-derived factors that aggravate glomerular injury [7].

There is strong evidence that thrombin acts as a powerful modulator of many processes, such as regulation of vascular tone, permeability, migration and proliferation of VSMC, recruitment of monocytes into the atherosclerotic lesions, and induction of diverse proinflammatory markers. All of these contribute to the progression of atherosclerosis-related diseases. Thrombin-induced mechanisms contribute to initiation, formation, progression, and destabilization of atherosclerotic plaques [39]. Recent studies in transgenic mice models indicate that deletion of the natural thrombin inhibitor heparin cofactor II promotes an accelerated atherogenic state. Moreover, administration of the direct thrombin inhibitor melagatran attenuates plaque progression and promotes stability in advanced atherosclerotic lesions in apolipoprotein-E-deficient mice. Mesangial cells also express thrombin receptors. Thrombin may stimulate proliferation of these cells and ECM production. Protection against glomerular injury afforded by thromboxane synthesis inhibition and other anticoagulant agents has been attributed to prevention of capillary thrombosis. Interestingly, these are the same interventions that attenuate atherosclerosis-related diseases.

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Aortic Stiffness, Kidney Disease, and Renal Transplantation

19

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Abstract In individuals with chronic kidney disease (CKD), treatment of elevated systolic blood pressure (SBP) is a key element in preventing disease progression and occurrence of cardiovascular events. For a given stroke volume, increased arterial stiffness is a key determinant of SBP. Therefore, the relationships between large conduit arteries and kidney function have been extensively studied in different CKD populations. In individuals with mild to severe renal insufficiency, increased aortic stiffness and reduced creatinine clearance are closely related, independently of standard cardiovascular risk factors but in the presence of significant arterial calcifications. In renal transplant patients, aortic stiffness is significantly increased irrespective of blood pressure level. In transplantation from living donors, arterial stiffness of the donor seems to contribute independently and significantly to the renal function of the recipient. In individuals with CKD, an increase in brachial pulse pressure is frequently observed, particularly in the elderly, and may be transmitted to the glomeruli, thus initiating renal damage each time a defect in renal autoregulation is present. Finally, in individuals with mild to moderate renal insufficiency, pharmacological modulation of the renin–angiotensin system may prevent both CKD progression and occurrence of cardiovascular events.

Keywords: Arterial stiffness • Chronic kidney disease • Pulse pressure • Calcification

19.1 Introduction

Chronic kidney disease (CKD) is associated with a significant increase in cardiovascular disease (CVD) morbidity and mortality, independently of standard CVD risk factors such as hypertension, diabetes mellitus, lipid levels, and smoking habits [1].

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In clinical studies, hypertension proves to be the most important modifiable CV risk factor, and blood pressure (BP) reduction leads potentially to prevention of CV events and reduction in CKD progression [1]. Blockade of the renin–angiotensin system (RAS), particularly in association with salt and water restriction, may reduce CV events and progression of renal failure [2]. However, an important observation emerges from the clinical management of CKD patients: baseline brachial systolic blood pressure (SBP) and its adequate control (≤ 140 mmHg) represent a better predictor than diastolic blood pressure (DBP) for both renal and CV outcomes [3]. This finding is observed both in diabetic and nondiabetic patients.

In patients with end-stage renal disease (ESRD), central (aortic) SBP and pulse pressure (PP = SBP–DBP) have been shown to be better predictors of CVD outcomes than brachial SBP, DBP, or PP taken individually [3, 4]. Central SBP and PP are influenced by three independent hemodynamic factors: ventricular ejection, large artery stiffness, and defective wave reflections. In individuals with ESRD, ventricular ejection is normal or enhanced, and increased central SBP and PP is mainly influenced by changes in arterial stiffness and wave reflection profile, including timing, amplitude, and dispersion of this last parameter [5]. Thus, the goal of this report is to determine under which conditions changes in arterial stiffness classically measured from aortic pulse wave velocity (PWV) and wave reflections may participate, in addition to SBP and PP, to progression of renal glomerular dysfunction and development of CV events.

This chapter addresses three main questions. First, what are the characteristics of large artery damage in CKD? Second, under which conditions may arterial calcifications influence mechanical properties of large arteries in CKD? Third, how may PP per se contribute in CKD to alterations in kidney structure and function, particularly in transplanted patients?

19.2 Large Artery Damage in Chronic Renal Disease

The principal factor determining CV complications in ESRD patients is classically atherosclerosis [3, 5, 6]. However, in CKD, several indicators of vascular dysfunction have been found in recent years despite clinically undetectable atherosclerotic plaques.

19.2.1 Individuals with ESRD

In patients with advanced CKD (stage V) and those on hemodialysis, BP profile is frequently characterized by increased SBP alone with normal or even low DBP. Increased SBP and PP are consistently associated with increased stiffness of large conduit arteries and disturbed wave reflections. Such alterations are independent of

mean arterial pressure (MAP) but largely influenced by the presence of large artery calcifications, often related to poorly controlled calcium–phosphate homeostasis [5]. Arterial calcifications are more extensive and occur earlier in patients with CKD compared with the general population [7]. Altered calcium homeostasis and positive phosphate balance caused by early reduction in urinary phosphate excretion in renal patients is likely associated with important tissue accumulation, including arterial segments of the vascular system. Therefore, the two most important, interrelated factors modulating the CVD risk profile in patients with advanced CKD are increased arterial stiffness and medial calcification. These alterations are usually associated with endothelial dysfunction and vascular remodeling, including dilation of elastic and muscular-type arteries and increased wall thickness [5]. In ESRD patients, increased aortic stiffness is a strong, independent predictor of all-cause and mainly CVD mortality [8]. A therapeutic trial in ESRD patients by Guérin et al. [9] has shown that long-term BP reduction improves survival in patients with CVD and is observed mainly in patients showing adequate BP and aortic stiffness control, particularly in the presence of salt and water restriction associated with angiotensin-converting enzyme inhibition (ACEI) [9]. In contrast, patients with appropriate BP reduction but who maintain elevated aortic stiffness had a worse prognosis.

The mechanisms responsible for arterial stiffening in patients undergoing hemodialysis is observed both in diabetic and nondiabetic individuals and cannot be exclusively related to standard CVD risk factors, such as glucose intolerance, hypercholesterolemia, being overweight, or smoking habits [5]. Studies comparing structural and functional alterations of carotid and radial arteries have shown that the observed vascular alterations are largely independent of age and local mechanical factors, such as increased wall stress and/or high MAP [10]. Observations are reported for both central elastic and peripheral muscular arteries [5, 10]. In vivo studies performed on the radial artery, a blood vessel poorly affected by aging and atherosclerosis [10], have shown that the major mechanism of vascular alterations is increased stiffness of the vascular-wall matrix. Other studies, performed on the aorta obtained from experimental rat models of renal failure, revealed comparable findings [11]. In vitro studies performed on arterial specimens obtained from uremic patients have shown striking structural alterations characterized by an increase in wall thickness, cross-section of the media, and total extracellular matrix involving collagen but not elastin [5, 11]. In addition, important calcifications of elastic lamellae are present, suggesting the potential role of parathyroid hormone and/or other factors derived from changes in the bone–kidney axis (see later).

19.2.2 Individuals with Mild to Moderate Renal Insufficiency

In more recent clinical studies, significant associations between increased arterial stiffness and reduced renal function have been described in individuals with mild to moderate renal insufficiency and normal or high BP levels. Glomerular filtration rate (GFR), estimated from Cockcroft-Gault equation or measured from direct isotopic

determinations, was used. In 1,290 untreated individuals with plasma creatinine < 130 μmol/l, creatinine clearance was divided into three tertiles adjusted for age and gender [12]. Only in the lower tertile was an elevated aortic PWV observed and was significantly associated with GFR [12]. Plasma glucose and cholesterol, obesity, smoking habits, and heart rate did not influence the findings. Furthermore, in untreated hypertensive individuals, decreased GFR was independently associated with reduced carotid artery compliance (but not with radial artery compliance). In this latter finding, the contribution of GFR to the total variance of carotid compliance was very high: 20% [12].

In individuals with mild to moderate renal insufficiency, the negative association between reduced GFR and increased arterial stiffness was independent of BP, using either 24-h ambulatory or conventional BP measurements [13]. In addition, the results were observed even in healthy individuals, suggesting that increased arterial stiffness might be the final principal factor initiating increased local PP, which in turn might influence reduction in renal function. Recent longitudinal studies have shown that independently of MAP, aortic stiffness increases more rapidly with age in individuals treated for hypertension than in untreated normotensive control individuals [14]. From all factors known to influence the increase in PWV with age, the most important is baseline plasma creatinine level, together with the presence of sodium and calcium metabolic alterations [15, 16].

Finally, recent histomorphometric data suggest that there are two different processes leading to glomerulosclerosis. Arterial stiffening with increased PP is important to consider, especially at the level of the afferent arteriole where its value likely plays an important role in the progression of glomerular lesions. Loss of renal autoregulation with glomerular hypertrophy, hyperfiltration, and focal segmental glomerulosclerosis is now recognized to contribute significantly to nephrosclerosis, particularly in the black population. Ischemic glomerulosclerosis, however, may ultimately be the most important lesion, with consequent hypoxia in the parenchyma beyond, leading to tubular atrophy and interstitial fibrosis.

19.3 Calcium and Arterial Calcifications

Arterial calcification is known to occur at two different sites in the vessel wall: in the intima, mainly in atherosclerosis; and in the media, in aging, diabetes, and mainly, ESRD. Calcification at either site is associated with an increased risk of myocardial infarction [17]. It is now clear that one of the major pathological effects of medial calcification is an increase in arterial stiffness. Nowadays, arterial calcification is described as a regulated, cell-mediated process similar to that of bone formation [15]. Normally, local and circulating inhibitors of soft tissue calcification are continuously generated. Local potent inhibitors are constitutively produced by vascular smooth muscle cells (VSMCs) in the tunica media of the normal arterial wall, such as matrix γ-carboxyglutamic acid protein (MGP). During the calcification process, expression

of endogenous inhibitors such as MGP is reduced, and VSMCs exhibit markers of both osteocyte and chondrocyte differentiation. Circulating inhibitors include the ?-2-Heremans–Schmid glycoprotein or fetuin-A, a protease inhibitor produced by the liver that is extensively involved in the prevention of apatite crystal formation in the arterial wall. In vitro preparations of human VSMCs in the presence of high calcium and phosphate show apoptosis of some of these cells, release of matrix vesicles (MV) from injured living cells, and phenotypic transformation into osteocytes and chondrocytes. Apoptotic bodies and MV contents, in the presence of a high mineralization potential (osteo/chondrocytes), form a nidus for hydroxyapatite (HA) deposition. (In culture, human VSMCs spontaneously convert to an osteocytic or chondrocytic phenotype, and calcification is initiated by the release of apoptotic bodies and matrix vesicles (MV)-like structures from VSMCs that act as a nidus for HA nucleation [18]. In addition, matrix proteoglycans can even play a role in the vascular deposition of calcium [19]. Patients with ESRD develop accelerated vascular calcification, and this process is likely caused by so-called damage-inducing agents, such as a high calcium–phosphorus product, hyperparathyroidism and vitamin D_3 treatment, which affect VSMCs vesicle release and modify their normal phenotype [16, 17]. In vitro, elevation of extracellular calcium and phosphate acts synergistically to increase VSMCs calcification. Vesicles released under these conditions contain preformed HA and calcify extensively in vitro. However, these mineralization-competent MVs are only produced when VSMCs are cultured in the absence of serum. The human serum protein fetuin-A acts by reducing apoptosis and enhancing phagocytosis of extracellular vesicles. More importantly, fetuin-A is taken up by VSMCs and incorporated into MVs, where its presence completely abrogates their ability to nucleate HA. The VSMC -derived protein, MGP, is also found to be incorporated into vesicles, and inhibition of MGP γ-carboxylation by pretreatment of VSMCs with warfarin has been shown to increase vesicle calcification [15, 18]. Taken together, these studies elucidate an important role for VSMC-derived vesicles and VSMC damage in the calcification process and suggest that this represents a real cell-mediated mechanism involving the kidney. Finally, aortic calcification represents a specific situation in which increased arterial stiffness develops independently of MAP but in relation with the age-mediated increase in calcium and phosphate concentrations of the arterial wall.

19.4 Pulse Pressure, Renal Autoregulation, and End-organ Damage

19.4.1 Kidney Damage and Glomerular Pressure

In the case of physiological glomerular microcirculation of the kidney, because efferent arteriolar resistance is normally greater than afferent resistance, the pressure drop proximal to the glomerular network is relatively small. Mean and pulsatile pressures

in the glomerulus are relatively high, representing roughly 60% of aortic values [19]. These findings allow the maintenance of filtration rate but expose the glomerular microcirculation to high pressure damage. In the past, we have shown that in individuals with renovascular hypertension, glomerular pressure observed in the contralateral kidney is augmented (71 ± 3 mmHg) by comparison with glomerular pressure (54 ± 1 mmHg) of the ischemic kidney ipsilateral to the stenosis or of the kidney (63 ± 2 mmHg) in individuals with essential hypertension (Table 19.1) [20]. It has been considered for many years that transmission of BP to glomerular microcirculation was mainly due to increased systemic steady MAP pressure. More recently, the role of BP fluctuations (i.e., PP) has been taken into considerations [19]. In the kidney contralateral to the stenosis, reduced preglomerular resistance in the contralateral kidney by comparison with the stenotic kidney favors the possibility that pressure fluctuations (i.e., PP) play a deleterious role on the kidney. Moreover, histopathologic studies of the glomerulus have shown that in hypertensive individuals with advanced renal failure, preglomerular vasodilatation is present and has been clearly shown on the basis of direct arterial diameter measurements [21]. Thus, this process may lead to transmission of both steady and pulsatile pressure inside the glomerulus [22–24].

Table 19.1 Renovascular hypertension: hemodynamics of stenotic and nonstenotic kidney [20]

Renovascular hypertension: 41 men	Stenotic	Nonstenotic
C_{PAH} (ml/min/m^2)	92 ± 48	194 ± 64***
C_{IN} (ml/min/m^2)	23 ± 9	48 ± 13***
Preglomerular vascular resistance (dyn/s/cm^{-9})	30,900 ± 4,500	11,300 ± 1,000***
Glomerular pressure (mm Hg)	54 ± 1	71 ± 3

C_{IN}, inulin clearance; *C_{PAH}*, para-aminohippuric acid clearance

19.4.2 Kidney Damage and Autoregulation Loss

In humans, renal blood flow is normally autoregulated over a wide range of perfusion pressure [24]. Under physiological conditions, systemic BP is not transmitted within the kidney. The combination of immediate myogenic response in the afferent arteriole and, more distally, the tubuloglomerular feedback mechanism, is mainly responsible for glomerular filtration autoregulation.

Myogenic tone in the afferent arterioles may be influenced by both steady and pulsatile pressure. There are, indeed, specific circumstances in which a disproportionate increase of PP compared with steady pressure is noted. Systolic hypertension with a nearly preserved MAP (around 100 mmHg) and elevated PP (> 50–60 mmHg) is a good example. When systemic PP becomes disproportionately high (> 60 mmHg) for

the level of MAP (around 100 mmHg), renal hemodynamics may become directly and exclusively influenced by it. In animals, this hemodynamic profile is widely observed in the classic model of the remnant kidney [24]. In humans, we have shown that this hemodynamic profile is observed with aging (beyond the fifth decade) and therefore provides a distinctly possible mechanism for an age-related decline in renal function [23]. Studies in the elderly population with isolated systolic hypertension have shown that in individuals older than 60 years, increased PP is significantly associated with reduced GFR and renal blood flow, a result not observed in younger individuals. Cross-sectional (Fig. 19.1) [22] and longitudinal (Figs. 19.2 and 19.3) [23] studies have shown this particular profile. A similar aspect is known to occur in type 2 diabetic individuals in whom a significant increase in arterial stiffness and pulsatility is frequently observed very early in the development of the disease [19]. Finally, living kidney donation for transplantation represents the best model in humans to examine the long-term adaptation of the donor kidney to the recipient's environment [18].

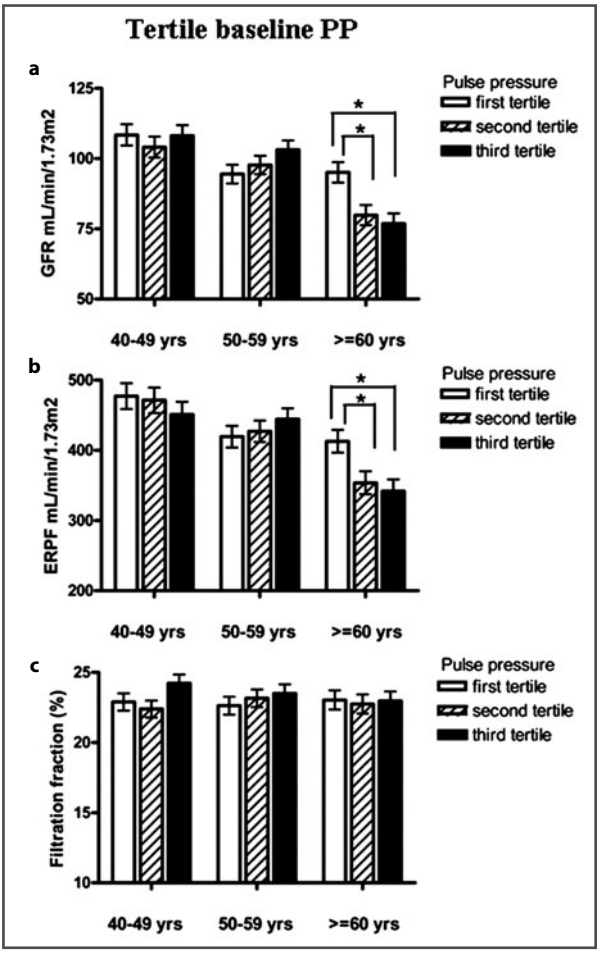

Fig. 19.1 Individuals with systolic hypertension: adjusted values of glomerular filtration rate (GFR) (**a**), effective renal plasma flow (ERPF) (**b**), and filtration fraction (**c**) according to pulse pressure (PP) tertiles in each age category. *P < 0.05. Reproduced from [22] with permission

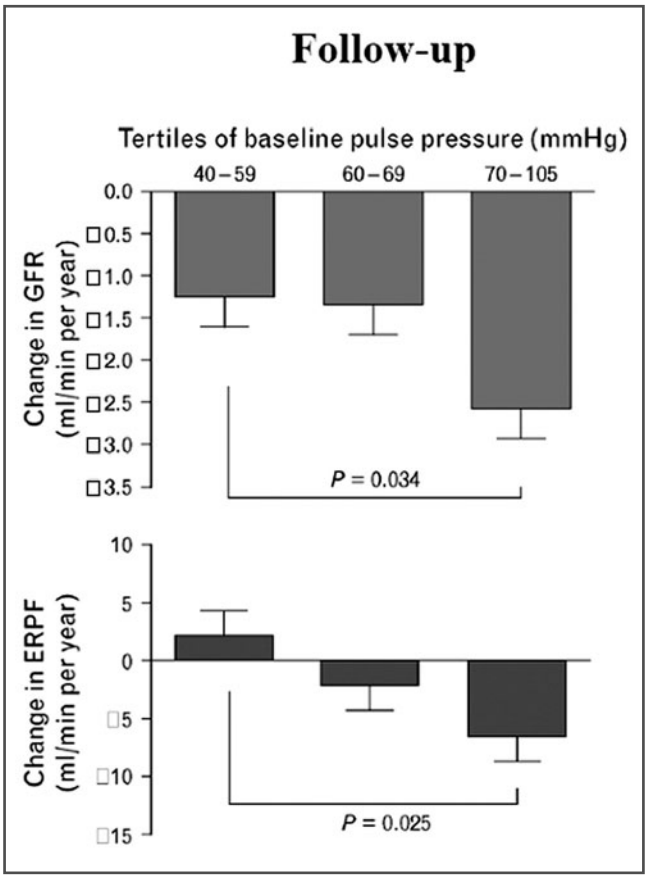

Fig. 19.2 Individuals with systolic hypertension: yearly changes in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) according to PP baseline tertiles [23]. Values are expressed as the mean ± standard error of mean (SEM) and are adjusted for age, baseline GFR, and baseline- and treatment-associated change in mean blood pressure (MBP). Reproduced from [23] with permission

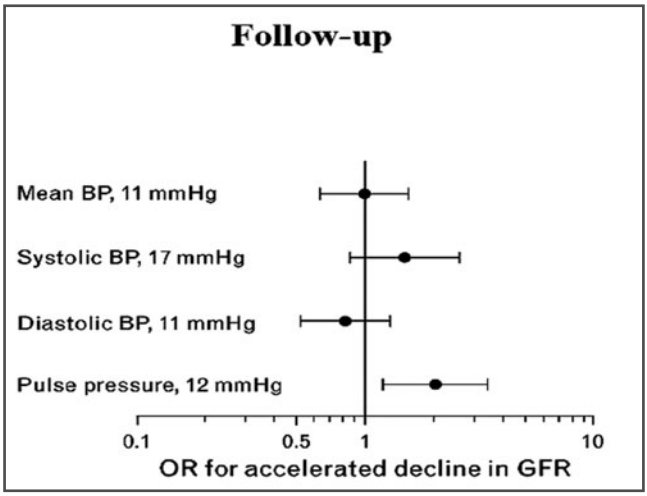

Fig. 19.3. Adjusted odds ratio (OR) (95% confidence interval) of the accelerated decline in glomerular filtration rate (GFR) (above the median value of 1.5 ml/min per year) associated with 1standard deviation (SD) higher baseline blood pressure (BP) components. Reproduced from [23] with permission

19.4.3 Arterial Stiffness and Living Donors of Kidney Transplantation

Increased arterial stiffness has been widely observed in recipients of kidney graft, whether from cadaver or living donors [25–30] (Fig. 19.4). In living donors, this increased aortic stiffness is frequently observed during long-term follow-up after kidney donation, together with increased PP [26]. Aortic stiffness is positively and independently correlated with the interval duration between donation and the moment of stiffness measurement. Increased PP is frequently associated with the occurrence of proteinuria. Both results suggest the role of renal factors contributing to modulate arterial stiffness in uninephrectomized living donors. Usually, in both animal and human models of uninephrectomy, kidney size increases significantly, and preglomerular arteriolar resistance decreases, resulting in greater transmission to the kidney of systemic BP. In most cases, this arteriolar vasodilatation is not accompanied by substantial impairment of renal autoregulation, severe hypertension, or exaggerated age-related loss in kidney function. Under such conditions, only a modest renal function alteration is expected, as documented in most uninephrectomized

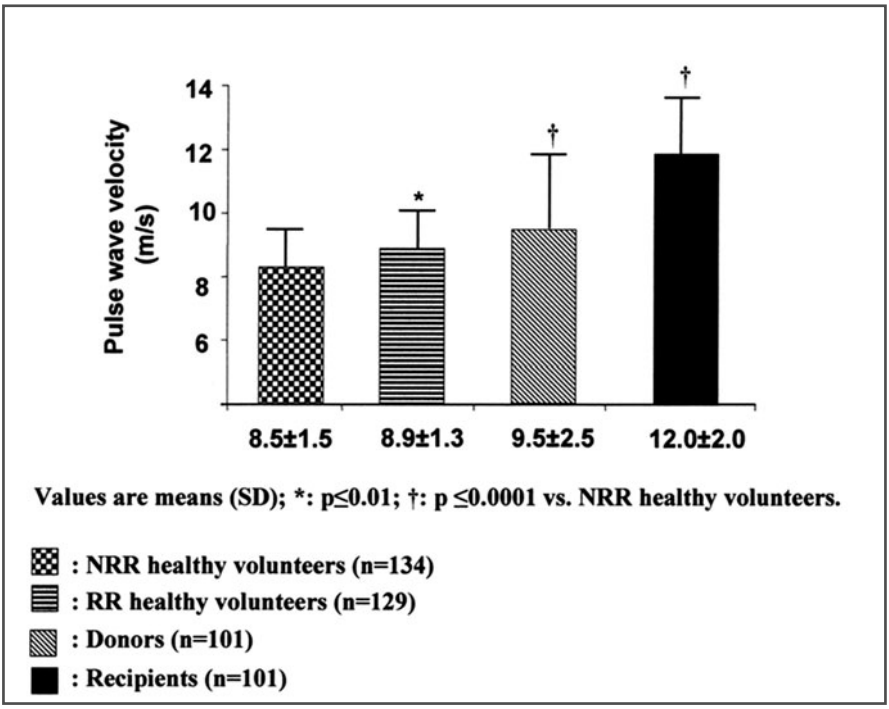

Fig. 19.4 Aortic pulse wave velocity (PWV) [± standard deviation (SD)] in living kidney donors and recipients by comparison with relative recipient (RR) and non-relative-recipient (NRR) healthy volunteers [analysis of variance (ANOVA) adjusted for age, gender, and mean blood pressure (MBP)]. Reproduced from [26] with permission

individuals [24]. In some cases, however, additional factors may interfere, including age, diabetes mellitus, metabolic syndrome, smoking habits, or even arteriolar preglomerular vasodilatation due to chronic administration of calcium channel blockers [24, 26]. Such observations are undoubtedly observed in related living donors [25, 26] and indicate a consistent link between the kidney and arterial matrix elasticity in populations of chronically uninephrectomized individuals. In this context, it is important to remember that in diabetic or remnant-kidney animal models there are unique elastic properties of glomerular structure. Even small and transient increases in intraglomerular pressure are reported to be associated with increments of glomerular volume by about 30%. Glomerular expansion is associated with stretching of its structural components, affecting mainly mesangial cells, a critical step to initiation of glomerulosclerosis [31].

19.5 Conclusions

This review shows that in individuals with CKD, the negative association between increased SBP and reduced GFR is mediated by arterial stiffness and wave reflections but not by MAP and/or traditional CVD risk factors (dyslipidemia, diabetes mellitus, obesity, and smoking habits) or exclusive atherosclerotic alterations.

In this line of evidence, rodent models, including those with arterial calcifications [32, 33], have been proposed. Mostly, recent studies describe a novel role of fibroblast growth factor-23 (FGF23)-Klotho activity in the systemic regulation of calcium and phosphate homeostasis [34]. Both FGF23 and Klotho-ablated mice develop models of extensive vascular and soft tissue calcification. Inability of the kidney to clear the required amount of phosphate due to the absence of FGF23-Klotho activity leads to increased accumulation of serum phosphate in these genetically modified mice, causing extensive calcification. Serum calcium and 1.25-hydroxyvitamin D as well as renal phosphate reabsorption levels are also elevated in such models. Collectively, all these observations bring new insights into our understanding of development of renal vascular and soft tissue calcification.

Clinically, such alterations between the kidney and large arteries are strong predictors of CVD risk and become potentially reversed by ACEI or angiotensin AT1 receptor blockade, but not their association. The sequence of events leading to progression of renal disease and CV events involve several steps. First, development of increased arterial stiffness and disturbed wave reflections is responsible for increases in central SBP and PP and therefore age plays a major role [30, 35]. Second, through defective renal autoregulatory mechanisms, transmission of PP to the glomerular microcirculation may occur even in the presence of normal MAP [22, 23]. Third, this process leads to progression of renal failure and finally CV events. Thus, very early prevention of such abnormal evolution is important, particularly before the development of PP widening.

Another important problem is to discuss the specific role of BP propagation, PP,

and arterial stiffness in the mechanism(s) of CV events and progression of renal failure. Until recently, only individual values of SBP or DBP were taken into consideration to predict CVD risk and to guide CVD preventive and intervention measures. The data presented here show that, in addition to BP amplitude, BP propagation should be also taken into consideration to evaluate CVD risk. Indeed, in chronic renal failure, the main factors predicting CVD risk are: brachial PP; aortic stiffness; alterations of wave reflections; incremental elastic modulus of the carotid artery; and central SBP, PP, or even PP-amplification profile [36]. Renal transplantation also contributes to this general process.

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Disturbed Calcium–Phosphorus Metabolism/Arterial Calcifications: Consequences on Cardiovascular Function and Clinical Outcome

20

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Abstract Arterial calcification is an active process resulting from the interaction of factors that both promote and inhibit the process. Interaction of these factors results in phenotype transdifferentiation of vacular smooth muscle cells and pericytes into osteoblast-like cells. In addition to this active process, oversaturation of extracellular fluid with high serum calcium and phosphate contributes to calcium apatite precipitation. Arterial calcifications exist in two frequently interrelated types: intimal and medial. Intimal calcification is a part of advanced atherosclerosis and results in plaque development, arterial lumen decrease or occlusion, and ischemic lesions downstream. Medial calcifications result in the stiffening of arterial walls, with increased systolic and decreased diastolic pressures, resulting in cardiac pressure overload, left-ventricular hypertrophy, and decreased myocardial perfusion. Both types are associated with increased cardiovascular morbidity and mortality.

Keywords: Arterial calcification • Chronic kidney disease • End-stage renal disease • Cardiovascular morbidity • Intima • Media • Vascular smooth-muscle cells

20.1 Introduction

Damaged large arteries represent a major contributory factor to cardiovascular complications as a leading cause of mortality in patients with chronic and end-stage renal disease (ESRD) [1, 2]. In these patients arterial structural and functional changes are, in many aspects, similar to an accelerated age-related process [3]. Whereas atherosclerosis and plaque-associated occlusive lesions are frequent causes of these complications, the spectrum of arterial alterations includes outward remodeling and stiff-

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ening of large arteries, i.e., arteriosclerosis [2]. The traditional risk factors do not fully explain the severity of arterial disease, implicating other factors associated with chronic kidney disease (CKD) and ESRD [4]. Arterial calcification (AC) is a common complication of CKD and ESRD [5, 6], and the extent of AC in the general population and in patients with kidney disease are predictive of subsequent cardiovascular mortality rates beyond established conventional risk factors [7–9]. AC develops in two distinct sites: the intima and media layers of the large and medium-sized arterial wall. Intima calcification occurs when minerals are deposited within atherosclerotic plaque in the arterial wall intima. This process is a progressive feature of common atherosclerosis found in the general population and is not specific to CKD, except for its higher frequency in ESRD patients [1]. These two forms are frequently associated, as common atherosclerosis is also common in diabetic and renal-disease patients. AC is closely associated with ageing and arterial remodeling, including intima-media thickening, but also changes of aortic valve geometry and function, e.g., decreased aortic valve surface area and smaller valve opening [10].

20.2 Mechanisms of Arterial Calcification

Experimental and clinical studies have shown that AC is a process akin to bone formation, reflecting changes in the phenotype of vascular smooth-muscle cells (VSMC) regulated by proteins involved in bone metabolism in arterial tissues [11, 12]. In vitro, VSMC transformation into osteoblast-like cells, with subsequent mineralization, is induced or regulated by the balance between a multitude of factors inducing or inhibiting calcification, including calcium and phosphate [11, 12]. Calcium and phosphate act synergistically and independently on VSMC calcification [13]. Phosphate may initiate calcification by enhancing the activation of Runx2 (Cbfa1) and osterix, factors that promote differentiation of mesenchymal cells into the osteoblastic lineage [14]. Pooled uremic serum with high phosphate concentration, compared with pooled control normal human serum, induced Runx2/Cbfa1 expression in bovine VSMC, thereby supporting the view that this key regulatory factor is up-regulated in response to uremic toxins independently of the proper role of serum phosphates [15].

In vitro, phosphate-stimulated apatite production can be completely inhibited by adding pyrophosphates that antagonize the cellular sodium–phosphate cotransport system (PIT-1) [16]. VSMC synthesize bone-associated proteins, including alkaline phosphatase, osteocalcin (OCN), osteopontin, and a coat of collagen–rich extracellular matrix, and include formation of matrix vesicles, nodules, and apoptotic bodies, which serve as initiation sites for apatite crystallization [13]. In the presence of normal serum, VSMCs do not calcify and can inhibit spontaneous calcium and phosphate precipitation in solution, indicating that systemic calcification inhibitors are present in the serum and also in VSMCs, which constitutively express potent local inhibitors of calcification, such as matrix gamma carboxy glutamic acid (GLA) pro-

tein [13, 17], which may limit AC by binding to bone morphogenic proteins (BMP-2) [18]. Osteopontin and osteoprotegerin are potent inhibitors of AC in vivo, and inactivation of their gene enhances the calcification process [19]. Osteoprotegerin-deficient animals develop severe AC of the media of aorta and renal arteries, and osteoporosis [19]. Fetuin-A (α_2-Heremans–Schmid glycoprotein) is a potential circulating AC inhibitor that is abundant in plasma [20]

Arterial calcifications and osteoporosis, bone mineral density or bone activity, are frequently observed in the same individuals and are a major cause of morbidity and mortality in elderly individuals and postmenopausal women [21]. Population-based study has demonstrated association between osteoporosis and arterial stiffness [22] and a strong association between the progression of vascular calcifications and bone demineralization [21]. Several studies demonstrated that this relationship, considered as resulting from the ageing process, remains significant after adjustment for age and all potential confounders [21]. Although the role of ageing cannot be completely dismissed, the clinical coincidence of vascular calcifications with low bone-mineral activity and osteoporosis suggests a direct biological link between arteriosclerosis and osteoporosis. Osteoporosis and vascular calcifications are influenced by several common risk factors, such as ageing, inflammation, dyslipidemia, oxidative stress, estrogen deficiency, vitamin D and K deficiencies [23, 24] and involvement of the receptor activator for nuclear factor κ B ligand and receptor activator of nuclear factor κ B osteoprotegerin (RANKL/RANK/OPG) system [25].This association between bone and vascular disorders was also observed in patients with CKD or ESRD [26–28].

Whereas the osteoporosis–AC association could be observed in the general population in the absence of overt mineral metabolism disorders, in CKD or ESRD patients, the relationship is associated with deterioration of mineral and bone metabolism caused by changes of serum phosphate and calcium concentrations and disruption of endocrine and humoral pathways, including parathyroid hormone (PTH), calcitriol, fibroblast growth factor (FGF)-23–klotho axis, and others [29–31]. In patients with CKD or ESRD, the association involves two aspects of bone disorders, i.e., high bone turnover [secondary hyperparathyroidism (SHPT)] and low bone turnover [adynamic bone disease (ABD)]. The increased bone resorption seen in SHPT is frequently associated with AC. Endogenous release of phosphate and calcium from bone probably plays an important role in the induction of AC. The direct association of PTH is less clear. Chronically elevated PTH up-regulates *RANKL* and down-regulates *OPG* gene expression and raises the RANKL/OPG ratio [31]. However, intermittent PTH increases exert an anabolic action on bone, and intermittent PTH treatment prevents AC [32].

The association between bone activity and aortic calcification and stiffness could also suggest the existence of a direct bone–arterial crosstalk, with osteoblast function possibly playing a primary role [33]. Bone remodeling is regulated by multiple hormones, including those involved in endocrine regulation of energy metabolism, such as adiponectin (ADPN) or leptin [34, 35]. Lee et al. [33] showed that osteoblasts exert an endocrine regulation on energy metabolism, with OCN playing an important role. OCN can stimulate ADPN release and expression in adipocytes. In the general

population and uremic patients, serum OCN was positively associated with ADPN [36, 37]. Reduced plasma levels of ADPN are found in metabolic syndrome and type 2 diabetes. In patients with diabetes type 2, serum levels of OCN were inversely correlated with arterial stiffness evaluated by brachial-ankle pulse-wave velocity [36]. Whether this low ADPN could account for decreased osteoblastogenesis and frequently observed ABD in diabetic patients remains to be investigated. Leptin favors the calcification [38], suggesting that in ESRD leptin might promote AC.

20.3 Clinical Impact of Arterial Calcifications

Both intima and media calcifications are associated with increased morbidity and mortality rates [7–9], but they alter arterial functions by different pathological mechanisms [2]. Intima plaque calcification occurs in the context of common atherosclerosis and progresses in parallel with plaque evolution and arterial or cardiac valve remodeling (Fig. 20.1). Intima calcification induces arterial dysfunctions resulting from arterial lumen narrowing, with ischemia affecting tissues and organs downstream. Media calcification (Mönckeberg's sclerosis or media calcinosis) is characterized by diffuse mineral deposits within the arterial tunica media. Whereas media calcification is frequently observed with ageing in the general population, it is significantly more pronounced in patients with metabolic disorders, such as metabolic syndrome, diabetes, or CKD. Because calcification advances with atherosclerosis progression, it is uncertain whether, by itself, it represents a risk factor or is just a surrogate marker of plaque burden and a marker of disease extension. Acute coronary events and infarction are more related to biomechanical stability of atherosclerotic

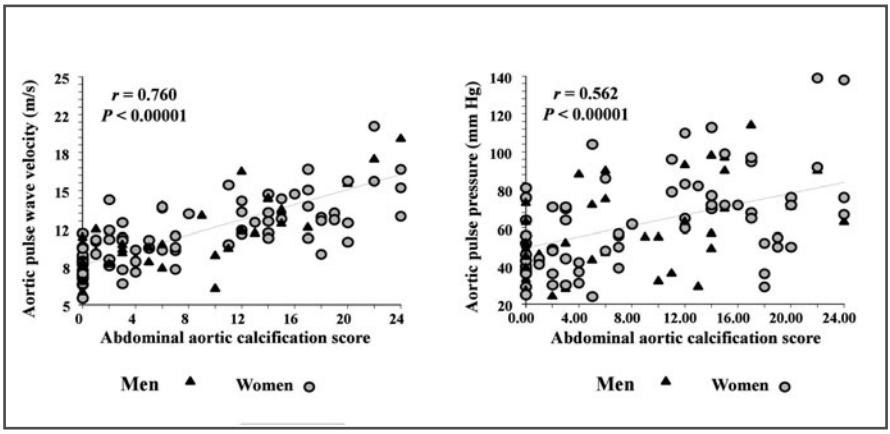

Fig. 20.1 Correlation between abdominal aortic calcification score and aortic pulse-wave velocity and aortic pulse pressure in end-stage renal disease patients. Triangles men; circles women

plaques and rupture of the plaques' fibrous cap. Although a higher coronary AC score is associated with a poorer cardiovascular prognosis, the influence of calcification on plaque stability is controversial. The results of several studies indicate that AC does not increase plaque vulnerability, which seems more attributable to a large lipid pool, thin fibrous cap, and intensity of local inflammation [39, 40].

Media calcification is concentric, not extending into arterial lumen in its typical pure form, and is associated with abnormal cushioning function of blood vessels (arteriosclerosis – arterial hardening) by promoting arterial stiffness [41]. The principal consequences of arterial stiffening are an abnormal arterial pressure wave, (characterized by increased systolic and decreased diastolic pressures, resulting in high pulse pressure) and increased aortic characteristic impedance, a measure of the opposition of the aorta to oscillatory input (i.e., stroke volume) [42]. Because the two forms of AC are frequently associated, the conduit and cushioning abnormalities may be associated.

20.4 Management and Prevention

Once present, AC rarely regresses. Therefore, the primary goals are preventing calcifications and stabilizing existing ones. Because intimal AC is related to atherosclerosis and atherosclerosis-associated microinflammation (Fig. 20.2), the general approach is nonspecific, as advocated for patients with atherosclerosis: control of blood lipids (but no evidence of a benefit with statins), use of aspirin, treatment of obesity and hypertension, physical activity, smoking cessation, and diabetes control. More specific preventive measures for patients with CKD or ESRD include control-

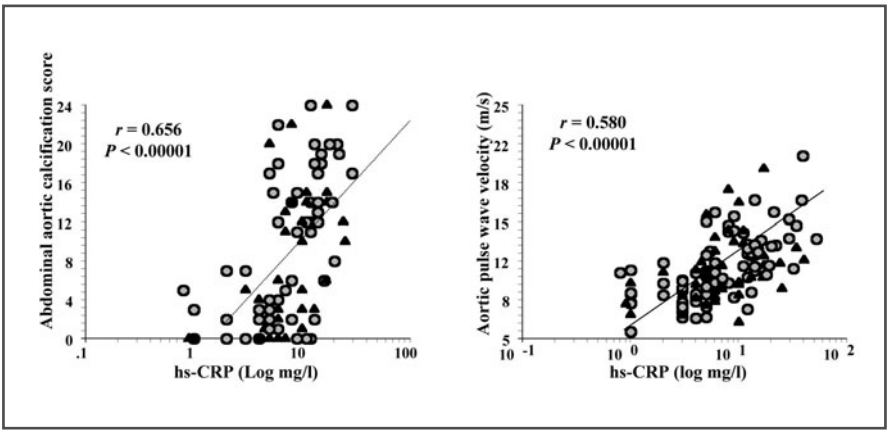

Fig. 20.2 Correlation between high-sensitivity C-reactive protein (hs-CRP), aortic calcification score, and aortic pulse-wave velocity. Triangles men; circles women

ling serum calcium and phosphate levels, thereby avoiding oversuppression of parathyroid activity and ABD [43]. Disturbances in calcium and phosphate metabolism are associated with uremic bone disease, and the results of several studies indicated that calcium overload is associated with AC development and progression, suggesting that the overuse of high doses of calcium-based phosphate binders, pharmacological doses of vitamin D, and high calcium concentration in the dialysate should be avoided [43, 44]. The randomized study on hemodialyzed patients did not demonstrate higher mortality rates for patients treated with calcium-containing phosphate binders but indicated a significant age effect for patients >65 years [45]. Aging adversely affects bone formation. An association of calcium supplementation with an upward trend for cardiovascular event rates was observed in elderly healthy postmenopausal women [46]. Those data suggest that the use of calcium-containing phosphate binders, high intradialytic calcium load, and overuse of active vitamin D should be avoided in elderly patients and in those who already have AC. Several endogenous calcification inhibitors (BMP-7; osteopontin), are in early developmental stages and may be of clinical benefit in treating ectopic calcification. Teriparatide (PTH 1–34) is an anabolic bone-stimulating agent [32], but it is not approved for treating ABD. The restoration of pulsatile PTH secretion in patients with calcimimetics could be considered in the presence of ABD [43].

20.5 Conclusions

CKD is associated with bone and mineral disorders frequently associated with vascular and heart-valve calcifications. The principal mineral and hormonal disorders associated with development of bone and vascular complications are primarily phosphorus retention in association with changes in calcium balance. Vascular calcification is an active process associated with phenotype transition of VSMCs to osteoblast-like cells. This transition is associated with disrupted balance between factors inducing calcifications and those preventing it. Vascular calcification is associated with changes in bone status, and an inverse relationship was observed between osteoporosis and/or low bone turnover, suggesting the existence of bone–vascular axis and crosstalk. The principal consequences of arterial calcifications depend on location: Intimal calcification occurs in the context of common atherosclerosis, progresses in parallel with the plaque evolution, and induces arterial dysfunction resulting from arterial lumen narrowing. Media calcification is concentric, does not extend into the arterial lumen in its typical pure form, and is associated with abnormal cushioning function of blood vessels by promoting arterial stiffness. Evaluation of the biochemical parameters (primarily phosphorus, calcium, PTH, and vitamin D levels) in early CKD stage 3 and bone status assessment should be used to guide treatment decisions. Early reduction of phosphorus load should be the primary goal.

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Role of Neurohormonal Activation in the Pathogenesis of Cardiovascular Complications in Chronic Kidney Disease

21

A. Stella, G. Castoldi

Abstract Cardiovascular disease (CVD) is the leading cause of mortality in patients with end-stage renal disease. Combined cardiac and renal dysfunction amplifies disease progression in both organs and increases the incidence of morbidity and mortality it these patients. This clinical condition is defined as cardiorenal syndrome, which was recently classified into five subtypes defined according to pathophysiology, time frame, and nature of coexisting cardiac and renal dysfunction. Chronic kidney disease (CKD) is an independent risk factor for CVD on a scale similar to that of traditional risk factors. The sympathetic nervous system and the renin–angiotensin system, both of which can be activated in CKD patients, are two major cardiovascular connectors contributing to cardiac and renal functional derangement and structural damage of the cardiorenal syndrome and thus are significant contributors to the pathogenesis of CVD morbility and mortality.

Keywords: Chronic kidney disease • Cardiovascular complications • Cardiorenal syndrome • Sympathetic nervous system • Renin angiotensin system

21.1 Introduction

Increasing evidence indicates that combined cardiac and renal dysfunction amplifies disease progression in both organs and leads to a high incidence of morbility and mortality. The combined clinical condition is defined as cardiorenal syndrome (CRS) and was recently classified into five subtypes according to pathophysiology, time frame, and nature of concomitant cardiac and renal dysfunction [1]. However, for evaluating CRS, different models are used by different physicians either by looking for common denominators (connectors) in heart and renal failure [2] or by primarily considering the different clinical conditions [3]. This chapter focuses on the poten-

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tial mechanisms involved in the pathogenesis of cardiovascular complications in chronic kidney disease (CKD), which creates a clinical condition similar to type 4 CRS proposed by Ronco et al. [1]. In particular, we examine mechanisms leading to activation of two major connectors as presented by Bongartz et al. [2]: i.e., the sympathetic nervous system (SNS) and the renin–angiotensin system (RAS).

21.2 Epidemiological Considerations

The life span of dialysis patients is reduced and concomitant cardiovascular disease (CVD) accounts for premature death in about 50% of dialysis patients. The mortality rate from CVD in dialysis patients far exceeds that observed in the general populations, with the greatest impact on younger patients in whom the early mortality rate is >100 times larger than that of their counterparts with normal kidney function [4]. Accelerated atherosclerosis or arteriosclerosis (or both) might be an important cause of the high cardiovascular mortality in this patient group [5]. Several aspects of hemodialysis, such as membrane incompatibility, impure dialysate, and the presence of vascular-access-related infections, can favor the atherogenic process. In addition, the incidence of arrhythmias, hypertension, coronary heart disease, peripheral vascular disease, and sudden death from heart failure, is markedly increased in dialysis patients.

However, the burden of CVD begins to accumulate long before patients reach end-stage renal disease and renal replacement therapy. Mild or moderate decreases in renal function correlates with significant morbidity and mortality in patients with congestive heart failure or myocardial infarction and those undergoing cardiovascular surgery [6]. Even in the absence of overt heart disease, the risk for CVD morbility and mortality is increased in patients with mild chronic renal insufficiency. CKD is recognized as one of the most important risk factors for CVD. Several large prospective population studies show that mild CKD is an independent risk factor for CVD of a similar magnitude to those of traditional cardiovascular risk factors, such as diabetes and hypertension [7].

Traditional cardiovascular risk factors such as advanced age, arterial hypertension, diabetes mellitus, dyslipidemia, and left ventricular hypertrophy are highly prevalent in patients with CKD. In addition, reduced glomerular filtration rate (GFR) is associated with nontraditional, or uremic, cardiovascular risk factors, which include anemia, uremic toxins, altered calcium–phosphate metabolism, hyperparathyroidism, urinary albumin excretion, hyperhomocysteinemia, prothrombotic factors, and volume overload. Recently, a major role has been ascribed to novel cardiovascular risk factors that are highly prevalent in uremic patients, such as chronic inflammation, endothelial dysfunction, increased oxidative stress, malnutrition, and cardiovascular calcifications.

Increased SNS activity and RAS activation play an important role in the pathogenesis of CVD morbility and mortality. Both systems can be activated in CKD and

are two major cardiovascular connectors contributing to the cardiac and renal functional derangement and structural damage of the CRS [2].

21.2.1 Increased Sympathetic Nervous System Activity

Recent data clearly support the notion that the SNS is activated in chronic renal disease and substantially contributes to the poor prognosis in this patient group [8]. In a cohort of 228 patients undergoing hemodialysis and who did not have congestive heart failure at baseline, the predictive power of plasma norepinephrine for all-cause mortality and cardiovascular outcomes was studied [9]. As shown in Fig. 21.1, cumulative mortality and cumulative cardiovascular events in patients with plasma norepinephrine values >5.57 nmol/l (75th percentile) were consistently higher than in patients showing lower values. These data demonstrate that SNS overactivity, estimated by plasma norepinephrine levels, is associated with mortality and CVD outcomes in patients with end-stage renal disease [9].

Early observations demonstrating increased plasma catecholamine concentrations in patients with CKD, in whom increased sensitivity to norepinephrine and enhanced hypotensive response to adrenergic inhibition were reported, were the first indicators of SNS hyperactivity in this patient group [8, 10]. By employing clinical microneurographic techniques, Converse et al. [11] first reported that muscle sympathetic nerve activity (MSNA) is 2.5-fold higher in patients receiving hemodialysis than in normal individuals. Interestingly, in patients who underwent bilateral nephrectomy, MSNA was substantially equal to MSNA measured in the control group (Fig. 21.2). It was concluded that chronic renal failure may be accompanied by reversible SNS activation, which appears to be mediated by an afferent signal arising in the failing

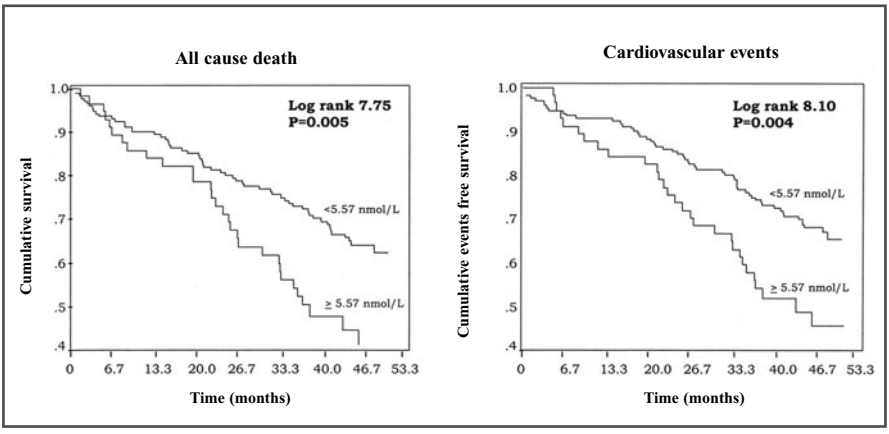

Fig. 21.1 Kaplan–Meier survival curves for all-cause death and cardiovascular events (fatal and nonfatal) in patients below and above the 75th percentile of plasma norepinephrine (NE). Reproduced from [9] with permission

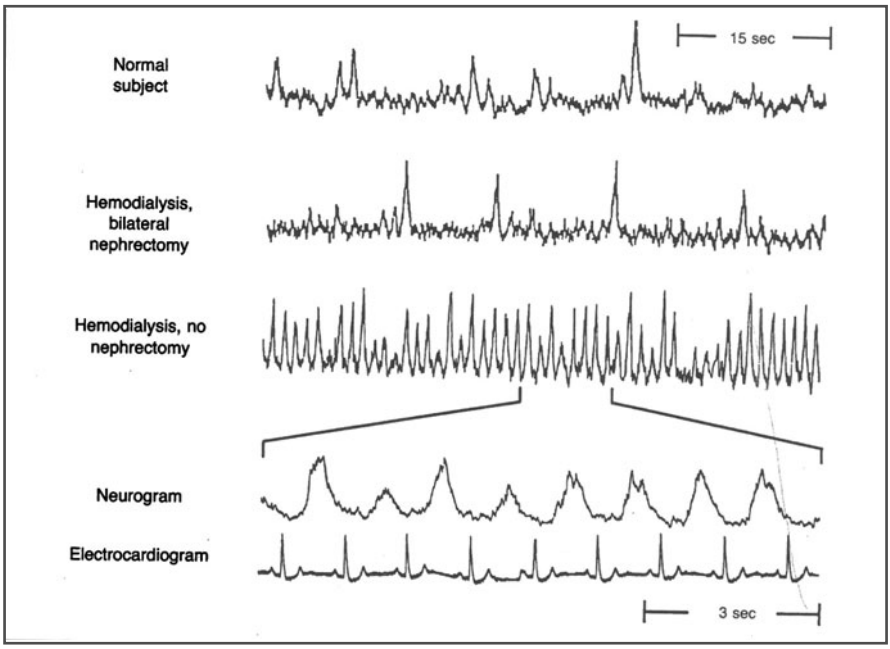

Fig. 21.2 Recordings of sympathetic-nerve discharge to the vasculature of the leg muscles in a healthy individual and in two patients receiving hemodialysis: one with and one without bilateral nephrectomy. The *top three panels* are representative segments of the neurograms from the three individuals, and the *bottom two panels* display the neurogram and simultaneous electrocardiogram from the third individual on an expanded time scale. On these mean-voltage displays of sympathetic-nerve activity in the muscle, each *peak* represents a spontaneous burst of sympathetic-nerve discharge. The rate of sympathetic-nerve discharge was much higher in the patient undergoing hemodialysis who had not had a nephrectomy than in the patient undergoing hemodialysis who had had a bilateral nephrectomy, with the rate in the latter being indistinguishable from that in the normal individual. Despite the elevated rate of sympathetic-nerve discharge, the sympathetic-nerve activity retained its normal relation to the cardiac cycle. Reproduced from [11] with permission

kidney [11].This finding was later confirmed in renal transplantation patients with diseased native kidney in which MSNA was higher than MSNA measured in normal individuals and equal to that observed in chronic hemodialysis patients, despite the correction of uremia [12]. Similarly to previous results [11], MSNA was found to be significantly lower in renal transplant recipients who underwent bilateral nephrectomy and was similar to that observed in healthy volunteers. Again, it was concluded that increased SNS activity seems to be mediated by signals arising in the native kidneys, independent of circulating uremia-related toxins [12].

Increased SNS activity has been shown also in patients with mild or moderate renal insufficiency [6, 10]. It is likely that activation of this system plays an important role in the pathogenesis of arterial hypertension often associated with CKD [10, 13]. In the development of hypertension in patients with kidney diseases, a major role has been ascribed either to an excess of extracellular volume (volume-dependent hypertension) or excessive activation of the RAS in relation to sodium balance

(renin-dependent hypertension) [13]. Klein et al. [14] provided evidence that the increase in SNS activity in patients with polycystic kidney disease is associated with arterial hypertension. MSNA in patients with polycystic kidney disease and hypertension was significantly higher than MSNA measured in patients with polycystic kidney disease without hypertension. GFR, measured by creatinine clearance, was normal in all patients, and no differences in plasma renin activity were observed among the groups. This study shows that hypertensive patients with polycystic kidney disease have increased SNS activity regardless of renal function [14].

21.2.1.1 Renal Mechanisms of Increased Sympathetic Nervous System Activation

Clinical evidence described above suggests that the failing or damaged kidneys can trigger a reflex activation of the SNS. In this regard, it is well known that the kidney can be considered a 'sensor' organ capable of sending information, by its neural afferent connections, to the central nervous system, thus participating in the reflex control of several bodily functions [15]. The role of renal mechanoreceptors (sensitive to changes in arterial, venous, and pelvic pressures), renal chemoreceptors (sensitive to renal ischemia or ionic composition of pelvic fluid), and renal receptors activated by intrarenal or intrapelvic administration of adenosine, bradykinin, and urea, have been clearly established [15]. Neural signals arising from the kidney can be enhanced or inhibited in many physiological and pathophysiological conditions. Interaction between mechanical and chemical stimuli is illustrated in Fig. 21.3,

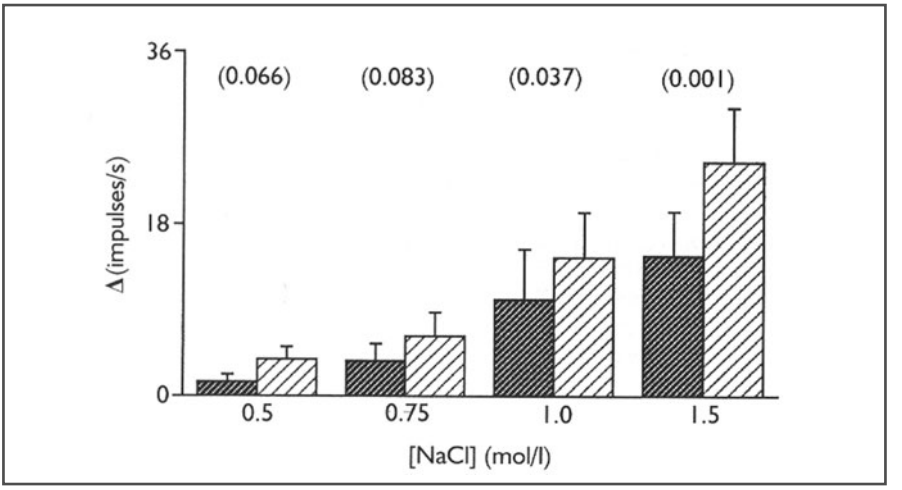

Fig. 21.3 Changes in afferent renal nerve activity (impulses/s) between test and saline periods (chemical activation), during renal pelvic perfusion at low (0.2 ml/min; *left-hand histograms*) and high flow rates (0.8 ml/min) with sodium chloride (NaCl) solutions of increasing concentration: 0.5 mol/l ($n = 8$), 0.75 mol/l ($n = 8$), 1.0 mol/l ($n = 8$), and 1.5 mol/l ($n = 9$). *P* values (given in parentheses) refer to comparisons between high and low flow rates. Reproduced from [16] with permission

showing results obtained in anesthetized rabbits in which afferent renal nerve discharge elicited by chemical stimuli [hypertonic sodium chloride (NaCl) solutions] is markedly enhanced by concomitant pelvic pressure increases [16]. An experimental model of chronic heart failure demonstrated that responsiveness of renal mechanosensory nerves is impaired due to an inhibiting effect of increased angiotensin II (Ang II) on the prostaglandin-mediated release of substance P from pelvic nerves [17]. Recent evidence in mouse models demonstrates that hypertension secondary to administration of the calcineurin inhibitor cyclosporine A is mediated by renal sensory endings [18]. In this experimental model, activation of renal afferent fibers is dependent on the integrity of synapsins, a family of synaptic vesicle phosphoproteins. Indeed, in knockout mice lacking synapsin I and II, reflex activation of the SNS and the increase in blood pressure caused by cyclosporine A administration are greatly attenuated compared with the control group [18].

21.2. 1.2
Neurogenic Hypertension in Kidney Disease

By experimental studies done in rats, Campese and co-workers [13] provided the most convincing evidence for the role of the SNS in the pathogenesis of hypertension associated with kidney disease. In 5/6 nephrectomized rats, there was an increase in turnover rate and secretion of norepinephrine from the posterior hypothalamic nuclei. This effect was mediated by renal afferent fibers originating in the failing kidney, which was prevented by severing bilateral dorsal roots at the T10–L3 level. These studies suggest that increased renal sensory impulses generated in the diseased kidney converge to the central nervous areas involved in noradrenergic control of the cardiovascular system. Later, Campese et al. developed a model of neurogenic hypertension caused by renal injury (injection of 50 µl of phenol in the lower pole of one kidney) without measurable alterations in kidney function. Renal injury caused a sharp and sustained rise in blood pressure and efferent SNS activity, which were prevented by renal denervation. As illustrated in Fig. 21.4, it was concluded that renal injury may stimulate renal afferent pathways, resulting in activation of areas of the brain involved in cardiovascular control that, in turn, enhance efferent SNS activity by increasing locally released Ang II [13]. It is likely that in clinical conditions, focal or generalized renal ischemia may trigger an increase in afferent renal nerve activity. At present, however, other types of acute or chronic renal damage able of increasing afferent neural discharge cannot be excluded.

21.2.1.3
Reflex Increase in Sympathetic Nervous System Activity and Organ Damage

SNS activity is always enhanced in chronic heart failure, and indices of neurohumoral activation such as norepinephrine, aldosterone, and plasma renin activity correlate with both severity and prognosis of the disease and with treatment efficacy. In

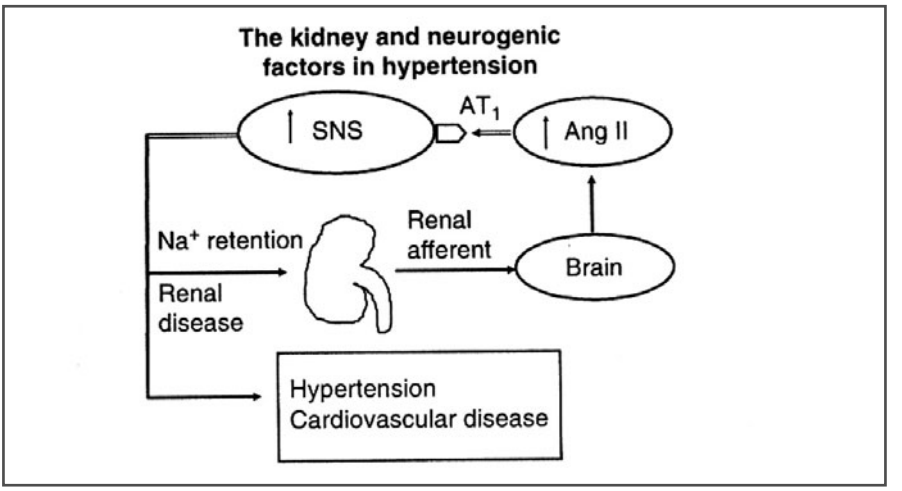

Fig. 21.4 Summary of current concepts linking renal damage with increased sympathetic nervous system (SNS) activity. Renal damage/ischemia stimulates afferent pathways, which integrate with key brain structures involved in the noradrenergic control of blood pressure. The central mediator of this pathway appears to be angiotensin II, which stimulates SNS activity through specific angiotensin II type 1 receptors (AT_1). Specific blockers of these receptors abrogate central SNS activation mediated by renal injury. Efferent SNS pathways may cause hypertension and contribute to cardiovascular and renal damage. Reproduced from [13], with permission

CRS, to which extend the presence of CKD participates in the reflex activation of the SNS is less clear. Recently, evidence has been provided for a role of CKD in promoting neurohumoral activation [19]. In patients with chronic heart failure, for a given degree of cardiac dysfunction, the plasmatic concentration of norepinephrine, aldosterone, and plasma renin activity were significantly higher in patients with concomitant abnormal renal function than in patients with normal renal function. On the other hand, for a given degree of renal function, neurohumoral activation is more evident when a more depressed cardiac function is present [19]. These data suggest that dysfunction of the heart and the kidney exerts an additive and independent effect on the neurohormonal system. It has also been confirmed that neurohormonal activation is strictly related to long-term survival of this patient group [19].

According to this conclusion, it has recently been demonstrated that, in patients with CKD, sympathetic hyperactivity was associated with the composite of all-cause mortality and nonfatal cardiovascular events, despite treatment with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs), which are known to reduce SNS activity [20]. These data extend previous observations done in dialysis patients [9] indicating that SNS activation is a negative prognostic marker in patients who were not yet in dialysis at the beginning of the study [20].

In patients with moderate to severe CKD, MSNA and plasma norepinephrine values were significantly higher than values measured in healthy volunteers [21]. However, no differences in skin sympathetic nerve traffic were observed between

patient and control groups. These data suggest that the SNS activation that characterizes renal failure is not generalized to the entire cardiovascular system [21]. The possibility that heart failure and renal failure activate SNS activity by different reflexogenic areas has been raised.

The increase in efferent SNS activity in CKD patients is frequently associated with arterial hypertension, and it is well known that hypertensive patients are characterized by an elevated sympathetic tone. By comparing MSNA recorded in a small group of hypertensive patients with mild renal failure (mean creatinine clearance = 35 ± 4 ml/min) with values measured in hypertensive patients with normal renal functions (mean creatinine clearance = 110 ± 5 ml/min), it was found that SNS activity was higher in the former than in the latter group [22]. SNS activity of both patient groups was greater than that measured in the control group of normotensive patients with normal renal function [22]. SNS hyperactivity in CKD patients is clinically relevant, not only because it participates in sustaining high blood pressure, which is known to be one of the major cardiovascular risk factor and the major promoter of progression of kidney disease, but also because catecholamines are clearly involved with the development of left ventricular hypertrophy, arrhythmias, atherogenesis, and vascular remodelling [23]. Additionally, SNS activation promotes progression of kidney damage independently of systemic blood pressure, as it has been shown that catecholamines have direct proliferative effects on podocytes and can directly stimulate the release of renin from juxtaglomerular cells [23]. Together, these data suggest that the increased SNS activity in CKD patients is an important contributor to maintaining high cardiovascular risk in these patients.

21.2.2 Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system (RAAS) plays a central role in two important physiopathological models proposed by (1) Guyton [24] for the pathogenesis of arterial hypertension, and (2) Brenner [25] for CKD progression. Therefore, it is not surprising that RAAS is activated in renal failure and that this activation appears to be inappropriate considering the coexistence of an expanded fluid body volume.

Indeed, systemic hypertension secondary to renovascular disease (i.e., renovascular hypertension) or associated with renal parenchymal disease is largely due to an increase in RAAS activity and/or an excess of extracellular volume. The role of increased circulating or tissue Ang II in promoting progression of renal failure is indirectly proved by the beneficial effects ascribed to drugs capable of blocking the RAS. Similarly, several clinical trials have demonstrated that ACEIs and Ang II receptor antagonists reduce mortality and morbidity rates in patients with heart failure and improve clinical outcomes in patients with asymptomatic left ventricular systolic dysfunction or CVD predisposing to the development of heart failure.

A wide variety of physiological and pathophysiological conditions, including CKD and chronic heart failure, activate the RAAS mainly by enhancing the release of renin from juxtaglomerular cells. The RAS has been traditionally considered a

classic endocrine system with an effector hormone, Ang II. In the past, it was considered that only two enzymes, renin and ACE, were responsible for production of angiotensin I and II. Ang II exerts multiple systemic (vasoconstriction, sodium retention) and direct effects on tissue remodelling processes (hypertrophy/hyperplasia, inflammation, fibrosis), which are mediated mainly by the Ang II type 1 receptor (AT_1) [26, 27]. An example of the tissue effect of Ang II mediated by AT_1 is shown in Fig. 21.5.

Administration of a specific AT_1 antagonist (losartan) inhibits Ang–II-mediated expression of an inhibitor of tissue metalloproteinases (Fig. 21.5), the main enzymes involved in tissue remodelling. Ang II is not only generated in the circulation but is also produced locally in different tissues, such as heart, vessels, and kidney, and tissue RAS amplifies the action of the circulating Ang II [28]. Today, greater complexity of the RAS is recognized. The discovery of tissue-specific enzymatic pathways, resulting peptides, and new receptors into the RAS, in addition to the traditional elements, has improved our understanding of the RAAS in the physiopathological control of cardiac and renal functions. New components of the RAS, such as (pro)renin receptors [(P)RR] and Ang-(1–7)/Mas receptor/ACE2 axis have been described [29].

(P)RRs play an important role in cardiovascular and renal damage through Ang II independent pathways. In fact, activation of (P)RR fully activates prorenin, increases renin enzymatic activity, and promotes cardiovascular fibrosis and glomerulosclerosis. Ang-(1–7), which is produced by the action of ACE2 from Ang I and Ang II, may counteract, through Mas receptors, the hemodynamic and tissue effects of Ang II. ACE2 is the main enzyme involved in Ang-(1–7) production. Experimental and clinical evidence support the physiological and pathophysiological role of ACE2 in cardiovascular and renal systems. In fact, genetic deletion of ACE2 causes a reduction in cardiac contraction and an up-regulation of hypoxia-induced genes in the

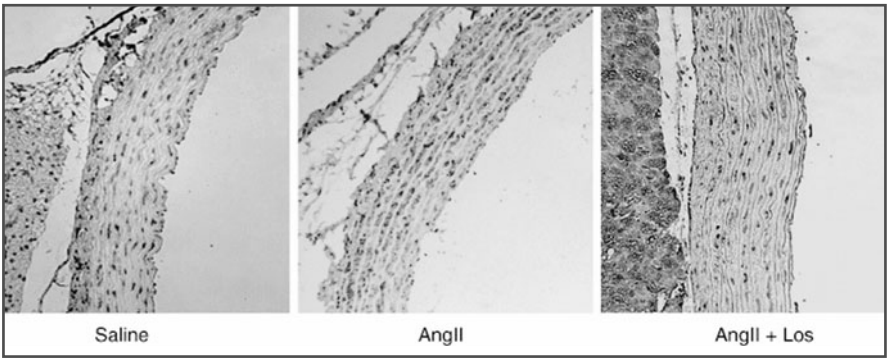

Fig. 21.5 Tissue-specific inhibitor of metalloproteinase (TIMP)-2 protein expression evaluated by immunohistochemistry in rat aortas. Immunohistochemistry for TIMP-2 expression in rat aortas was performed for all aortas in each group [saline-treated rats: $n = 7$; angiotensin II (Ang–II)-treated rats: $n = 6$; Ang-II + losartan (Los)-treated rats: $n = 6$]. Representative photomicrographs (×10) of immunostaining for TIMP-2 antigen show a stronger immunostaining for TIMP-2 (located mainly in the perinuclear area) in Ang-II- treated rats than in aortic smooth muscle cells of saline and Ang-II + Los-treated rats. Reproduced from [27] with permission

heart [30], whereas in the kidney, it promotes albuminuria and glomerulosclerosis [31]. Furthermore, the Ang-(1–7)/Mas/ACE2 axis represents an important counter-regulatory pathway in the RAS in the kidney and the cardiovascular system.

Aldosterone is another important mediator of the effects of RAAS. Its binding to mineralocorticoid receptors (MR) stimulates the transcription of MR-responsive genes. Increasing evidence indicate a complex crosstalk between Ang II and aldosterone [32]. Aldosterone up-regulates Ang II receptors and ACE activity, causing a vicious cycle in which aldosterone stimulates the production of Ang II, and the following increase of Ang II causes an increase in aldosterone levels that, by modulating Ang II signal transduction, finally leads to pathophysiological events in the cardiovascular system and kidney.

21.2.3 Interactions Between the Sympathetic Nervous System and the Renin–Angiotensin System

Renal nerves control renin release by direct action on juxtaglomerular cells, which is mediated by β-adrenoreceptors. The neural control of renin release acts in physiological conditions such as during postural changes or during the modification of systemic arterial pressure and extracellular volume. It has been also shown that neural control of renin release is not limited to modulation of renin secretion but can amplify the response of juxtaglomerular cells to other stimuli, such as a reduction in renal perfusion pressure or in sodium load to the macula densa. On the other hand, Ang II can stimulate SNS activity by a direct effect on the vasomotor center in the brain stem and by enhancing sympathetic neurotransmission at the adrenergic nerve terminal, increasing the release or decreasing the reuptake of norepinephrine [10]. As described in the experimental model of sympathetic hyperactivity caused by kidney damage, locally released Ang II in the cerebral vasomotor areas mediates the effect on efferent SNS elicited by activation of the renal afferent fibers [13].

These pathophysiological interactions appear to be largely involved in clinical conditions, such as CKD and chronic cardiac failure. In CRS, simultaneous activation of the RAS and SNS occurs, resulting in a reciprocal reinforcement that can amplify the damage caused by norepinephrine and Ang II on target organs such as heart, vessels, brain, and kidney.

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Impaired Autonomic Blood Pressure and Blood Volume Control in Chronic Renal Failure

22

G. Grassi, R. Dell'Oro, F. Quarti-Trevano, G. Mancia

Abstract Renal failure is characterized by impairment in autonomic cardiovascular control, with reduced baroreceptor heart-rate modulation and altered cardiopulmonary reflex control of sympathetic vasoconstrictor tone. The autonomic abnormalities also include chemoreflex activation and muscle metaboreceptor reflex dysfunction. These reflex changes contribute to disease progression by promoting and aggravating the adrenergic overdrive seen in patients with renal failure. The adverse cardiovascular effects of this autonomic impairment make autonomic dysfunction a target for the therapeutic approach to renal failure.

Keywords: Arterial baroreflex • Cardiopulmonary reflex • Chemoreflex • Sympathetic nervous system activity • Parasympathetic nervous system activity • Reflex cardiovascular control

22.1 Introduction

Kidney failure originates from derangement of renal excretory function, causing impairment in blood volume and blood fluid homeostasis. This primary impairment is followed by a number of alterations that affect not only the renal organ but also the cardiovascular system as a whole, making renal failure not merely a pathologic state affecting the kidney but a disease of the entire cardiovascular system.

This chapter focuses on an alteration occurring in chronic renal failure for which there is overwhelming experimental and clinical evidence, i.e., impairment in autonomic cardiovascular control. First, the main features of reflex control of circulation in patients with renal failure are described. Then analysis of the possible mechanisms responsible for this reflex dysregulation and its potential adverse cardiovascular effects is presented. Finally, the possibility that autonomic abnormalities can be reversed by treatment to restore normal neural circulatory control is addressed.

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Cardiorenal Syndrome. Adel E. Berbari, Giuseppe Mancia (Eds.)

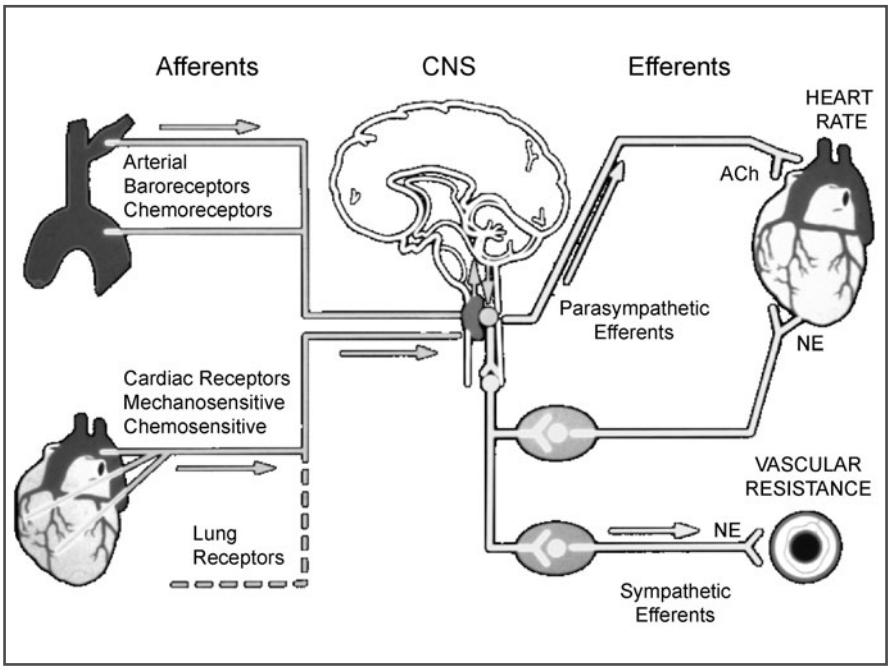

Fig. 22.1 Major reflexogenic areas (arterial baroreceptors and cardiopulmonary receptors) involved in blood pressure and blood volume control; *Ach,* acetylcholine; *CNS,* central nervous system; *NE,* norepinephrine

22.2 Reflex Control of Circulation in Renal Failure

Experimental studies in animal models of renal failure show that the major reflexogenic areas involved in blood pressure and blood volume control, i.e., arterial baroreceptors and cardiopulmonary volume receptors, undergo profound changes in their functional role of preserving cardiovascular homeostasis [1–4] (Fig. 22.1). Human studies also document this alteration, the main features of which are summarized here.

22.2.1 Arterial Baroreflex

Assessment of baroreflex heart-rate control via the classic intravenous bolus injection of phenylephrine or inhalation of amyl nitrite to obtain baroreflex stimulation and deactivation, respectively, has shown that impairment in baroreceptor modulation of sinus-node activity characterizes the disease [5–7]. The magnitude of the

reflex heart-rate impairment is related to the severity of the uraemic state, to the presence of hypertension, and autonomic neuropathy [5–7]. Furthermore, bradycardic responses to carotid baroreceptor stimulation via the neck-collar device are significantly attenuated in renal failure patients with different clinical severity and etiology [7]. Taken together, these findings provide evidence that renal failure is characterized by a marked reduction in arterial baroreflex sensitivity, i.e., a functional baroreceptor denervation. This means complete or nearly complete loss of baroreceptor enhancement of carotid vagal influences. These reflex alterations were recently confirmed by evaluation of the baroreflex effectiveness index, a novel marker of baroreflex function reflecting the times the baroreflex is effective in modulating heart-rate responses to spontaneous blood pressure fluctuations [8, 9].

Whether and to what extent impairment in baroreflex modulation of heart rate (and thus of parasympathetic nervous system function) also applies to baroreceptor–blood pressure control [and thus to sympathetic nervous system (SNS) function] was recently addressed in two studies in which baroreflex modulation of the adrenergic drive was found to be virtually superimposable to that characterizing age-matched healthy individuals [10, 11]. It thus appears that, as has been shown in essential hypertension [12, 13], the marked impairment in baroreceptor modulation of heart rate in renal failure is not accompanied by a similar impairment in baroreceptor modulation of blood pressure and SNS cardiovascular drive (Fig. 22.2).

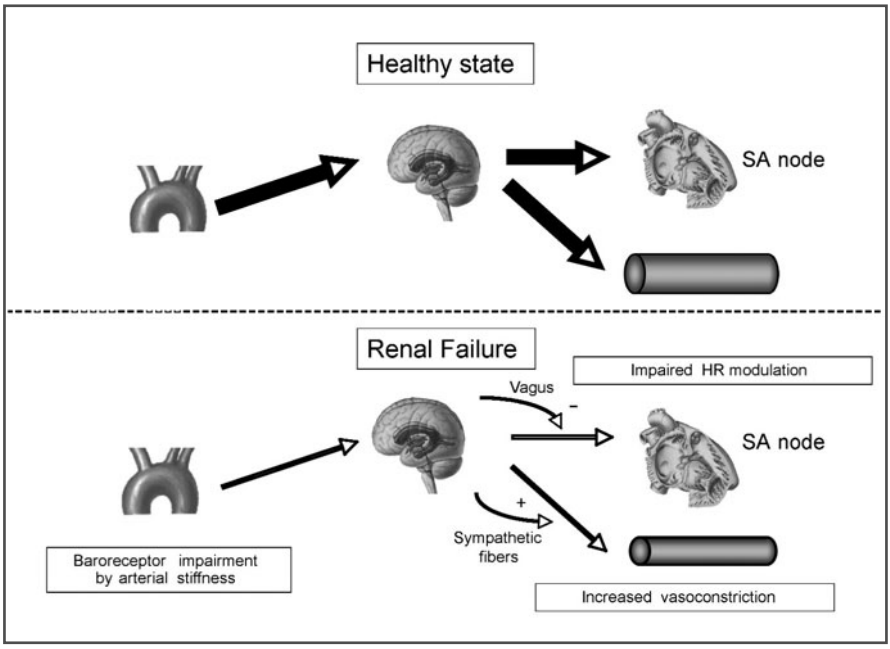

Fig. 22.2 Summary of major consequences of abnormalities in baroreflex control of circulation in renal failure. *HR,* heart rate; *SA,* sinoatrial

22.2.2
Cardiopulmonary Reflex

Volume-sensitive receptors located within the thickness of the cardiac chambers as well as in the pulmonary arteries exert inhibitory influences on peripheral vasoconstriction tone and secretion of humoral substances, such as renin, vasopressin, and atrial natriuretic peptides, which are of major relevance in regulating cardiovascular homeostasis [14]. Similarly to arterial baroreceptors, cardiopulmonary receptor modulation of SNS vasoconstrictor tone and juxtaglomerular secretion of renin is strikingly impaired in renal failure, particularly when disease severity is so advanced as to be reversed only by the dialytic procedure [7].

22.2.3
Other Cardiovascular Reflexes

Several other reflexes participate at cardiovascular control, but their modifications in the presence of renal failure have not been studied extensively. An exception is chemoreceptors, the tonic activation of which has been shown to contribute – together with other above-mentioned reflexes – to the SNS overdrive characterizing renal failure [15]. A further exception is the reflex originating from skeletal muscle metaboreceptors, which display impairment in inhibitory influences on central SNS neural outflow [16]. Thus, metaboreceptor dysfunction may be regarded as a further mechanism responsible for the adrenergic overdrive seen in patients with kidney disease [4].

22.3
Mechanisms Responsible for Reflex Abnormalities

Reflex impairment characterizing renal failure does not appear to depend on a nonspecific reduction of effector responsiveness to autonomic stimuli, because cardiac and vascular responses to cold pressor test are preserved in this condition [5–7]. Other possibilities are represented by: (1) impairment of the central integration of afferent baroreceptor or cardiopulmonary receptor signals, (2) receptor structural or functional damage, and (3) reduced compliance of the vascular structure in which arterial baroreceptors are located. This latter possibility has received experimental support by studies showing that arterial stiffness is markedly increased in renal failure, thus markedly reducing arterial distensibility or compliance [17, 18]. The hypothesis can be thus advanced that increased arterial stiffness of large elastic arteries, where baroreceptors are anatomically located, may prevent arterial baroreceptor signals from being properly modified in response to blood pressure changes, thereby

being responsible for arterial baroreflex impairment. It is also likely that impaired compliance of cardiac walls, in which volume-sensitive receptors are located, may be responsible for the concomitant reflex impairment. Other mechanisms may participate, however. This is particularly the case for left ventricular hypertrophy (LVH), which is commonly detected in renal-failure patients [19] and may per se impair cardiopulmonary reflex function [20].

22.4 Consequences of Cardiovascular Reflex Dysfunction

There are several direct and indirect adverse effects of reflex abnormalities characterizing renal failure. The leading one relates to activation of the neurohumoral systems, such as renin, angiotensin II, vasopressin, and atrial natriuretic peptides, which are involved in cardiovascular homeostasis control [21]. These humoral factors, when elevated in circulating plasma levels, may trigger adverse cardiovascular effects such as arterial and arteriolar vasoconstriction, reduced organ perfusion, and sodium and water retention.

A further adverse consequence is development and progression of SNS activation, which represents a hallmark of renal failure both mild and more severe degrees [4], and which appears to be involved in a number of cardiovascular and metabolic alterations characterizing renal failure (Table 22.1). This provides the pathophysiological background for evidence that in renal failure, increased circulating plasma levels of noradrenaline are associated with reduced survival rate [22].

Table 22.1 Adverse consequences of sympathetic nervous system (SNS) activation in renal failure

Myocardial necrosis
Cardiac arrhythmias and sudden death
Increased cardiac oxygen consumption
Reduced coronary blood flow
Left ventricular hypertrophy
Reduced arterial distensibility
Tissue anoxia
Peripheral congestion and edema
Sodium retention
Insulin resistance
Activation of renin–angiotensin system

22

22.5 Therapeutic Implications

The findings discussed so far emphasize the importance that both nonpharmacologic and pharmacologic interventions employed in renal failure treatment should be aimed not only at improving renal function and slowing clinical progression of the disease but also at restoring normal baroreflex function. This is the case for drugs actively interfering with the renin–angiotensin system, which have been shown to exert sympathomodulatory effects, presumably by improving baroreflex function [23, 24]. This is also the case for dialytic procedure, which is associated with impairment in both arterial baroreceptor and cardiopulmonary receptor control of the circulation [25, 26]. Improvement results in sympathoinhibition of a more sustained degree when dialysis is performed during the nighttime [27] or in a short daily fashion [28]. An even more pronounced improvement of reflex function can be seen after kidney transplantation [25, 29], which almost completely normalizes homeostatic cardiovascular control in transplanted patients. This restoration allows SNS activity to decrease, although not infrequently the direct and indirect indices of the adrenergic drive remain elevated due to the sympathoexcitatory effects of some immunosuppressive drugs [30].

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Role of Novel Biomarkers in Chronic Kidney Disease: Urotensin II

23

F. Mallamaci, D. Leonardis, M. Borrajo

Abstract Urotensin II (UT) is an 11-amino-acid peptide widely expressed in the nervous system, heart, and kidneys. High UT levels are implicated in myocardial and renal dysfunction, and UT antagonists are considered as a possible treatment for these conditions. However, some studies involving patients with coronary heart disease, chronic kidney disease (CKD) and end-stage renal disease (ESRD) suggest that UT could have a dual role for the cardiovascular and renal systems in these diseases. In the cardiovascular system, UT acts as a vasoactive and inotropic substance. The kidney actively synthesizes UT, and urinary UT concentration far exceeds plasma UT concentration. Clinical outcomes are inversely related to UT levels, and this association was reported for the first time in a cohort of patients with ESRD. In uremic people, high UT may underlie a cardioprotective situation. In agreement with this hypothesis, relatively higher UT levels were associated with a better left ventricular (LV) systolic function and relatively low LV posterior wall thickness in ESRD. These findings could be explained by the interference of UT with sympathetic activity and nitric oxide (NO) synthesis.

Keywords: Cardiovascular risk • End-stage renal disease • Renal diseases • Urotensin II

23.1 Introduction

In the past decade, identification and validation of biomarkers of kidney injury and chronic kidney diseases (CKD) is considered of paramount importance to many diagnostic biotechnology companies as well as academic research institutes. So far, several substances, such as C-reactive protein, troponin, and natriuretic peptides have been claimed to play a key role as biomarkers in renal diseases. More recently, a new substance, urotensin II (UT), has enriched this already ample scenario. UT is a small pep-

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tide formed by 11 amino acids widely expressed in the nervous system, heart, and kidney. High UT levels are implicated in myocardial and renal dysfunction, and those substances that antagonize UT are considered as a possible treatment for these conditions [1]. However, some studies involving patients with coronary heart disease, CKD, and end-stage renal disease (ESRD) suggest that UT could have a dual role for the cardiovascular (CV) and renal systems in these diseases. Very recently, the expression and functional role of UT and its receptors were demonstrated in a paper by Giuliani et al. [2], giving new insights into the pathophysiology of primary aldosteronism.

The purpose of this review is to focus on the role of UT in renal diseases. However, in order to achieve a broader view of this important hormone, we proceed by following this pathway: first, notes on UT biochemistry; second, the role of UT in the CV system in health and disease, and third, the role of UT in the kidney and in renal diseases.

23.2 Notes on Urotensin II Biochemistry

UT is a small peptide originally identified, isolated, and cloned from fish urophysis in 1969. Subsequently, UT isopeptides have been found in many animal species and humans [1]. The human isoform was found to be the human orphan G-protein-coupled receptor GPR14 and was named the UT receptor. An isoform peptide is the prepro-UT that consists of two alternative splicing variants of 124 and 139 amino acids, the main difference with UT being in their amino terminus. Prepro-UT is highly represented in human tissues, including the central and peripheral nervous system, gastrointestinal tract, vascular system, and kidney [1]. The prohormone contains a C terminus, which is cleaved to produce UT, an undeca amino-acid residue peptide. The biological activity of UT potency is markedly higher than the C-terminal fragment of the prohormone, which suggests that the proteolytic cleavage is crucial for its biological function.

The human form of UT is composed of a cyclic hexapeptide sequence, which is fundamental for the action of this substance [3]. The metabolic pathway leading to the production of UT is still not completely understood. Although multiple mono- and polybasic amino-acid sequences in the UT molecule have been identified as post-translational cleavage sites [4], what remains unclear are the sites where the prohormone is processed; in other words, whether it is handled intracellularly or is secreted and processed at distant sites or cleaved in the circulation. An arteriovenous gradient between 36% and 44% has been demonstrated for UT across the heart, liver, and kidney, indicating local UT production [5]. Thus, systemic UT derives from these sources, and this peptide may play a role as a circulating hormone.

Besides UT, the UT receptor binds various UT fragments, some of them deriving from a different precursor, such as urotensin-related peptide (URP) [6]. URP is shorter than UT (eight instead of 11 amino acids), but its hexapeptide sequence property is critical for the action of UT receptor ligands.

23.3 Role of Urotensin II in the Cardiovascular System in Health and Disease

Although UT has various biological and physiological actions, such as stimulation of cell proliferation [7], positive inotropic action [8], stimulation of insulin release, and interference with sleep and behavior, this substance is mainly considered as a CV autacoid/hormone. In the CV system, UT acts as a vasoactive and inotropic substance. The vasoactive properties of UT are of vasoconstriction or vasodilation, depending upon species, strains, vascular beds, and even regions from the same vascular bed. In vitro, the thoracic aorta from male Sprague–Dawley rats has been shown to be the most sensitive and reactive vessel [9]. However, it appears that UT is a potent vasoconstrictor, an effect mediated via UT receptors in smooth muscle cells, whereas it has little or no effect on venous tone. On the other hand, its vasodilating properties are well documented in the endothelium, where UT acts as an endothelium-dependent vasodilator, via UT receptors, in isolated human pulmonary and mesenteric vessels [10].

In vivo, vascular effects of UT in humans range from local vasoconstriction in the forearm or no effect by systemic infusion to cutaneous vasodilatation (reviewed in [11]). These differences implicate that the CV effects of this substance should be analyzed, taking into account many variables such as animal species, site, modality of injection, dose, vascular bed, and functional conditions of the experimental model [12].

Other important properties of UT are its interaction with angiotensin II and with the sympathetic system both peripherally and centrally. In fact, using isolated rat aortic rings with intact adventitia, the coadministration of UT and angiotensin II, which is the leading system involved in CV regulation, produced effect levels significantly greater than those predicted by additivity, suggesting a synergistic response [13], whereas neither of these two peptides administered alone affects the contractility of this vessel. In another study, endothelial nitric oxide synthase (eNOS) appears crucial for the UT–angiotensin II interaction because such synergism manifests only after eNOS inhibition [14].

UT interference with the sympathetic nervous system is somewhat more complex than with angiotensin II. In rats that underwent anesthesia, UT was about three times more powerful in antagonizing systemic pressor responses to the selective α-1 adrenoreceptor agonist phenylephrine than responses to the nonselective α-1 agonist norepinephrine [15]. Microinjection of UT into the A1 region of the medulla oblongata decreased blood pressure (BP) and heart rate, whereas the effects of microinjection into the paraventricular or arcuate nucleus were opposite to the previous ones [16]. Apart from its interference with the sympathetic nervous system, UT influences the synthesis of cardiac natriuretic peptides [17].

Besides its vasoactive properties, urotensin, acutely, has a strong inotropic effect when applied to human right atrial trabeculae [8] or rat LV papillary muscles [18]. On a chronic basis, this hormone in the rat reduces cardiac performance [19]. Moreover, in other species, such as the cynomolgus monkey, it reduces myocardial

contractility and provokes circulatory collapse and death [20, 21]. However, observations in a chronic volume overload model in the rat [22] indicate that continuous administration of UT may help preserve myocardial contractility in this model. Similarly, in an experimental ischemia–reperfusion injury in isolated rat heart [23], both UT and URP exhibit myocardial protective property. Indeed, these peptides increase flow through the coronary circulation, reduce myocardial energy, and attenuate myocardial reperfusion damage.

The relevance of UT for the CV system is described by Behm et al. [24] in prepro-UT-deficient mice. This model is characterized by cardiac hypertrophy, high circulating epinephrine, and hyperreactivity of mesenteric circulation to phenylephrine but normal reactivity to endothelin-1. The prepro-UT-deficient mice have unaltered heart rate, cardiac output, and LV end-diastolic volume and pressure, but this UT-deficient mouse model exhibits a trend for higher BP in comparison with wild-type mice.

As far as the link between UT and the CV system is concerned, it is important to remember that the heart is one of the major sources of circulating UT [5]. Plasma UT concentration has been shown to be increased in patients with heart failure [25–28], but there are controversial reports about whether this alteration is associated with the severity of heart failure, as defined by the New York Heart Association (NYHA) classification [25, 29]. Notably, plasma UT is proportional to the degree of LV systolic dysfunction [30] and to plasma concentration of major hormones involved in CV homeostasis, such as endothelin-1, adrenomedullin, and brain natriuretic peptide [25, 31, 32]. Both UT and its receptors are represented in proportion to disease severity in the hearts of patients with heart failure [33], and these findings would suggest a pathophysiological role for UT in cardiac failure. However, it remains to be elucidated whether this role is beneficial or not. Indeed, a protective role is suggested by a recent study documenting that in patients with acute cardiac ischemia, circulating UT is lower than in patients with stable coronary artery disease and in normal individuals [34]. Clinical outcomes are inversely related to UT levels, and this association was reported for the first time in a cohort of patients with ESRD [35]. This relationship was not peculiar to patients with advanced renal failure. Indeed, high plasma UT signalled a lower rather than a higher risk of adverse clinical events in a series of patients with myocardial infarction as well [36]. These clinical observations in high risk diseases, such as acute cardiac ischemia and ESRD, are in keeping with the previously mentioned experimental studies in animals.

23.4 Role of Urotensin II in the Kidney and in Renal Diseases

The kidney actively synthesizes UT. In fact, urinary UT concentration far exceeds plasma UT concentration, and UT is 33% higher in the renal vein than in the renal artery [5]. In humans, UT is expressed in endothelial and smooth muscle cells of the renal arterial system, in the distal and collecting tubules, as well as in the renal

medulla [37]. As with UT, URP is expressed in the rat kidney and may induce effects similar to those described for UT [38].

So far there are few studies about the renal effects of UT. Moreover, the results of these studies show a great variability in renal response, such as the variability noted for the UT effects on vascular tone. In brief, intravenous boluses (in the nanomolar range) of UT in normal rats caused minor reductions in glomerular filtration rate (GFR and no effect on sodium excretion [30], whereas in another study in the same rat model, continuous UT infusion at low doses determined an increase in GFR and a clear-cut, NO-dependent, diuretic and natriuretic effect [31]. These findings are in disagreement with another study by Song et al., in which bolus injections (in the picomolar range) caused a GFR decrease together with reduced urine flow and sodium excretion [38]. On the other hand, in a model of chronic volume overload, such as rats with an aortocaval fistula, showed that UT boluses in the nanomolar range give beneficial effects on renal hemodynamics via the NO system [30]. Therefore, it seems reasonable to speculate that the effect of UT on renal function depends both on the modality of UT administration and on the experimental conditions. Moreover, as with other peptides, UT response is regulated by its receptors, and this fact could in part explain the huge variability in renal and vascular response to UT administration. Another possible explanation for the variability to UT is UT binding density, which correlates with vasoconstrictor response in the rat. Indeed, under normal conditions, most UT receptors are already occupied by UT, but in the presence of abnormal UT levels, changes in unoccupied receptor reserves might at least in part explain the variability in studies of renal and vascular function [25]. Selective UT receptor antagonists represent a fundamental pharmacological tool for the study of UT on renal hemodynamics. Urantide is to date the most potent antagonist available. Studies employing the use of this substance are available in experimental animals only, and in the normal rat, continuous administration of this compound increases GFR as well as urine flow and sodium excretion [38], suggesting a tonic influence of UT on renal function.

In renal diseases, as well as heart failure [25–28], liver cirrhosis [39], diabetes [40], and essential hypertension [41], plasma UT has been reported to be high [42–45]. However something that should be taken into account is the important differences in available methods of UT assays and, for this reason, the interpretation of UT levels is somewhat difficult and controversial. In fact, radioimmunoassay (RIA)- and enzyme-linked immunosorbent assay (ELISA)-based methods measure UT and in part URP or UT fragments independently from their biological relevance. A radioreceptor assay (RRA) measures all biologically compounds active on the UT receptor [46], and with this assay, prepro-UT and inactive fragments of UT are excluded. Indeed, RRA captures multiple bioactive species distinct from UT and URP, which are unmeasured by RIA and ELISA. The variation of UT concentration that has been reported in many studies in humans is largely due to these analytical differences [11]. Because RRA picks up all biologically active substances but may not be able to measure active compounds with relatively low UT receptor affinity, and RIA and ELISA measure UT and variable amounts of peptides structurally closer to UT independently of biological activity, to date there is no method that could represent a

standard. Although these methodological problems make data interpretation on UT more difficult than other substances, studies of UT concentration have given important information about its role in the pathophysiology of CV and renal disease.

The first paper in patients with renal failure was published in the *Lancet* by Totsune et al. In this study involving dialysis patients, they reported high plasma UT [42]. This study appeared 2 years after the seminal study by Ames et al. [20], which implicated UT as a proatherogenic peptide. The proatherogenic properties of UT have been recently confirmed in vitro [47]. In another study by Loirand et al. [48], activation of UT receptors by UT stimulates endothelial and smooth muscle cell proliferation and monocyte chemotaxis. Therefore, in addition to its primary vasoactive effect, UT and UT receptors could be advocated to have a role in the initiation and/or progression of atherosclerosis, giving a new key to explain the exceedingly high CV risk in ESRD patients. Indeed, in dialysis patients, such a high risk is not attributable to classical risk factors, and UT could be seen as a novel uremic CV toxin. Independently of renal dysfunction, high UT was subsequently reported in glomerulonephritis [49], diabetic nephropathy [44], and minimal change disease [45].

The prevalence of myocardial derangements is high in ESRD patients, and plasma UT is about two times higher than normal in this population [42, 43]. Moreover, it appears inversely, rather than directly, related to norepinephrine and neuropeptide Y (NPY) [43], two substances called stress hormones, and UT is also linked to the endogenous inhibitor of NO synthesis, asymmetric dimethylarginine (ADMA), in this category of patients [50]. With UT being a potent NO-dependent vasodilating substance in pulmonary and mesenteric circulation in humans [10], these associations may imply a kind of regulatory adaptation to mitigate the high risk associated with sympathetic overactivity and NO inhibition in ESRD. This hypothesis seems in line with recent studies showing that, regardless of other risk factors, high plasma UT predicts better CV outcomes in ESRD [51] (Fig. 23.1) and longer survival in patients

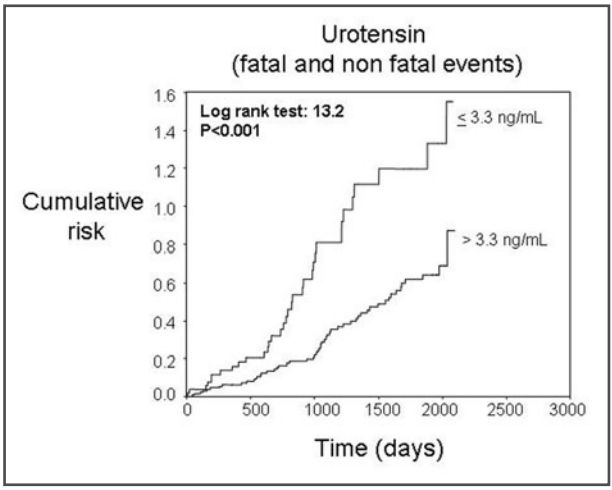

Fig. 23.1 Cumulative risk of fatal and nonfatal cardiovascular events in end-stage renal disease patients stratified according to the median value of urotensin II (cutoff 3.3 ng/ml) in 167 healthy blood donors well-matched to dialysis patients as for age and sex

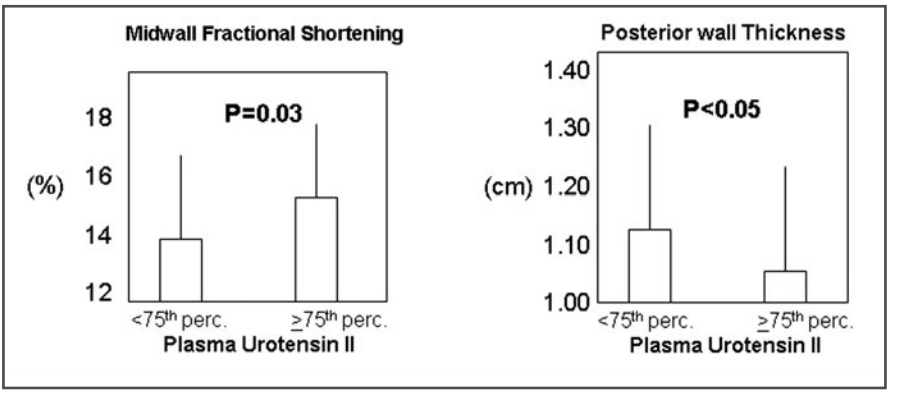

Fig. 23.2 Mean wall thickness and midwall fractional shortening in hemodialysis patients stratified according to the 75th percentile of plasma urotensin II in hemodialysis patients (cutoff 11.5 ng/ml)

with stage 3–4 CKD [52]. Interestingly, UT in ESRD correlates inversely with a powerful biomarker of LV mass and function such as brain natriuretic peptide (BNP) [43]. Thus, high UT may underlie a cardioprotective situation in uremic individuals. In agreement with this hypothesis, relatively higher UT levels were associated with a better LV systolic function and relatively low LV posterior wall thickness in ESRD [53] (Fig. 23.2), and interference of this peptide with sympathetic activity and NO synthesis may be the intermediate mechanism underlying the favorable LV systolic function profile of patients with high UT.

UT antagonists were well tolerated in phase 1–2 studies, but one of these inhibitors tested in patients with diabetic nephropathy [54], palosuran, was eventually not advanced into a clinical development program. Observational data in CKD and ESRD patients produced so far suggest that further mechanistic and observational studies are needed before launching long-term clinical trials aimed at interfering with UT in patients with cardiac ischemia and those with compromised renal function.

23.5 Conclusions

UT, a recently discovered biomarker, has been shown to have beneficial renal hemodynamic effects and inotropic myocardial activity in rats chronically volume-overloaded. Moreover, it protects the myocardium from ischemia–reperfusion injury. UT plasma levels are low in acute cardiac ischemia and predict fatal and nonfatal clinical outcomes after myocardial infarction. Correspondingly, in patients on chronic renal insufficiency, low UT levels are associated with cardiomyopathy, CV events, and death. This novel biomarker could, at least in some clinical sets, have a cardiovascular protective role.

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Role of Novel Biomarkers in Chronic Kidney Disease: Renalase

24

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Abstract Renalase, a novel, secreted flavin-adenine-dinucleotide-dependent amine oxidase regulates cardiac function and blood pressure. The enzyme is rapidly activated in plasma by either modest increases in blood pressure or catecholamines. Protein expression in kidney and heart and its activation in plasma are markedly reduced in chronic kidney disease. The renalase knockout mouse is mildly hypertensive and more likely to develop severe ischemic renal and cardiac injury. Administration of recombinant renalase protects against myocardial injury and improves cardiac function. Preliminary data suggest that renalase may serve as an early biomarker for acute kidney injury. Single nucleotide polymorphisms of the renalase gene are reported to be associated with essential hypertension and more severe cardiovascular complications. The molecular mechanisms that underlie renalase's action and its therapeutic utility are being examined.

Keywords: Chronic kidney disease • Cardiovascular disease • FAD/NADH-dependent oxidase • Hypertension • Diabetes • Single nucleotide polymorphism • Catecholamines • Dopamine • Epinephrine • Norepinephrine • Acute kidney injury • Secreted proteins

24.1 Introduction

A number of clinical studies have indicated that patients with chronic kidney disease (CKD) are at significantly higher risk for developing cardiovascular disease (CVD), a risk correlated with heightened sympathetic nervous system tone, increased oxidative stress, and widespread arterial calcification [1–7]. Two large, recent studies document the extent of the problem. In a secondary analysis of the Valsartan in Acute Myocardial Infarction (VALIANT) study, renal dysfunction was found to be an independent risk factor for cardiovascular events for patients who had had a prior myocardial infarction [5]. The risk was progressive, and those with a glomerular fil-

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tration rate (GFR) of 20 ml/min had a sixfold increase in the unadjusted risk of death from any cause. In another study, investigators examined more than 1 million adults within a large, integrated health care delivery system and documented an independent, graded association between reduced estimated GFR (eGFR) and the risk of death, cardiovascular events, and hospitalization [4]. These findings confirm other studies documenting excess CVD in CKD that is not accounted for by hypertension, hyperlipidemia, and inflammation and provide more precise assessment of the cardiovascular risk associated with CKD. The challenge is to develop novel therapeutic regimens that can reduce cardiovascular risks in patients with CKD.

24.2 Renalase: Discovery and Characterization

In that vein, we wondered whether the kidney might secrete hitherto unknown proteins with important roles in cardiovascular physiology. Therefore, we screened publicly available gene databases using an algorithm designed to select novel proteins likely to be secreted [8]. Tissue expression was determined by Northern blot analysis, genes preferentially expressed in kidney were further studied, and the encoded proteins were examined in detail to determine their biological function and assess their potential impact on cardiovascular health.

One hundred and fourteen candidate genes were identified out of the 13,000 human genes analyzed. One clone, which we now call renalase, was selected for further study on the basis of its robust expression in kidney and restricted tissue distribution. The renalase gene (*RNLS*) is located on chromosome 10 at q23.33, spans 311,000 bp, contains seven exons, and encodes at least four alternatively spliced proteins (hRenalase 1–4); hRenalase1 is the largest, consisting of 342 amino acids with a calculated molecular mass of ~38 kDa. Its key structural features include a signal peptide, a flavin-adenosine-dinucleotide/nicotinamide adenine dinucleotide (FAD/NAD)-binding domain at the N terminus (amino acids 5–60) and an amine oxidase domain at amino acids 75–339. The renalase protein has been well conserved during evolution, and orthologs are present in cyanobacteria. hRenalase1 is expressed in kidney, heart, skeletal muscle, endothelium, and liver [8]. In the kidney, expression in the proximal tubule predominates, although the protein is also present in the glomerulus and distal tubule. Western blot and polymerase chain reaction (PCR) analysis of samples from tissue donors indicate that renalase is also expressed in the central nervous system (CNS), including the hypothalamus, pons, medulla oblongata, cerebellum, pituitary gland cortex, and spinal cord [9]. Polyclonal antibodies raised against whole, soluble, recombinant hRenalase1 protein can easily detect renalase in human plasma [8, 10]. As discussed in more detail below, plasma renalase levels are markedly decreased in CKD and end-stage renal disease (ESRD), suggesting that the kidney regulates steady-state plasma renalase levels.

The mouse gene consists of seven exons and resides on mouse chromosome

19C1 [11]. The mouse renalase protein (mRenalase) has a 72% amino acid identity with hRenalase1, and the key structural features (signal peptide, FAD binding, and amine oxidase domain) are conserved. Secreted mRenalase has been documented in transfected eukaryotic cells. Of note, *mRNLS* is highly expressed in testicle, suggesting that this organ may be a significant source of secreted renalase in mice.

With regards to renalase's enzymatic activity, important clues were obtained by analyzing the protein's predicted secondary structure, which revealed an FAD-binding domain and a conserved amine oxidase domain. Recombinant renalase, generated in *Escherichia coli*, metabolizes catecholamines with the following rank-order potency: dopamine > epinephrine > norepinephrine [8]. Enzymatic activity is insensitive to known inhibitors of the FAD-containing amine oxidases: monoamine oxidase-A(MAO)-A and B. Under basal conditions, significant amine oxidase activity cannot be detected in human plasma [12]. We showed that renalase activity was undetectable in rat plasma under basal conditions, suggesting that native renalase may circulate as a proenzyme requiring additional signals for activation. To test that hypothesis, plasma catecholamines were increased in rats in vivo by infusing exogenous epinephrine [11]. This led to a rapid (30 s), tenfold increase in renalase activity. Rapidity of the initial increase in activity strongly suggests that it is mediated by activation of circulating renalase and not through de novo secretion, which does occur within 10-15 min after epinephrine administration. It is not yet known whether activation and secretion are mediated by increased plasma catecholamines, elevated blood pressure, or both. It is clear, however, that a 7-mm/Hg increase in systolic blood pressure by over baseline is sufficient to fully activate plasma renalase, suggesting that renalase may play a role in minute to minute regulation of blood pressure.

The molecular mechanisms that mediate acute activation of renalase in vivo are not yet understood. Several possibilities are being examined, including catecholamine-induced conformational changes leading to dissociation of an inhibitor or binding of an activator, proteolytic cleavage of blood renalase, or protein dimerization, a particularly attractive hypothesis, as the active forms of several amine oxidases are dimers.

24.3 Renalase Deficiency in Chronic Kidney Disease

Renalase can be detected in human plasma by Western blotting, and levels are decreased in CKD and nearly undetectable in ESRD [8]. That is surprising, as other tissues, such as heart and skeletal muscle, also express renalase and could compensate by increasing nonrenal renalase expression and secretion. These data suggest that the kidney is the major source of circulating renalase. This conclusion is supported by data obtained in rats subjected to subtotal nephrectomy (5/6 Nx). Examination of plasma levels by Western blotting revealed a progressive time-

dependent decrease in renalase blood level following 5/6 Nx, with plasma levels being nearly undetectable 4 weeks postsurgery [11]. Moreover, magnitude and duration of epinephrine-dependent activation of plasma renalase was markedly reduced in 5/6 Nx rats compared with controls. It is noteworthy that although plasma renalase in significantly reduced in 5/6 Nx rats, urinary renalase is increased threefold in these animals. This suggests that urinary renalase may be a useful biomarker in patients with normal renal function and in those with CKD, as will be discussed in more detail later. Data indicate that reduced kidney mass is associated with a significant decrease in blood renalase, supporting the notion that the kidney is the main regulator of circulating renalase levels. Additionally, renalase activation by catecholamines is blunted in CKD, suggesting that renalase deficiency may contribute to the increased sympathetic nervous system activity observed in CKD.

24.4 Renalase Deficiency and hypertension

A key question is whether or not renalase deficiency contributes to hypertension in patients with CKD. It is important to assess the role of renalase in blood pressure regulation in the absence of kidney disease, and available data indicate that renalase deficiency alone is associated with increased blood pressure. Indeed, when *RNLS* gene expression was down-regulated in the rat using small inhibitory RNAs (RNAi), mean arterial pressure increased by 12 mm/Hg [13]. Moreover, as salt-dependent hypertension developed in Dahl salt-sensitive rats maintained on a high-salt diet, renalase expression decreased by 70% [14].

To further test the effect of renalase deficiency in blood pressure regulation, the *RNLS* gene was disrupted by homologous recombination using a targeting construct designed to delete the promoter region and a large part of the coding region [15]. Renalase knockout (KO) mice had normal renal function and kidney histology but increased heart rate and blood pressure, with a relatively greater elevation in diastolic pressure, suggesting that vasoconstriction plays an important role in the pathogenesis of hypertension associated with renalase deficiency.

Human data also indicate a role for renalase in essential hypertension. For instance, Zhao et al [16] tested the association of the *RNLS* gene with essential hypertension by examining single nucleotide polymorphisms (SNPs) of the gene and identified two SNPs (rs2576178 GG genotype and rs2296545 CC) that were associated with essential hypertension. It is quite notable that rs2296545 CC results in an amino acid change (glutamic to aspartic acid at amino acid 37) within the FAD-binding domain. This conserved amino acid change may significantly affect FAD binding and alter renalase function. These findings not only point to novel genetic susceptibility markers for essential hypertension but may also provide insights into the molecular pathways involved in the development of essential hypertension.

24.5 Renalase Deficiency and Myocardial Necrosis

As cardiac norepinephrine, a renalase substrate, increases by ~600-fold during cardiac ischemia, and given that renalase is expressed in the heart, we tested whether the KO mice were more susceptible to cardiac ischemia [17]. Isolated mouse hearts obtained from either KO mice or littermate controls [wild type (WT)] were subjected to 15 min of global ischemia and then reperfused for 90 min using a Radnoti Working Heart System. Myocardial infarct size was assessed by computer-assisted planimetry of tetrazolium-stained sections. Left ventricular function was worse and infarct size threefold greater in KO compared with WT mice. To test whether recombinant renalase could ameliorate cardiac ischemic damage in KO mice, 15 min of global ischemia was followed by 90 min reperfusion with either buffer or recombinant renalase. We found that recombinant renalase reduced cardiac ischemic damage in KO mice by 3.2-fold.

We conclude that renalase deficiency worsens myocardial damage during acute ischemia and administration of recombinant renalase protects against excessive cardiac damage. We speculate that cardiac renalase deficiency may partly explain the increased susceptibility to ischemic myocardial damage and ventricular arrhythmias observed in patients with CKD.

24.6 Urinary Renalase and Acute Kidney Injury

Acute kidney injury (AKI) is a common condition that is associated with significant morbidity and mortality. Great progress has been made in defining the pathogenetic mechanisms mediating the loss of kidney function following acute kidney injury in animal models, and there are a number of excellent recent reviews of the literature [18, 19]. Three broad categories have emerged over the past two decades, namely, vascular and tubular defects and inflammation. The most evident renal vascular abnormalities are loss of autoregulation, an unexpected increase in renal vasomotor tone, and endothelial damage. Kidney injury stimulates sympathetic traffic and norepinephrine (NE) overflow and potentiates the vasomotor response to NE and endothelin. These observations are most relevant to the potential role of renalase in AKI, as tubular injury decreases renalase levels and reduces the kidney's ability to regulate local NE levels. Tubular injury leads to abnormalities in the actin cytoskeleton and translocation of sodium/potassium adenosine triphosphatase (Na/K ATPase) from the basolateral to the apical membrane, possibly accounting for the decrease in Na absorption observed in AKI. Other abnormalities include tubular obstruction, increased sensitivity of glomerular tubular feedback, and tubular fluid backleak. Lastly, there is strong experimental evidence supporting the hypothesis that the inflammatory processes observed in AKI decrease GFR.

Several biomarkers of AKI have recently been identified, and many have been tested in animal models and human studies. A number of excellent reviews have been published recently [20–23]. AKI has a strong adverse effect on clinical outcomes and ranges from minimal injury, with no change in serum creatinine, to complete loss of renal function requiring dialysis. Preclinical studies in mice and initial human studies suggest that urine interleukin 18 (IL-18) and neutrophil-gelatinase-associated lipocalin (NGAL) levels are early markers of AKI. Both are elevated 24–48 h before the clinical diagnosis of AKI becomes apparent. Cystatin C is a better predictor of premature death than serum creatinine and may be a superior marker of GFR, as it is not affected by age, gender, muscle mass, or race.

Renalase is abundantly expressed in kidney proximal tubule, and its tissue concentration is estimated (Western blot) at 0.1 mg/g of wet tissue. The protein is secreted in blood and excreted in urine. It is likely that the renalase detected in urine is the result of active secretion by the proximal tubule, although incomplete reabsorption of filtered protein has not been completely ruled out. Nonetheless, we tested the hypothesis that renal ischemia might adversely affect renalase secretion in the urine and that renalase excretion rates might serve as sensitive, early markers of renal ischemia.

The urinary excretion rate of renalase at baseline in rats was compared with that following mild and moderate bilateral ischemia (unpublished data). Urinary renalase levels were measured in urine samples collected hourly over several hours by Western blot using an antirenalase monoclonal antibody. A severe ischemic insult (global ischemia for 45 min) caused a dramatic and long-lasting decrease in urinary renalase excretion. These data are very exciting and suggest that urinary renalase may be an early biomarker for ischemic AKI.

It is been postulated that excess catecholamines may aggravate ischemic renal injury. We obtained preliminary data suggesting that renalase KO mice are more susceptible to ischemic renal damage than WT mice. Bilateral renal ischemia was achieved in renalase KO and age-matched WT mice by ligating the renal pedicles for 20 min. This ischemia time was chosen because it is not expected to cause significant renal damage in control animals. The animals were sacrificed at day 3, and kidneys were harvested and examined by light microscopy for evidence of tubular injury. The renalase KO-mouse kidney sustained significant tubular injury, as evidenced by the presence tubular dilatation, casts, and disruption of the tubular architecture (unpublished data). In contrast, WT-mouse kidney exposed to a similar ischemic insult showed no evidence of significant tubular damage.

24.7 Renalase Pathway

In summary, renalase is an FAD-dependent amine oxidase secreted by the kidney into blood as a proenzyme, which can be activated by catecholamines. It is likely renalase metabolizes other substrates besides catecholamines. CKD and ESRD are associated with significant plasma renalase deficiency and abnormalities in the activation path-

way. As renalase KO animals are more susceptible to cardiac ischemic damage and acute kidney injury, we speculate that renalase deficiency may account for the increased cardiovascular risk in patients with CKD and that renalase replacement therapy may improve CVD outcome in CKD.

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Section VI
Regression/Progression of Chronic Kidney Disease

Diabetic Kidney Disease

25

J. Redon

Abstract Diabetic nephropathy (DN) is the leading cause of chronic kidney disease and end-stage renal disease (ESRD). Patients with diabetic nephropathy have a high burden of cardiovascular morbidity and mortality. Therefore, interventions that reduce the incidence and progression rate of DN will reduce morbidity and mortality rates as well as health care costs. Hyperglycemia and arterial hypertension are the two main risk factors for DN, but even in the presence of hyperglycemia and elevated blood pressure (BP) for long periods, DN develops only in susceptible patients. Family studies have confirmed the presence of hereditary factors in the development of DN. Besides these four key factors, others have also been implicated, although their impact is less relevant. A systematic approach aiming at prompt diagnosis and intervention can reduce the incidence of DN and slow progression toward ESRD

Keywords: Diabetes • Nephropathy • Proteinuria • ESRD • Hypertension • Hyperglycemia

25.1 Introduction

Diabetic nephropathy (DN), defined as an elevated albumin excretion rate in a person with diabetes mellitus (DM), occurs in 20–40% of patients and is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), not only in the United States, where a population prone to develop nephropathy exists, but also in Europe and other parts of the world. In recent years, the increased prevalence of CKD is no doubt linked to the rising prevalence of DN and DM, which is attributed largely to a dramatic increase in obesity [1]. Likewise, a growing incidence of ESRD due to DN has been recorded mainly in patients older than 65 years of age.

DN progresses through five stages: Stage 1 is characterized by an increase in

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glomerular filtration rate (GFR). Stage 2 corresponds to a clinically silent phase, with continued hyperfiltration and hypertrophy. Stage 3 is characterized by incipient nephropathy, and albumin is present in the urine in very low quantities (microalbuminuria, i.e., urinary albumin excretion (UAE) >30–300 mg/d or 20–200 μg/min) that cannot be detected by conventional assays but only by more sensitive methods. In this stage, blood pressure (BP) tends to increase although it is still within the normal range, and GFR may start to decline. Stage 4 shows overt nephropathy, UAE increased to >300 mg/d (microalbuminuria or proteinuria), BP is almost invariably increased above normal, and GFR progressively declines until renal replacement therapy (RRT) is required, which is stage 5.

Development of DN largely increases cardiovascular morbidity and mortality rates. In fact, patients with CKD have a high burden of cardiovascular morbidity and mortality. The vast majority of patients with CKD do not progress to ESRD, but they do have a significantly higher incidence of all cardiovascular comorbidities. Then, interventions leading to reduction in the incidence and rate of DN progression will decrease morbidity and mortality rates as well as health care costs. A better understanding of the factors and mechanisms driving renal damage in diabetic patients can help delineate the most effective approaches to halt the disease.

25.2 Physiopathology and Pathology

The first change that appears in the kidneys of patients with diabetes is hyperglycemia-induced hyperfiltration. Hyperglycemia leads to increased GFR in approximately 5–10% of patients, and normalization of blood sugar levels has been shown to normalize GFR. Other factors that influence hyperfiltration include increased ketone concentration, overactivity of the growth hormone/insulin-like growth factor system, and disturbances in renal prostaglandins and the kallikrein-kinin system. In the early stage, these abnormalities are frequently associated with enlarged kidneys. Hyperfiltration is typically followed by loss of negatively charged glomerular filtration barrier, allowing negatively charged proteins such as albumin to pass through the glomerulus and into the urinary space. Overexcretion of albumin typically increases at a rate of 15% per year and can result in macroalbuminuria (>300 mg per 24 h) or even nephrotic-range proteinuria (>3.5 g per 24 h).

Once macroalbuminuria appears, GFR begins to decline. Progressive mesangial and interstitial capillary occlusion then occur, restricting the glomerular filtration surface and leading to a further decrease in GFR. A negative feedback loop is thereby initiated, wherein increased proteinuria leads to increased tubulointerstitial injury and renal scarring, both of which further reduce GFR.

Although microalbuminuria is considered a risk factor for the development of macroalbuminuria, not all patients progress to this stage, and some may regress to normoalbuminuria [2]. Recent studies suggest that only 30–45% of microalbuminuric patients will progress to proteinuria over 10 years of follow-up in contrast to

older studies that showed higher progression rates. This might be the result of more intensive glucose and BP control strategies employed in the last decade than in the initial studies. Likewise, GFR has been expected to decrease when proteinuria is established; however, about 10% of individuals with type 2, and fewer in type 1, DM will have low GFR without micro- or macroalbuminuria [3].

DN is characterized by excessive amassing of extracellular matrix (ECM), with thickening of glomerular and tubular basement membranes and increased amount of mesangial matrix, which ultimately progressed to glomerulosclerosis and tubulointerstitial fibrosis. Other changes include hyalinization of arterioles and at times thickening of branches of intrarenal arteries, which leads to impairment in "autoregulation" of glomerular microcirculation.

The morphologic lesions in type 1 DM predominantly affect the glomeruli, with thickening of glomerular basement membrane (GBM) and mesangial expansion, although podocytes, renal tubules, interstitium, and arterioles also undergo substantial changes, especially at later stages of disease [4]. Both mesangial expansion and GBM and tubular basal membrane (TBM) thickening are a consequence of ECM accumulation, with increased deposition of the normal ECM local components of types IV and VI collagen, laminin, and fibronectin. Podocyte damage also appears to be involved in the glomerulosclerosis process. A smaller number of podocytes per glomerulus is the greatest predictor of increased UAE and progression to clinical DN. When this finding is present, normoalbuminuric individuals have a higher risk of progressing to renal disease than those who do not have a podocyte lesion. In addition, the expression of nephrin, a protein synthesized by the podocyte and considered vital to stability of the glomerular barrier, is reduced in DN. Administration of angiotensin-converting enzyme inhibitors (ACEIs) to individuals with DM results in nephrin expression at levels similar to those of individuals without DN.

In contrast to glomeruli lesions, initial interstitial expansion is produced by an important cellular component, whereas fibrosis is prominent in advanced stages. Diabetic glomerulopathy lesions explain most of the increments in UAE or overt proteinuria and GFR changes in type 1 DM. These structural–functional relationships are present in patients with more advanced lesions and clinical functional abnormalities. In patients without functional abnormalities, structural changes are highly variable.

The situation in type 2 DM is more complex. In fact, only a minority of patients have DN patterns typical of those seen in type 1 DM patients; the remaining have mild or absent diabetic glomerulopathy with or without tubulointerstitial, arteriolar, or global glomerulosclerosis changes. The disproportionately high tubulointerstitial lesions, glomerulosclerosis, and vascular changes of type 2 DM could be related to aging, atherosclerosis, or systemic hypertension, although other reasons cannot be excluded. Mesangial expansion is a crucial structural change leading to renal function loss in these patients. Whereas UAE is directly related to both GBM width and mesangial volume, GFR is inversely related only to the latter.

Until now, it has been clear that practically all cellular elements of the kidney, i.e., glomeruli endothelia, mesangial cells, podocytes, and tubular epithelia, are targets of hyperglycemic injury. Conceivably, high glucose levels activate various path-

ways via similar mechanisms in different cell types of the kidney, except for minor exceptions that are related to selective expression of a given molecule in a particular renal compartment.

In general, cellular events include increased flux of polyols and hexosamines; generation of advanced glycation end products (AGEs); increased activity of protein kinase C (PKC), transforming growth factor beta–Smad– mitogen-activated protein kinase (TGF-?-Smad-MAPK) and G-proteins; altered expression of cyclin kinases and their inhibitors and of matrix-degrading enzymes and their inhibitors, with a conceivable common signalling denominator as reactive oxygen species (ROS); and a final outcome of increased synthesis and deposition of ECM. ROS, whether mitochondrial or cell-membrane-derived, may also be responsible for renin–angiotensin system (RAS) activation, contributing to further compromise in renal functions. As suggested by recent studies, it is conceivable that there may be crosstalk between the common metabolic denominator, i.e., ROS and RAS, and that both in synchrony may amplify signalling events [5, 6].

In hyperglycemia, there is increased activity of the accessory polyol pathway and advanced glycation end product (AGE) formation [7]. Whereas the former induces oxidative stress, the latter is a heterogeneous group of macromolecules that are normally formed nonenzymatically by the interaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids. Extracellular AGEs interact with their receptor, RAGE, inducing various intracellular events [7]. Intracellular AGEs also initiate several signalling events by activating PKC, MAPK, and transcription factors such as nuclear factor kappa B (NF-αB), which increase the activity of various growth factors, i.e. TGF-α, and thereby alter expression of ECM proteins. Another important AGE-induced cellular event includes ROS formation.

Beside hyperglycemia, hemodynamic stress also contributes to kidney damage. In fact, a clear interaction and crosstalk exists between metabolic and hemodynamic components in the glomeruli. Hyperglycemic environment sensitizes target organs to BP–induced damage, most likely by activating the RAS, with local production of angiotensin II (Ang II) in the kidney. Increased capillary pressure would induce stretch stress on glomerular cells, which in parallel changes in glomerular volume and activation of various signalling pathways.

25.3 Factors Related to Diabetic Nephropathy Development and Progression

Hyperglycemia and arterial hypertension are the two main risk factors for DN, but even in the presence of hyperglycemia and elevated BP for long periods, DN develops only in susceptible patients [8]. Familial studies have confirmed the presence of hereditary factors in the development of DN. Besides these four key factors – hyperglycemia, hypertension, familial susceptibility, and proteinuria – other factors have also been implicated, although their impact is less relevant.

25.3.1 Hyperglycemia

Hyperglycemia plays a crucial role in the development and progression of DN, as has been demonstrated in type 1 DM by the Diabetes Control and Complications Trial (DCCT) [9], and in type 2 DM by the United Kingdom Prospective Diabetes Study (UKPDS) [10]. These studies conclusively showed that development and progression of DN is strongly related to deficiencies in glucose control. In prospective epidemiologic studies, the incidence of micro- or macrovascular events is directly associated with the degree of hyperglycemia, as measured by plasma glucose or glycated hemoglobin (HbA1c) level. Thus, after adjusting for other risk factors, an increase of 1% in the glycated hemoglobin level is associated with an increase of 18% in the risk of cardiovascular events, an increase of 12–14% in the risk of death, and an increase of 37% in the risk of retinopathy or renal failure. Optimizing blood glucose control reduces the risk for microvascular complications, nephropathy, and retinopathy, although the impact in reducing macrovascular events is less evident, at least in studies including high-risk patients with advanced disease.

Recently available evidence sheds light on the role of glucose control to reduce DN risk. First was the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [11], which demonstrated that a reduction in glycated hemoglobin level to <6.5% yielded a 21% relative reduction in nephropathy. Second was the publication of the extended follow-up of two trials – the DCCT [12] and the UKPDS [13] – in which benefits persisted despite the early loss of within-trial differences in HbA1c levels between the intensive-therapy group and the conventional-therapy group – a so-called legacy effect. Better glucose control over a 5-year period translated to benefits in the following 10 years in microvascular disease and even in macrovascular events. This legacy effect could be attributed in part to reduced DN progression observed during the intervention phase of the trials [12, 13].

25.3.2 Hypertension

Hypertension is a major determinant in progression to proteinuria then to CKD and ultimately ESRD. Hypertension clearly accelerates progression of overt DN to ESRD; its treatment, on the other hand, delays it [14, 15]. The relationship between high BP and the initial stages of renal damage is less clear. Whereas in type 1 diabetics overt hypertension is usually absent when microalbuminuria is seen, in type 2 diabetics, hypertension is present when microalbuminuria is detected. Whether BP alterations antecede or occur in parallel to the development of microalbuminuria had been a matter of interest, with clinical relevance clarified by using ambulatory BP monitoring (ABPM).

In a cohort of adolescents and young adults with type 1 DM, an increase in blood pressure, detected by ABPM and involving mainly systolic blood pressure during

sleep, precedes the development of microalbuminuria [16]. By contrast, in type 1 diabetics, who did not develop microalbuminuria throughout a follow-up of >5 years, sleep as well as awake BP did not increase significantly. Thus, the potential of developing microalbuminuria, a marker of kidney disease in type 1 DM, appears very low in individuals who remain normotensive by strict assessment of normal BP that includes not only a lack of increase in clinically measured and awake BP over time but, importantly, a lack of increase in systolic BP during sleep. In contrast, an increase in sleep systolic BP with a blunted BP nocturnal fall seems the earliest detectable manifestation of altered BP regulation in type 1 diabetics. This early increase in sleep arterial BP during the natural evolution of DN may have a key pathogenic role in its development. For instance, systemic BP overload, initially restricted to systolic BP during sleep, when transmitted into the glomerular circulation, could cause intrarenal hemodynamic changes leading to microalbuminuria, structural renal damage, or both. Therefore, ABPM should be used to better assess high BP in diabetic individuals. Documentation of a nondipping status in a patient with type 1 DM may warrant consideration of intervention. Although a blunted nocturnal decline in arterial BP is also seen in type 2 DN [17], its presence antedating the development of renal disease is less clear and more difficult to detect.

25.3.3 Genetics

Epidemiologic and familial studies strongly support genetic factors as contributing to the development of microalbuminuria and renal damage in DM. Moreover, high heritability of albumin/creatinine ratio (ACR) and ethnic differences in risk to develop ESRD also support the existence of genetic influences.

Candidate genes, linkage analysis, and genome-wide association studies (GWAS) have been used to unravel genetic variants of susceptibility to microalbuminuria and renal damage in types 1 and 2 DM. In general, candidate gene strategy has led to conflicting results. Although some variants have been replicated in different populations, the majority were not associated or showed association in certain subgroups of patients only. Between the different physiological pathways that have been explored, the RAS system is probably the most studied with positive results. The *D* allele of the I/D polymorphism of the *ACE* gene has been related with ACE levels in plasma. Although meta-analyses are not conclusive, one large case–control study [18] in three different European type 1 diabetic populations gave credit to the role of the *D* allele, alone or within haplotypes, in the development of albuminuria.

Linkage studies have given credit to some of the previously described candidate genes and have also identified some others [19]. The high heritability for ACR in these studies suggests an interaction between genetic and environmental factors. Some linkage peaks deserve special attention because of the replication in different studies and the association with different renal traits. This is the case for chromosomal region 3q, which has been associated with DN, especially in Caucasian type 1 DM [20]. In type 2 DM, association with DN has been defined by ACR in Pima

Indians and with eGFR in African Americans. Initially it was though that the *AGTR1* gene was responsible for this peak but other studies rule out this hypothesis, and it seems that the adiponectin gene may be responsible for this peak [21]. Adiponectin is thought to be involved in the atherosclerosis process and therefore in glomerular damage. This adipocytokine can block several mechanism involved in atherogenesis. Also in 3q is *TRCP1*, but this gene seems not to be involved, at least in the initial phases of DN.

Chromosome 7 has also been repeatedly associated with DN, especially in type 2 DM. The region 7q was associated with type 2 DN in Pima Indians and with DN and low eGFR, especially in Mexican American, within the Family Investigation of Nephropathy and Diabetes (FIND) study [22]. The fact that this chromosomal region contains interesting candidate genes reinforces its possible role in the pathogenesis of at least type 2 DM. Among these genes are *ALDR1* and *eNOS*, which have shown association with nephropathy in candidate gene studies. The short arm of chromosome 7 has also been linked with eGFR in Caucasian type 2 DM and with ESRD in African American type 2 diabetes patients [23]. Among the genes that could be responsible for these peaks are the *Il-6* and *hNPY*. Also on 7p lies the *ELMO1* gene, which was linked with DN in Japanese with type 2 diabetes according to GWAS [24]. GWAS have been useful for discovering new and potential genes associated with DN. Among these genes are the *PLEKHH2*. Protein coding by this gene has been demonstrated to be expressed in the glomerular podocytes, and therefore it constitutes an interesting research pathway. Other interesting genes, such as *ELMO1*, *SLC12A3*, *NCALD*, and *PVT1*, have been identified in Japanese populations and Pima Indian with type 2 diabetes [25]. These genes could be involved in mesangial proliferation and fibrosis associated with DN. Further in vitro and replication studies could clarify whether they are or are not susceptibility genes for DN.

Recently, micro-RNAs nonencoding short RNAs that induce posttranscriptional protein modifications have also been studied in relation to DN development in rodent models which mirR-192 expression was increased [26].

25.3.4 Proteinuria

Previous analyses of the Ramipril Efficacy in Nephropathy (REIN) study [27], Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study [15], and Irbesartan Diabetic Nephropathy Trial (IDNT) [14] indicate that albuminuria is a major renal risk factor in patients with nephropathy and that the degree of short-term albuminuria reduction under treatment is important in terms of long-term clinical outcome. The benefit of reducing proteinuria seems to be partially independent of BP reduction, as demonstrated in a post hoc analysis of the RENAAL study [28]. In this study, a reduction in either albuminuria or systolic BP is important in terms of renal outcome and the combined reduction in both albuminuria and systolic BP results in the most favorable clinical outcome in hypertensive patients with DN. Even with albuminuria-lowering medication such as losartan, near-

ly 40% of patients had a dissociation of antihypertensive and antialbuminuric responses.

Direct toxicity of filtered protein leading to tubulointerstitial damage is widely accepted as a mechanism underlying the acceleration of progressive injury to the kidney, because proteinuria has long been known to correlate with both the severity of glomerular barrier impairment and the rate of renal function decline. Evidence indicates that this process occurs through multiple pathways, including induction of tubular chemokine expression and complement activation that lead to inflammatory-cell infiltration, with a prominent presence of macrophages in the interstitium and sustained fibrogenesis. Chemoattractants and adhesive molecules for inflammatory cells are upregulated by the excess ultrafiltered protein load of proximal tubular cells via activation of NF-κB-dependent and NF-κB-independent pathways. An important question that has not yet been adequately addressed in this area is whether albumin in proteinuric ultrafiltrate may promote proximal tubule cell injury through enhanced endocytosis.

25.3.5 Others

Other factors have also been implicated in DN progression, although not all the studies clearly demonstrated independent association. Nevertheless, these need to receive attention in order to optimize interventions looking for improving therapeutic success.

25.3.5.1 Smoking

Smoking is considered a potential risk factor for DN. Recently, the role of tobacco in DN development has been reinforced due to the independent significance in some predictive models of risk to develop microalbuminuria in type 1 DM. In the most recent study of predictive models, having ever smoked increases the risk by 40% [29]. Smoking cessation is recommended in any phase of DN, not only to protect kidneys but also to reduce associated cardiovascular disease.

25.3.5.2 Dyslipidemia

Dyslipidemia is another factor to consider. Type 1 DM is usually associated with normal low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels and high triglyceride levels, the latter being due primarily to poor glycemic control from reduced activity of lipoprotein lipase and consequent inability to clear chylomicrons and very-low-density lipoproteins (VLDL). When control is poor, HDL

cholesterol levels also may decrease and LDL cholesterol levels may elevate. In contrast, dyslipidemia is much more prominent in type 2 DM, which generally is associated with reduced HDL cholesterol, elevated triglycerides, and normal LDL cholesterol, albeit there is a shift in the LDL particle size to the more atherogenic small, dense particles. These changes are due to increased hepatic production of VLDL and impaired clearance of VLDL and chylomicrons, resulting in increased production of the small, dense, LDL subspecies.

The concept that lipids might contribute to the progression of CKD was proposed, and a meta-analysis was carried out of a number of small studies using lipid-lowering therapy to reduce CKD progression, This meta-analysis showed there were small beneficial effects on the GFR decrease of 0.156 ml/min per month and on proteinuria [30]. Secondary analysis in individuals with GFR <60 ml/min/1.73 m^2 from trials with cardiovascular outcomes have also been done. Two trials, the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) [31] and the FIELD study [32], in which dyslipidemia was treated with gemfibrozil or fenofibrate, respectively, were discordant. Whereas treatment with fenofibrate resulted in significantly more patients regressing or not progressing in their UAE results [32], gemfibrozil did not [31].

Studies on statin treatment also produced discordant results. Whereas in the Assessment of Lescol in Renal Transplantation (ALERT) study with fluvastatin [33] and the Cholesterol and Recurrent Events (CARE) [34] study with pravastatin showed no significant effect on GFR decline compared with placebo, in the pravastatin pooling project, there was a significant 34% reduction in the rate of GFR decline, but the magnitude of this reduction was minimal at 0.22 ml/min/1.73 m^2 per year [35]. This reduction was similar to the observed effect of simvastatin in the Heart Protection Study (HPS) [36]. Results of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study [37] merit additional comments. In this study, patients treated with atorvastatin experienced a 12% increase in creatinine clearance estimated by the Cockcroft–Gault formula, and those treated with various statins in usual care experienced a 4.9% increase, whereas those on no statin therapy experienced a 5.2% decrease. Whether or not it was a real improvement or an artifact of creatinine measurements or changes in body weight needs to be established. The success of treating dyslipidemia in cardiovascular risk warrants the introduction of statins, even though the potential impact in renal damage progression has not been established.

25.3.5.3 Diet

Diet is also an important part of patients care. Protein content and lipid quality have been linked to renal protection. An incremental increase in protein intake seems to be associated with higher UAE as a consequence of hyperfiltration, and diets rich in polyunsaturated fatty acids seem to produce a certain level of protection. Salt reduction not only improves BP control but also reduces proteinuria by itself, despite the

phenomenon of the salt paradox observed in early DM in which high-salt diets can reduce hyperfiltration due to enhanced proximal tubular reabsorption mediated by increased sodium–glucose cotransport.

25.4 Prevention and Treatment

DN causes a progressive decline in renal function, which may be retarded by treatment. Research on treatment strategies aiming to halt DN development and progression has been a priority in medical research during the last two decades due to DN's huge socioeconomic impact, not only on the development of ESRD but also on the elevated risk for cardiovascular disease. As a consequence, a list of recommendations has generally been accepted, although there is lack of evidence-based medicine or controversy surrounding some of them. Table 25.1 provides a summary of the most widely accepted recommendations.

It is generally accepted that the principles of DN prevention and treatment are similar, although the role of each factor could be different in each stage of the disease. Consequently, it is important to define the DN stage that is the target of intervention (microalbuminuria, proteinuria, GFR) and the most convenient outcome at each stage.

At the time of patient screening for UAE, GFR assessment and BP measurements are mandatory, besides metabolic status and lipid levels.

Table 25.1 Recommendations to slow progression of diabetic nephropathy

Screening of UAE	
Evaluation of eGFR	
Intervention	
Glycemic control	HbA1c <7%
Blood pressure control	<130/80 mmHg
	Out-of-office measurement
Inhibition of the RAS	Urinary protein excretion <0.3 g/24 hour
Treatment of dyslipidemia	LOL cholesterol <100 mg/dl (2.6 mmol/L)
Others	
Smoking cessation	
Loosing weight	
Physical exercise	
Diet: reduction of protein, alcohol and salt	

eGFR, estimated glomerular filtration rate; *HbA1c*, glycated hemoglobin; *LDL*, low-density lipoprotein; *RAS*, renin–angiotensin system; *UAE*, urinary albumin excretion

25.4.1 Screening for Urinary Albumin Excretion

Early recognition of renal changes or risk increases the chance of preventing progression from incipient to overt nephropathy. A routine dipstick urinalysis, and if negative, microalbuminuria assessment, should be performed at the time of diagnosis and thereafter. If the test is positive for protein, analysis of a 24-h urine sample is recommended for quantification of urinary protein excretion. Although microalbuminuria has been considered as UAE >29mg/24 h, or equivalent in timed samples or in spot urine assessment, the continuous relationship between albuminuria and cardiovascular risk raises the question of the value of albuminuria where there is a substantial increment of risk and, consequently, where intervention is justified. Defining the risk of albuminuria at an early stage would be adequate for guiding therapies geared to preventing UAE progression [38]. UAE should be targeted during interventions.

25.4.1.1 GFR Estimation

By measuring serum creatinine level and using that value in either the Modification of Diet in Renal Disease (MDRD) or Cockcroft–Gault equations, information about GFR is obtained. The widely used MDRD calculation is considered more accurate than the Cockcroft–Gault equation for patients with CKD stage 3 or greater (GFR <60 ml/min/1.73 m^2). Accuracy of estimates is improved if the clinical laboratory calibrates creatinine measurement. Both the MDRD and Cockcroft–Gault equations significantly underestimate filtration rate, especially in patients with DM and microalbuminuria [39]. Then, an alternative approach being investigated is the measurement of cystatin C concentration as a surrogate for GFR, although it is not recommended as a routine measurement.

25.4.1.2 Blood Pressure Measurement

Careful BP measurement is mandatory and requires out-of-office measurements to unmask subtle BP elevations, mainly at night, which represent early stages of risk. In type 1 DM of at least 5 years of disease duration and in type 2 DM at the time of diagnoses, 24-h ABPM should be performed. Likewise, 24-h ABPM and BP self-measurement at home is necessary to assess the degree of BP control during treatment [40–42].

25.4.2 Optimize Medical Management and Educate Patients

Early recognition of risk allows clinicians to optimize care in CKD so that patients can take measures to preserve residual renal damage. Such measures may include smoking cessation; weight loss if overweight; reduction in protein, salt, and alcohol intake; and nephrotoxin avoidance – in particular, use of nonsteroidal anti-inflammatory drugs. Furthermore, early awareness of DN may prompt clinicians to select appropriate treatment and adjust dosages of antidiabetic agents and to consider more frequent controls.

The three cornerstones of treatment are glycemic control, BP reduction, and RAS blockade. In addition, treatment of dyslipidemia plays an important role, although the benefits are more related to cardiovascular risk reduction that to preserving renal function.

25.4.2.1 Glycemic Control

As outlined above, hyperglycemia is a risk factor for DN, and in patients with overt nephropathy, the mean level of glycosylated hemoglobin is correlated with the loss of renal function.

Clinical trials have demonstrated that intensive hyperglycemia treatment is associated with decreased risk for DN development in type 1 and 2 DM patients, even if the beneficial impact can only be seen after several years. The DCCT in type 1 DM demonstrates that intensive therapy increases risk reduction for microvascular complications [9]. In a randomized study conducted in Japan, intensive control of type 2 DN with three or more insulin injections per day also resulted in a lower rate of new or progressive nephropathy over a period of 6 years than did conventional therapy with one or two injections per day (7.7% vs. 28%) [43]. The UKPDS [10] in type 2 DM showed that intensive control of blood glucose with sulfonylureas or insulin reduces the risk of DN and other microvascular complications. In the subgroup of participants who were overweight, the effect of the biguanide metformin in reducing the risk of renal failure was similar to that of other hypoglycemic agents. The extended follow-up 10 years after the end of the randomization period of the study demonstrated the persistence of benefit in the risk of DN [13].

Recent studies designed to evaluate the benefit of intensive glycemic control in large sets of patients showed a minor protective effect on albuminuria progression in patients with type 2 DM with high cardiovascular risk. In the ADVANCE trial, the group in the intensive arm for an average of 5 years showed a small reduction in the number of cases with new-onset microalbuminuria compared with the standard-therapy group, and no effect was observed in serum creatinine values [11]. Similar results were observed in the Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT) study [44]. Patients in the intensive arm for a mean of 5.6 years showed no benefit regarding changes in serum creatinine or GFR values,

and only a minor effect on albuminuria levels was observed.

Today, the recommendation is to reduce HbA1c to <7.0%, although <6.5% can result in further benefit on cardiovascular outcomes. More aggressive goals, HbA1c <6%, is no longer recommended mainly in individuals with high cardiovascular risk after the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [45] and the (VADT) trials [44, 45].

25.4.3 Blood Pressure Control and Renin–Angiotensin System Blockade

BP reduction and RAS blockade need to be addressed together due to the mutual interactions, as blocking the RAS results in BP reduction. The potential beneficial impact has been tested throughout the spectrum of DN, from early stages aiming to reduce the development of persistent microalbuminuria to reduction of risk to develop ESRD. In each of these stages, the outcomes analyzed differ in the different studies, although all studies searched for changes in albuminuria or proteinuria and GFR. In the studies carried out in patients with more advanced disease, cardiovascular events and total and cardiovascular mortality have also been included in the analysis.

In general, analyses of long-term clinical trials have shown that the lower the BP over a range of values, the greater the preservation of renal function. Currently, however, it is believed that lowering BP is not enough. It is becoming increasingly important to reduce proteinuria in overt DN, thus the use of antihypertensive drugs that attenuate increases or reduces proteinuria. Reduction by at least 30% seems to provide greater slowing of renal disease progression compared with agents that do not have this effect.

BP goals of <130/80 mmHg and <125/75 mmHg if >1 g of proteinuria have been recommended by the American Diabetes Association (ADA) and the European Society of Hypertension (ESH) [42], despite the fact that no medicine-based evidence exists. The recent reappraisal of the ESH guidelines recognize the necessity for further studies to obtain grounded information about this important issue [46].

25.4.4 Studies in Normoalbuminuria Stage

A few studies have evaluated the potential role of RAS-blocking drugs to prevent development of persistent microalbuminuria in normotensive diabetics. The first was the Ravid study [47]. The researchers studied type 2 DM patients >40 years of age who had a baseline mean BP <107 mmHg, equivalent to <140/90 mmHg. Enalapril therapy initially decreased albumin excretion, and this was followed by a gradual decrease that was significantly lower than that observed in the placebo control group. Likewise, the risk of developing microalbuminuria was significantly lower in the enalapril group. After 6 years of follow-up, differences in creatinine clearance were minimal in favor of the enalapril group.

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Until recently, no other studies in normotensive diabetics have been published. The Diabetic Retinopathy Candesartan Trials (DIRECT) [48], attempted to determine whether the angiotensin-receptor-blocker (ARB) candesartan compared with placebo affects microalbuminuria incidence or rate of change in albuminuria in types 1 and 2 DM by using three randomized trials in which the main outcome was retinopathy. Mainly normotensive patients or patients with well-controlled hypertension who were at low overall vascular risk were included, which resulted in a low rate of microalbuminuria. Individual and pooled results of the three trials showed that candesartan had little effect on risk for microalbuminuria.

Similar negative results were observed in the study by Mauer et al. [49] in which 285 normotensive patients with type 1 DM and normoalbuminuria were randomly assigned to receive losartan, enalapril, or placebo and followed for 5 years. The primary end point was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. Changes over the 5-year period did not differ significantly between the placebo and the enalapril or losartan groups, nor were there significant treatment benefits for other biopsy-assessed renal structural variables. At 5 years, cumulative incidence of microalbuminuria was higher in the losartan group, with no differences between the enalapril and placebo groups. In contrast to the negative results in nephropathy, early blockade of the RAS slowed progression of retinopathy in patients with type 1 DM.

The discrepancies observed among the studies can be explained by BP levels at the time of enrolment into the study. BP levels in the Ravid study, even in the range of normotension at the time of the study, were higher than the values in the DIRECT or Mauer et al. studies [48, 49]. Likewise, UAE values were also higher in the Ravid study compared with the others.

Whereas data in normotensive DN were not well grounded, treatment of hypertension leads to an important risk reduction in cardiovascular and microvascular events in DM. The beneficial impact is greater than that observed in non-DM individuals, as diabetics have a higher risk at the same BP level. In the UKPDS [8], a reduction from 154 to 144 mmHg in systolic BP reduced risk of development of microalbuminuria by 29%. No differences were observed between patients receiving treatment with atenolol or captopril.

In the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), hypertensive, type 2 DM, and normoalbuminuric patients were randomized to receive trandolapril or verapamil, alone or in combination, with the aim of preventing microalbuminuria. After 3 years of follow-up, trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent, whereas the effect of verapamil alone was similar to that of placebo. The relationships between baseline BP, BP reduction, and follow-up BP with the incidence of persistent microalbuminuria was analyzed [50]. BP reduction and ACEI therapy may both independently prevent microalbuminuria, but ACEI therapy was particularly effective when BP was poorly controlled. Verapamil alone was ineffective at any achieved BP level. Therefore, BP reduction per se reduces risk in hypertensive patients. Additional benefit of using RAS blockers was observed, although BP values influenced the extent of benefit [50]. The lower the BP, the higher the beneficial effect beyond the BP-lowering effect.

The ongoing Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP study will answer the question of whether an ARB can prevent or delay the onset of microalbuminuria and whether this translates into protection against cardiovascular events and renal disease in a placebo-controlled, multicentre, double-blind study including type 2 DM patients with normoalbuminuria during 5 years of follow-up. Results were presented at the American Society of Nephrology Annual Meeting 27 October – 1 November 2009 (not yet published).

25.4.5 Studies in Increased Urinary Albumin Excretion

Two main studies have been published involving diabetics with microalbuminuria or low-grade proteinuria and absence of renal failure. The first was the study by Parving et al. [51] in which irbesartan was compared with placebo in the time-to- onset of DN defined by persistent albuminuria in overnight specimens. A 70% relative risk reduction was observed in favor of irbesartan. Furthermore, albuminuria normalized in a high percent of individuals in the irbesartan group but not in the placebo arm. The differences in favor of irbesartan occurred without differences in BP values.

The second was the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study [52], which directly compared the renoprotective effects of telmisartan and enalapril in hypertensive type 2 DN with early nephropathy, microalbuminuria, or proteinuria < 1 g/24 h. The primary end point was the change in GFR, determined by measuring the plasma clearance of iohexol, between the baseline value and the last available value during the five-year treatment period. After five years, the change in the GFR was not significantly statistically different between treatment groups.

Besides these long-term outcome studies, a large number of studies assessing the short-term impact of antihypertensive treatment in albuminuria or proteinuria with or without RAS blockade has been collected in several systematic reviews and meta-analyses [53–55]. Each added complementary relevant information. Short- or mid-term studies tend to higher albuminuria or proteinuria reduction with ACEI or ARB compared with placebo or calcium channel blockers [54, 55]. However, other meta-analyses concluded that the benefits of ACEIs or ARBs on renal outcomes in placebo-controlled trials probably resulted from a BP-lowering effect. In patients with DM, additional renoprotective actions of these substances beyond lowering BP remain unproven, and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease. Sarafidis et al. [54] stressed that treatment of DN patients with an RAS blocker reduces the risks of ESRD but does not affect all-cause mortality.

In their meta-analysis, Kunz et al. [55] concluded that ARBs reduce proteinuria independent of the degree of proteinuria and of underlying disease, and the magnitude of effect is similar regardless of whether the comparator is placebo or calcium-channel blocker. Reduction in proteinuria from ARBs and ACEIs is similar, but their combination is more effective than either drug alone. The authors point to the uncertainty concerning adverse effects and outcomes that are important to patients, such as preservation of GFR.

Other approaches to blockade of the RAS system are the use of very high doses of ARBs, taking the advantage of the low rate of side effects, or adding an aldosterone blocker, spironolactone or eplerenone. Although further reduction in proteinuria has been obtained with the two options, evidence regarding the long-term impact is not available. In addition, aldosterone blockade in addition to ACEI or ARB, although producing additional BP reduction, also produces hyperkaliemia – mainly in diabetics with nephropathy. If used, potassium and creatinine values should be checked frequently.

Introduction of the first direct renin inhibitor, aliskiren, generates new ways to block the RAS. A recent study, AVOID [56], evaluated the renoprotective effects of dual blockade of the renin–angiotensin–aldosterone system (RAAS) by adding treatment with orally administered aliskiren compared with treatment with the maximal recommended dose of losartan and optimal antihypertensive therapy in patients who had hypertension and type 2 DN. The primary outcome was a reduction in the ratio of albumin to creatinine, as measured in an early-morning urine sample, at 6 months. Aliskiren, compared with placebo, significantly reduced the mean urinary albumin-to-creatinine ratio, pointing to a renoprotective effect that was independent of its BP-lowering effect.

25.4.6 Studies in Advanced DN

In the advanced stage of DN in patients at high risk of developing ESRD, hypertension treatment was beneficial. The initial Lewis et al. study [57] in type 1 DM patients demonstrated the beneficial effect of captopril treatment compared with placebo in terms of reduced risk of developing ESRD and other renal outcomes. Later, two seminal studies in type 2 DM patients with hypertension and overt nephropathy demonstrated that, in addition to their current medication, losartan compared with placebo (the RENAAL study [28]– and irbesartan compared with amlodipine or placebo (the IDNT [14] study) reduced the risk of developing a combined outcome of all mortality, ESRD, or doubling serum creatinine. Although there was a significant difference between the experimental drug and the comparators for the primary outcome (approximately 20% relative risk reduction), no differences in cardiovascular morbidity or mortality were observed. The beneficial impact attributable to BP reduction per se or to RAS blockade or albuminuria reduction is discussed in the IDNT and RENAAL studies, respectively. The lower the BP achieved during treatment, the lower the differences in risk among irbesartan and amlodipine or placebo in the IDNT. In contrast, across all categories of systolic BP change, a progressively lower ESRD hazard ratio was observed with a larger albuminuria reduction in the RENAAL study.

One additional study, the Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) [58] compared olmesartan to placebo. The randomized, double-blind, placebo-controlled study evaluated the renal protective benefits of olmesartan medoxomil in type 2 DM patients with overt proteinuria and renal insufficiency. The primary outcome is the composite endpoint of time to the first occurrence of doubling of serum creatinine, ESRD, or death. The

study has been completed, although results are not yet available.

Finally, the primary objective of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study [59] is to determine whether aliskiren 300 mg once daily reduces cardiovascular and renal morbidity and mortality compared with placebo when added to conventional treatment, including ACEI or ARB. This is a double-blind, placebo-controlled, parallel-group study, which will include three categories of high-risk patients with type 2 DM. The categories are individuals with proteinuria, microalbuminuria in stage 3 CKD, or patients with previous cardiovascular disease and CKD. Among the outcomes, risk to develop ESRD is included. The results should also determine whether dual RAS blockade with aliskiren in combination with an ACEI or ARB will reduce major morbidity and mortality in a broad range of high-risk patients with type 2 DM.

25.5 Discussion

From the information available there is no doubt about the relevant role of high BP in DN development and progression besides the metabolic abnormalities that define the disease. Therefore, BP reduction is a matter of high priority in managing these patients, for which it is relevant to consider the peculiar characteristics of the hypertension linked to diabetes. Recommendations based on these particularities are shown in Table 25.2.

Likewise, considering the multiplicity of factors contributing to the disease and the parallel increment in cardiovascular risk, a multiple treatment approach should be implemented. The benefits of this multiple intervention have been clearly demonstrated in the Gaede et al. studies [60].

Table 25.2 Characteristics of hypertension in diabetes and recommendation for blood pressure control

Characteristics	Recommendation
SSP and PP predominant	Early treatment Combination therapy 24-hour coverage
Non-dipping pattern	Distribute around the clock
Salt-sensitivity	Utility of diuretics
Trend to hyperkaliemia	Frequent controls
Frequent organ damage	Target surrogate endpoints
Tissular hyperactivity of the RAS	RAS blockade mandatory ACEi vs ARB vs dual blockade?

ACEi, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor; *PP*, pulse pressure; *RAS*, renin–angiotensin system; *SBP*, systolic blood pressure

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Nondiabetic Kidney Disease

26

P. Cravedi, P. Ruggenenti, G. Remuzzi

Abstract The burden of chronic kidney disease represents a major health problem. Experimental studies and evidence in humans suggest that renal damage progresses independently of the initial cause and follows pathogenic mechanisms that are common among different nephropathies. After an initial renal injury, the number of functioning nephrons declines and remaining ones undergo hypertrophy, with concomitant lowering of arteriolar resistance and increased glomerular plasma flow. This compensatory mechanism allows preservation of glomerular filtration rate but is ultimately detrimental. Indeed, high intraglomerular capillary pressure impairs the size selectivity of the membrane and allows passage of larger molecules, such as proteins. An excess of proteins in the tubular lumen exerts a nephritogenic effect that fuels progressive renal function loss. In animals with proteinuric renal disease, glomerular hypertension and sieving dysfunction are ameliorated by drugs that inhibit the activity of the renin–angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. RAS inhibitor therapy is the key component of intervention strategies aimed at retarding or preventing progression of chronic renal disease, and available data indicate that effective inhibition of the RAS may even regress established renal injury in experimental animals and improve kidney function in patients otherwise expected to relentlessly progress to end-stage renal disease.

Keywords: Chronic kidney disease • Proteinuria • Hypertension • Renin–angiotensin system (RAS) • Angiotensin-converting enzyme (ACE) inhibitor • Angiotensin receptor blocker • Remission • Combined RAS inhibitor therapy • End-stage renal disease (ESRD) • Regression

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26.1 Introduction

The incidence of chronic kidney disease (CKD) is increasing worldwide and is emerging as a major health problem. Many studies in animals and humans suggest that progression of renal damage is independent from the initial cause and follows pathogenic mechanisms that are common among different nephropathies [1]. After an initial renal injury, the number of functioning nephrons declines and remaining ones undergo hypertrophy, with concomitant lowering of arteriolar resistance and increased glomerular plasma flow [2]. This compensatory mechanism allows preservation of glomerular filtration rate (GFR) but is ultimately detrimental. Indeed, the high intraglomerular capillary pressure enlarges the radii of glomerular pores, impairing the size selectivity of the membrane and allowing passage of larger molecules, including proteins [2]. An excess of proteins in tubule lumen exerts a nephritogenic effect [1, 2] by direct tubular toxicity and a secondary process of tubular epithelial endocytosis. Moreover, enhanced protein ultrafiltration is associated with protein accumulation in podocytes, with podocyte injury and loss through a transforming growth factor beta-1 (TGF-β1)-mediated mechanism, a process that may further impair glomerular-barrier sieving properties and accelerate progression of glomerular lesions [3] (Fig. 26.1).

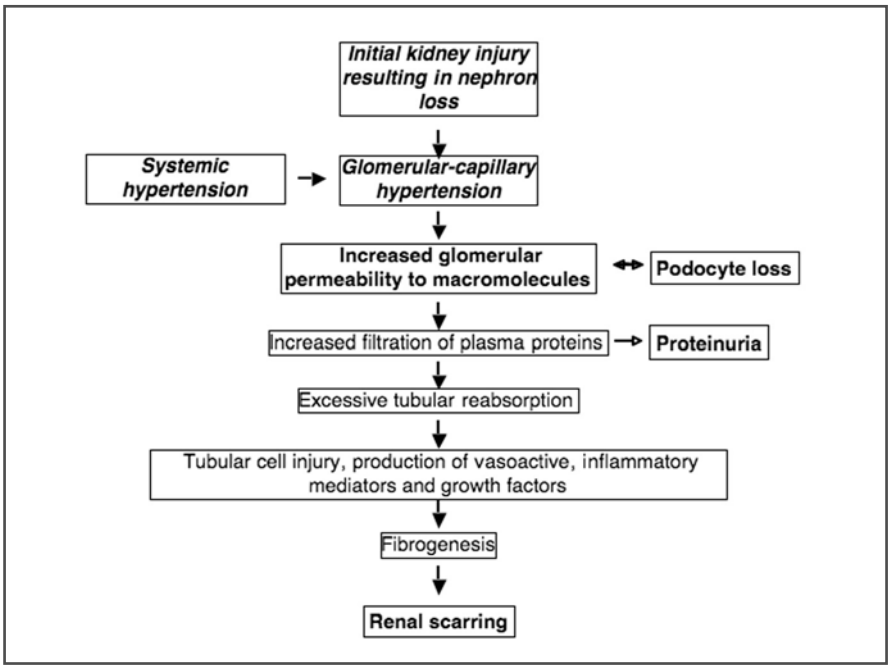

Fig. 26.1 Pathophysiological mechanisms of chronic proteinuric nephropathies. Modified from [2]

In animals with proteinuric renal disease, glomerular hypertension and sieving dysfunction are ameliorated by drugs that inhibit the activity of the renin–angiotensin system (RAS), such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) [1]. Prospective, randomized, placebo-controlled trials found that, at comparable blood pressure (BP) control, ACE inhibitors [4] are more effective than non-RAS-inhibiting therapy in limiting progression to end-stage renal disease (ESRD) in diabetic and nondiabetic patients with chronic proteinuric nephropathies [5]. RAS-inhibitor therapy is the key component of intervention strategies aimed at retarding or preventing progression of chronic renal disease, and data are available that indicate effective inhibition of the RAS may even regress established renal injury in experimental animals and improve kidney function in patients otherwise expected to relentlessly progress to ESRD.

26.2 Mechanisms of Progression of Chronic Nephropathies

26.2.1 Hypertension

In animal models of chronic nephropathies, systemic hypertension is associated with increased intraglomerular pressure, and BP reduction uniformly retards renal disease progression and reduces injury. In a seminal study published in 1976, Mogensen et al. showed that in five patients with type 1 diabetes and progressive renal function loss, antihypertensive treatment dramatically slowed the rate of progression of kidney impairment [6]. This finding has subsequently been confirmed by other studies, and similar observations have been reported in nondiabetic renal disease patients. The Ramipril Efficacy in Nephropathy (REIN) study in nondiabetic patients with chronic proteinuric nephropathies showed that systolic BP predicted GFR decline more reliably than did diastolic BP [4]. Systolic BP and pretreatment morning BP measurement were the most reliable predictors of disease outcome. In the Modification of Diet in Renal Disease (MDRD) study, patients with CKD and >1 g/day of proteinuria randomized to a mean arterial target of 92 mmHg had a greater reduction in proteinuria and a slower rate of GFR loss than patients who were randomized to a mean arterial pressure of 107 mmHg [7].

26.2.2 Proteinuria

Clinical studies found a significant correlation between the extent of urinary protein excretion and GFR decline rate, both in diabetic and nondiabetic chronic nephropathy patients [8, 9]. Protein overload in the tubules causes increased production of vasoactive, inflammatory mediators and growth factors, such as endothelin 1 (ET1),

monocyte chemoattractant protein 1 (MCP1), chemokime-ligand 5 (CCL5) and osteopontin. These molecules, in turn, induce abnormal accumulation in the interstitium of extracellular matrix collagen, fibronectin, and other components that are responsible for interstitial fibrosis [8]. In line with these experimental observations is the evidence that in humans with chronic nephropathy, more severe and persistent proteinuria is associated with faster disease progression. Interventional studies showed that whenever proteinuria is decreased, progression to ESRD is invariably reduced. The MDRD study found that proteinuria reduction, independent of BP reduction, was associated with a decrease in the rate of GFR decline and that the degree of protection of renal function achieved by lowering BP was dependent on the level of initial proteinuria [7]. In the REIN study, a rapid and sustained reduction in proteinuria prevented or limited long-term GFR decline in patients with nondiabetic chronic nephropathies [4]. Finding that the extent of residual proteinuria was also a major determinant of disease progression provided further evidence of the pathogenic role of urinary protein traffic [10]. A post hoc analysis of the REIN trial showed that renoprotection is maximized when ACE inhibition is started earlier and that long-lasting treatment may result in GFR stabilization and definitive prevention of ESRD [11]. A meta-analysis in 1,860 patients with chronic nephropathies consistently found that the benefit of ACE inhibition was greatest in patients with high urine protein excretion at baseline and more proteinuria reduction on follow-up [12].

26.3 Renin–Angiotensin System Inhibitors as the First-step Therapy to Control Blood Pressure and Reduce Proteinuria

The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study found that patients with nondiabetic renal disease on ACE inhibitor therapy had a slower progression to doubling of serum creatinine compared with controls on placebo [13]. Results from this trial, however, were flawed by lack of information on hard end points, such as dialysis or transplantation or on GFR decline rate. Even more important, patients on ACE inhibitors had significantly lower BP levels, which did not allow assessment of whether less increase in serum creatinine levels was explained by a specific renoprotective effect of ACE inhibition or merely reflected better control of arterial hypertension. More definite evidence of a specific renoprotective and dialysis-saving potential of ACE inhibitor therapy was provided by the REIN trial comparing the effect of ACE inhibitor therapy over placebo on hard renal end-points in nondiabetic patients with proteinuria [14]. On the basis of previous experimental evidence of a pathogenic role of proteinuria in renal disease progression, patients were stratified according to baseline proteinuria >1 and ≤3 g/day or >3 g/day. In the whole study population, patients receiving ACE inhibitor therapy had a significantly lower GFR decline and a reduced risk for doubling serum creatinine or ESRD compared with patients on conventional therapy, despite similar BP levels [14]. Importantly, the higher was the level of base-

line proteinuria, the greater was the beneficial effect of ramipril both in slowing GFR decline and reducing the risk of ESRD. This result further supported the notion that ACE inhibitors exert nephroprotective activity through a reduction in transglomerular traffic of plasma proteins and their consequent renal toxicity.

Recently, the Renoprotection of Optimal Antiproteinuric Doses (ROAD) study of 360 nondiabetic proteinuric patients showed that at comparable BP control, up-titrated doses of either the ACE inhibitor benazepril or the ARB losartan reduced proteinuria and renal function decline more effectively than standard hypertensive doses. This emphasizes the importance of maximized RAS inhibition to optimize renoprotection [15].

26.4 Is Dual RAS Blockade better than Single ACE Inhibitor/ARB Therapy?

The combination of an ACE inhibitor and an ARB has been suggested as a way to maximize RAS blockade by affecting both the generation of angiotensin II and its activity at the receptor level. Moreover, an ACE inhibitor may inhibit the compensatory increase in angiotensin II synthesis frequently observed during ARB therapy. On the other hand, an ARB may inhibit the activity of angiotensin II produced via ACE-independent pathways [16].

A recent review of experimental [3] and clinical studies [17, 18] consistently found that ACE inhibitors and ARBs in combination reduce proteinuria more effectively than the two agents alone [19]. In these studies, however, dual RAS blockade had a more consistent antihypertensive effect than single ACE inhibitor or ARB therapy. It was unclear whether the superior antiproteinuric effect of combined therapy really reflected more effective RAS blockade or was simply a function of greater BP reduction. To address this issue, a crossover study in patients with nondiabetic CKD [20] compared the antiproteinuric effect of fixed doses of the ACE inhibitor benazepril and of fixed doses of the ARB valsartan, both given alone or with halved doses of the two drugs in combination. In this approach, BP reduction was similar in the three treatment groups, but proteinuria decreased more consistently on dual therapy. Thus, the superior antiproteinuric effect of dual- compared with single-drug RAS blockade was not explained by a superior antihypertensive effect but by a more effective inhibition of the RAS [20].

No data are available on long-term effects on hard end points of dual RAS blockade. The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease (COOPERATE) trial compared incidence of ESRD in 263 patients randomized to the ACE inhibitor trandolapril, the ABR losartan, or a combination of both drugs at equivalent doses [21]. Combination treatment safely retarded renal disease progression compared with monotherapy, but data were questioned in subsequent comments and editorials [22], which eventually led to a retraction of the study [23].

We prospectively followed 20 nondiabetic patients with chronic proteinuric

nephropathies on dual RAS inhibitor therapy and compared their outcome at 6 years with that of 20 matched reference patients maintained on single-drug RAS blockade with the full dose of an ACE inhibitor. Decline of estimated GFR (eGFR) was significantly lower in patients compared with reference patients (Fig. 26.2), and proteinuria reduction independently predicted the slower eGFR decline observed in patients on dual RAS blockade. In these patients, GFR (measured by iohexol clearance), renal vascular resistances, and urinary protein to creatinine ratio decreased at 1 year, were stable up to 6 years, and recovered to baseline after treatment withdrawal. No patient had renal or cardiovascular events compared with six reference patients: two myocardial infarction, one stroke, one heart failure, one ESRD, and one doubling serum creatinine (plus ESRD). Notably, there were no drug-related adverse events. Data provided clear-cut evidence of superior long-term nephroprotective effect of dual compared with single-drug RAS blockade.

Data from Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) were recently taken to suggest that dual RAS blockade does not offer advantages over ACE inhibitor or ARB single-drug therapy [24]. The trial randomized 25,680 patients with established atherosclerotic vascular disease or diabetes with end-organ damage to the ACE inhibitor ramipril, the ARB telmisartan, or their combination. Over 56 months, the incidence of cardiovascular events was similar in the three treatment groups, whereas the prespecified composite outcome of "any dialysis, renal transplantation, doubling of serum creatinine, or death" was more frequent in patients on combined treatment than in those on telmisartan or ramipril alone. To some extent unexpectedly, the excess of renal events was associated with lower albuminuria and less progression to micro- or macroalbuminuria with combined therapy. This led some authors to hypothesize that proteinuria reduction cannot be considered a suitable surrogate endpoint for improvement in renal function [25]. However, only 4% of patients had proteinuric renal disease, 13% had microalbumin-

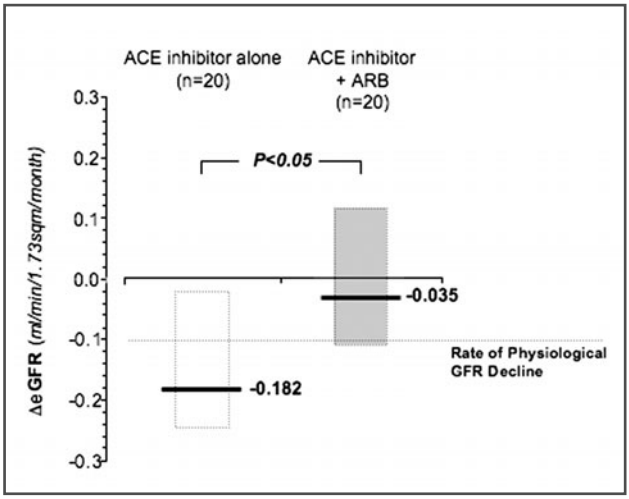

Fig. 26.2 Incremental estimated glomerular filtration rate (ΔeGFR) over 6 years of follow-up in 20 nondiabetic patients with chronic proteinuric nephropathies on benazepril (10 mg/d) plus valsartan (80 mg/d) therapy and in 20 reference patients on angiotensin-converting enzyme (ACE) inhibitor therapy alone. Physiological decline of GFR in people >40 years of age is –0.1ml/min/1.73m2 per month. Data: median (interquartile range)

uria, and 83% had a normal urinary albumin excretion [24]. In the REIN trial, slowing of GFR decline achieved by ramipril compared with non-RAS-inhibiting therapy correlated with the level of initial proteinuria and the extent of proteinuria reduction and achieved residual proteinuria [10]. Along the same line, in the REIN study, ramipril halved the rate of GFR decline in patients with a baseline 24-h proteinuria of 4.5 g or more. Treatment effect, however, progressively waned at decreasing levels of proteinuria and vanished when 24-h proteinuria ranged between 1 g and 2 g (Fig. 26.3).

Actually, patients with nonproteinuric renal disease (with specific exceptions such as those with polycystic kidneys) have a renal function loss that is close to that observed in the general population [25] and that is not affected to any appreciable extent by RAS inhibitor therapy. Consistently, GFR decline in ONTARGET patients averaged 0.9 ml/min per year, which is within the physiologic range of GFR loss (0.6–1.1 ml/min per year) observed in aging adults. Thus, it is not surprising that renal disease progression could not be affected by different RAS-inhibiting regimens in this population. On the other hand, the excess of renal events on dual RAS blockade was sustained by an excess in acute dialysis (that is, need for renal replacement therapy for <2 months), whereas death, chronic dialysis and doubling of serum crea-

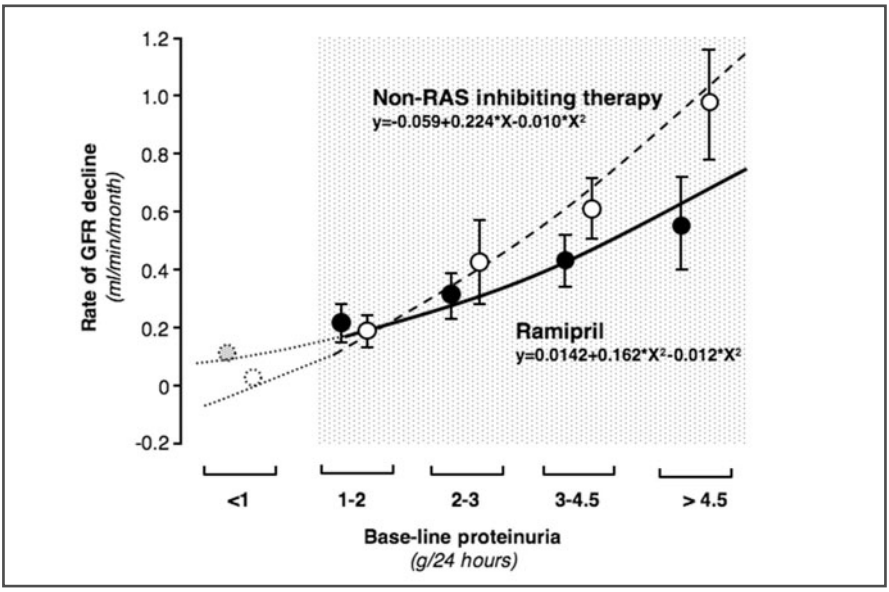

Fig. 26.3 Glomerular filtration rate (GFR) decline in 352 patients with nondiabetic proteinuric nephropathies included in the Ramipril Efficacy in Nephropathy (REIN) trial according to treatment and ranges of baseline 24-h proteinuria. The two equations describe the interpolates between the circles describing GFR declines within each treatment group [full and empty circles for ramipril and non-renin-angiotensin (RAS)-inhibiting therapy, respectively] at different ranges of proteinuria. Dashed circles describe the expected GFR declines for patients with 24-h proteinuria lower than 1g. Modified from [26]

tinine were not significantly different among treatment groups. Conceivably, this largely reflected a transient kidney hypoperfusion in patients with excessive blood pressure reduction, hypovolemia, or ischemic kidney disease that recovered with treatment withdrawal. Thus, this was a treatment-related adverse effect facilitated by RAS inhibition – in particular, when ACE inhibitors and ARBs were used together – and could not be considered as a renal outcome related to proteinuria or renal disease progression.

Thus, convincing data are available that dual RAS inhibition may optimize renoprotection in patients with nondiabetic proteinuric renal disease. Whether this applies also to patients with diabetes – in particular, those with type 2 diabetes – and overt nephropathy is still a matter of investigation. Two trials, the VALID (http://clinicaltrials.gov/; registry number NCT00494715) and VA NEPHRON-D ((http://clinicaltrials.gov/; registry number NCT00555217) are addressing this issue, and data are expected to be available by 2013.

26.5 Other Strategies to Further Decrease Proteinuria

26.5.1 Renin Inhibitors

In some patients on an ACE inhibitor and/or ARB therapy, compensatory renin activation may limit the antiproteinuric effect of RAS inhibition through specific activation of a renin receptor – which may eventually sustain proteinuria independently from the production of angiotensin and aldosterone – or by enhanced production of angiotensin I from angiotensinogen, which might fuel angiotensin II production and activity despite ACE inhibitor or ARB therapy [27]. Renin inhibitors initially developed were peptide analogues of the prosegment of renin or substrate inhibitory peptides of the renin cleavage site of angiotensinogen. Despite their efficacy in inhibiting renin activity in animals and humans, their clinical use was limited by the fact that they had to be administered parenterally. This pitfall was overcome by the development of aliskiren, a new orally administered active renin inhibitor with prolonged half-life, high bioavailability, and a high specificity for human renin [28].

Clinical trials in hypertensive patients showed the efficacy of aliskiren in lowering BP at a comparable or an even greater extent than angiotensin II receptor antagonists. However, clinical effects of orally administered renin inhibitors in relation to kidney damage remain to be determined. The only large clinical trial of aliskiren in patients with type 2 diabetes and overt nephropathy [the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study] receiving the maximum recommended renoprotective dose of losartan showed that aliskiren reduced the albumin/creatinine ratio by 20% compared with placebo [29]. These promising findings, however, should be tempered by the fact that the AVOID study had only 24 weeks of follow-up and could not provide information on long-term renal outcomes. Moreover, stud-

ies are needed to address whether the antiproteinuric effect of aliskiren is comparable with, superior to, or inferior to that of available RAS inhibitors and, even more importantly, whether aliskiren-based dual RAS blockade is superior to ACE inhibitor and ARB combined therapy in terms of proteinuria reduction, nephroprotection, and/or better tolerability with less hyperkalemia or cough.

26.5.2 Aldosterone Antagonists

Aldosterone, an often neglected component of the RAS, may also be the target of specific renoprotective therapy. This mineralocorticoid hormone is produced by the adrenal cortex and in endothelial and vascular smooth muscle cells in the heart, blood vessels, and brain. Although the molecular pathways of aldosterone-mediated renal injury have not been fully elucidated, they all seem to contribute to the final common pathway of renal fibrosis [28].

In the remnant kidney model in the rat, the aldosterone antagonist spironolactone induced regression of existing proteinuria and glomerular damage, which was paralleled by an amelioration of tubulointerstitial fibrosis and vascular lesions [30]. The renoprotective effects of spironolactone were potentiated when animals were given the aldosterone receptor antagonist in combination with the ARB losartan. Whether aldosterone blockade may achieve clinical benefits for patients with chronic nephropathies remains unclear, as available data are scarce and are mainly from uncontrolled or small, short-term controlled studies focused only on the effect on urinary protein excretion. The excess risk of severe hyperkalemia might also be a limitation to the clinical use of aldosterone antagonists, in particular, in patients with renal insufficiency and diabetes who are on concomitant therapy with other RAS inhibitors.

26.5.3 Statins

Almost all proteinuric patients, especially those with nephrotic syndrome, have an abnormal lipid profile because of overproduction and impaired catabolism of apolipoprotein B-containing lipoproteins. The degree of hyperlipidemia correlates directly with the severity of proteinuria and inversely with serum albumin [31]. Animal models of hyperlipidemia show that high cholesterol levels are injurious for the kidney [32] and that elevated lipid levels are associated with more rapid renal function loss in humans [33]. Possible mechanisms include accelerated atherosclerosis of arteries within the kidney and damaging effects of lipids on mesangial cells [34]. Studies in animal models show that treating dyslipidemia reduces renal injury by decreasing urine albumin excretion and reducing histological damage, such as mesangial matrix expansion and hypercellularity [35]. Therefore, optimal lipid control by statin therapy might be instrumental in reducing proteinuria and improving

renal function. In accelerated passive Heymann nephritis, combined administration of ACE inhibitor, ARB, and statin promoted regression of proteinuria, ameliorated glomerulosclerosis, and reduced tubular damage and interstitial inflammation more effectively than single treatments [36]. There are also data that show the addition of statins to antihypertensive treatment with or without RAS inhibitors may have an additive effect on reducing proteinuria, thus slowing the decline in renal function in humans [37]. A randomized trial is ongoing to formally assess whether statins combined with dual RAS blockade with an ACE inhibitor and an ARB is more effective than dual RAS blockade alone in reducing urinary protein excretion rates in patients with chronic proteinuric nephropathies (ESPLANADE, www.clinicaltrials.gov; registry number NCT00199927).

26.5.4 Vitamin D

In recent years, growing evidence has become available that vitamin D, in addition to modulating bone metabolism and calcium and phosphorus metabolism, may also play a role in the progression of CKD. In experimental animals, defective vitamin D bioavailability has been associated with renin activation and vitamin D supplementation, with inhibition of renin release through downregulation of relative messenger RNA (mRNA) expression [38]. Post hoc analyses of studies aimed at evaluating the effects of paricalcitol on serum parathormone levels in patients with CKD found that treatment with this selective vitamin D receptor activator was also associated with a significant reduction in urinary protein excretion [39]. A randomized, placebo-controlled, clinical trial recently found that 2 μg/day of paricalcitol add-on RAS inhibitor therapy decreased albuminuria by >30% in a large cohort of patients with type 2 diabetes and overt nephropathy, whereas the smaller dose of 1 μg/day had a nonsignificant effect on urinary albumin that was similar to that of placebo [40].

26.5.5 Smoking Cessation

Cigarette smoking is a major risk factor for different types of cancer, atherosclerotic vascular disease, and lung disease [41]. Recently, cigarette smoking has emerged as a risk factor for new-onset proteinuria and accelerated CKD progression [42]. Large clinical trials have suggested that cigarette smoking may accelerate CKD progression in diabetic and nondiabetic patients, such as those with polycystic kidney disease, lupus nephritis, and immunoglobulin A (IgA) nephropathy. Thus, smoking cessation represents an important measure to improve renal outcomes and overall morbidity and mortality rates of patients with CKD [42].

26.6 A Multimodal Strategy to Slow Progression of Chronic Proteinuric Nephropathies

In analogy to cancer and AIDS therapy, in which integrated use of different treatments against the same target (such as uncontrolled cell or viral replication) has dramatically improved patients' outcomes, experimental data suggest that combined therapies targeted to proteinuria reduction may further retard renal disease progression compared with single treatments [36]. Along this line, one integrated intervention with all available tools to target urinary proteins in patients with chronic renal disease – the so-called Remission Clinic approach [9] – might serve to optimize renoprotection in this population (Fig. 26.4).

In a long-term, matched-cohort study of 112 patients with severe proteinuric CKD and high risk for progression to ESRD, such a multidrug treatment titrated to urinary proteins compared with a conventional regimen titrated to BP significantly slowed GFR decline and reduced the risk of terminal kidney failure by 8.5-fold [43]. During 7 years of observation, only two patients who were treated according to the Remission Clinic protocol progressed to ESRD compared with 17 reference patients who were receiving conventional therapy. Serum potassium was similar in the two cohorts, and no patient withdrew from the program because of refractory hyperkalemia or other serious adverse events [43]. Thus, a standardized, multidrug,

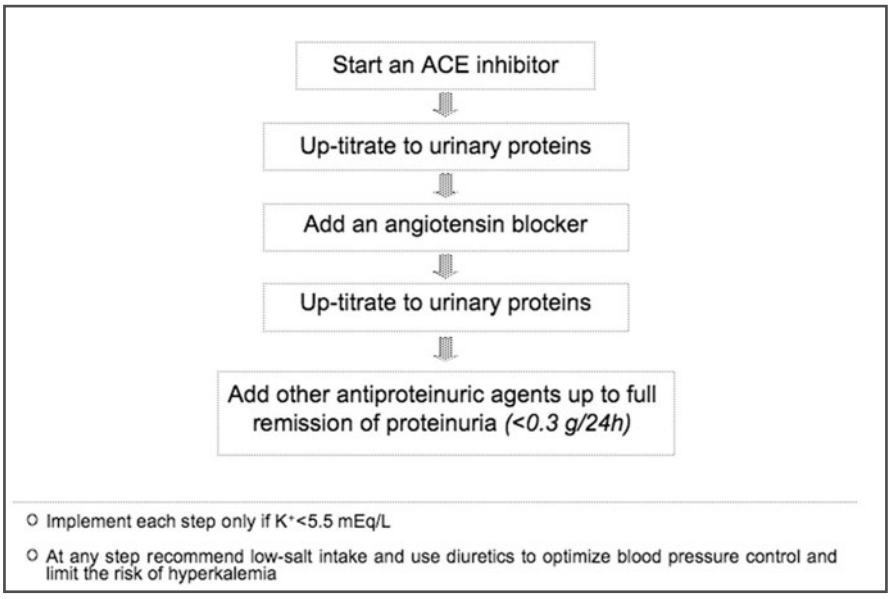

Fig. 26.4 Suggested steps in a multimodal therapeutic strategy targeted to maximal proteinuria reduction in patients with chronic proteinuric nephropathies. Modified from [44]

sequential treatment targeting urinary proteins can be safely and effectively applied in everyday clinical practice. Using this approach, heavy proteinuria can be normalized, even in cases resistant to standard therapy, and proteinuria reduction to normal range may translate into stabilization of kidney function and effective prevention of ESRD.

26.7 Is Regression of Chronic Kidney Disease Possible?

It is well established that RAS inhibition can reverse glomerulosclerosis in experimental animals. When an ACE inhibitor and an ARB were combined in a genetic model of progressive nephropathy, reduction of glomerular sclerosis was even more evident, particularly in glomeruli with less severe lesions [45]. This suggests that remodeling of glomerular architecture is possible, which would imply some form of regeneration of the capillary network.

Nephrotic patients of the REIN core study who continued on ramipril for another 2 years as part of the REIN follow-up study had a progressive time-dependent amelioration in the rate of GFR decline up to 1 ml/min per year, which is the physiological GFR decline after 40 years of age [11]. Intriguingly, among the 78 patients treated with the ACE inhibitor in this study, ten showed progressive improvement of GFR. This provided the first evidence that renal disease regression is achievable in humans – albeit, admittedly, in a small subgroup of cases.

Different hypotheses have been proposed to explain regeneration of renal functional tissue. Whereas glomerular, endothelial, and mesangial cells seem to proliferate in some circumstances, it is generally accepted that more differentiated podocytes do not usually proliferate [46], making it unlikely that new segment formation can occur simply by replication of resident cells. In the Bowman's capsule of adult human kidney, a renal stem cell niche with self-renewal potential and high cloning efficiency has been identified. A recent study documented that ACE inhibition may increase parietal podocytes, supporting a possible role for these cells as potential progenitors of visceral podocytes [47]. Therefore, it is possible to speculate that parietal podocytes might serve to repopulate visceral podocytes by migration from Bowman's capsule into the capillary tuft. Regeneration of capillary segments in the glomerular tuft may, however, depend on other cells as well. Bone marrow cells act as a reservoir for glomerular mesangial cells in rodents [48], and cross-bone-marrow transplantation from young to old mice allows partial regression of structural lesions associated with aging [49]. Regression of glomerulosclerosis and neoformation of glomerular tissue has indeed been linked to progenitor cells of renal or extrarenal origin [49].

In proximal and distal tubules and peritubular capillaries of the adult kidney, stem cells also exist that can retain mitogenic potential [50]. Following ischemia, such cells enter the cell cycle, divide, and migrate to the site of damage [48]. Renal papilla can also be a niche for kidney stem cells that start proliferating after renal ischemia [51].

Bone marrow stem cells, both hematopoietic and mesenchymal, also contribute to kidney regeneration [8]. Transplanting male bone marrow into female recipients yielded Y-chromosome–positive cells that localized and differentiated in tubular epithelium and glomerular podocytes [52]. In a mouse model of cisplatin-induced acute renal failure, mesenchymal stem cells limited renal injury and improved renal function by promoting resident tubular cell proliferation [53]. In the process of cardiac repair, stem cell migration and homing is facilitated by hepatocyte growth factor (HGF) [54]. Whether this applies to the kidney is yet to be confirmed. Angiotensin II blockade also limits TGF-α expression. As TGF- α suppresses HGF [55], one might speculate that ACE inhibitors exert a beneficial effect by preserving the HGF-dependent pathway of renal repair. Evidence in animals has shown that ACE inhibition prevents glomerular and tubular injury by upregulating renal messenger RNA (mRNA) levels of HGF [56]. HGF could therefore be pivotal in regenerating the kidney owing to its capacity for inducing renal cell proliferation and limiting apoptosis, which adds to its chemotactic effect on stem/progenitor cells.

26.8 Conclusions and Perspectives

Therapeutic approaches based on RAS blockade with ACE inhibitors and/or ARBs allowed remarkably improved outcomes of patients with chronic renal disease otherwise predicted to invariably progress to ESRD. Even more intriguing are the recent observations that regression of glomerular structural changes and remodelling of the glomerular architecture is achievable with RAS blockade. Whether and to what extent the renoprotective effects of dual RAS blockade are enhanced by combined therapy with statins or vitamin D remains to be addressed in adequately powered trials. In coming years, drugs now under development for clinical use, such as endothelin receptor antagonists, tumor necrosis factor alpha (TNF-α) blockers, anti-TGF-α antibodies, and gamma-secretase inhibitors [28], will hopefully open novel perspectives of therapy for renal patients, in particular, for those with advanced renal disease who appear to marginally benefit from available treatments. On the other hand, strategies to detect early renal disease in individuals at risk will allow renoprotective treatment to begin before irreversible changes in the kidney, which may limit the benefit of therapy. This is of paramount importance in resource-limited settings, such as in the poorest countries, where renal replacement therapy is not available for the large majority of patients in need.

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Section VII
Therapeutic Modalities

Approaches in the Management of Patients with Chronic Kidney Disease and Cardiovascular Disease

27

E. Ritz

Abstract Cardiovascular disease (CVD) risk is increased even in the earliest stages of chronic kidney disease (CKD) and is comparable to that conferred by diabetes. The main causes of death from CVD in CKD patients are a specific form of cardiomyopathy and accelerated atherosclerosis. Although the causes of the high CV risk are not yet fully understood, the main factors responsible for both progression of kidney disease and CV risk are hypertension, dyslipidemia, activation of the renin–angiotensin system and sympathetic nervous system, retention of sodium and phosphate, and vitamin D deficiency. All these factors are susceptible to intervention.

Keywords: Cardiovascular disease • Chronic kidney disease • Atherosclerosis • Hypertension • Dyslipidemia • Renin–angiotensin system • Sympathetic nervous system • Vitamin D

27.1 Introduction

As emphasized by recent consensus statements and guidelines [1, 2] chronic kidney disease (CKD) greatly amplifies cardiovascular disease (CVD) risk [3]. It is noteworthy that the pathogenetic factors causing CKD progression are almost, although not completely, identical with those causing CVD. Even in patients with essential hypertension and without CKD, serum creatinine predicts CVD risk. Such amplification of CVD risk by impaired kidney function has led to discussion whether – as for diabetes mellitus – CKD should be considered a CVD risk equivalent [4].

In the past, it was presumed that the major cause of death in end-stage kidney disease and hemodialysis was coronary atherosclerosis [5]. It has recently become clear, however, that the most frequent mode of death in end-stage renal disease (ESRD) is sudden death, and the second is heart failure. In the 4D study on hemodialyzed type 2 diabetic patients, sudden death accounted for 26%, heart failure for 6%, other cardiac causes, e.g. valvular disease, for 3%, and stroke for 6% of all-cause mortality,

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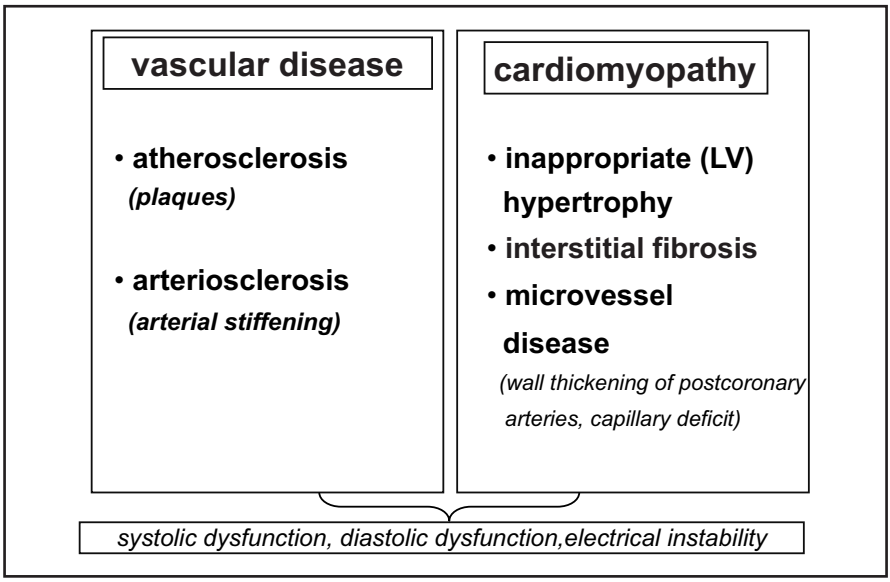

Fig. 27.1 Cardiovascular risk in chronic kidney disease

whereas adjudicated coronary heart disease only accounted for 9% [6]. This finding is in line with observations of the United States Renal Data System (www.usrds.org). The scope of prevention and treatment of increased CVD risk in CKD must therefore be expanded to include – apart from atherosclerotic coronary heart disease –a specific form of cardiomyopathy comprising inappropriate hypertrophy, interstitial fibrosis, and microvessel disease (i.e., wall thickening of intramyocardial arterioles and inappropriate capillarization) (Fig. 27.1).

27.2 Assessing Renal Function

The CVD risk starts to increase very early in the course of CKD. Assessing renal function and its disturbances is therefore crucial for assessing global CVD risk. Remarkably, in patients with CKD, the frequency of death from CVD exceeds the risk to progress to end-stage kidney disease by a factor up to 20 until the stage of preterminal kidney disease has been reached [7]. Therefore, it is important to start interventions to lower CVD risk as early as possible. It had been shown that when CKD has advanced to the preterminal stage, even aggressive multiple risk factor intervention when compared with conventional care failed to further reduce carotid

intima media thickness and improve endothelial function, and failed to reduce the frequency of CV events.

It has lately been appreciated that in order to assess renal function, serum creatinine concentration is not sufficiently accurate and predictive. Based on data of the Modification of Diet in Renal Disease (MDRD) study, an equation has been developed to estimate glomerular filtration rate (GFR), i.e. estimated GFR (eGFR) [8]; the equation is accurate only for values <60 ml/min/1.73m^2: GFR=175 × (standardized S_{cr})$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 (if the patient is female) or × 1.212 (if the patient is black). This formula has recently been slightly modified [9].

Cystatin C has emerged as a more reliable predictor of CVD risk compared with eGFR [10], particularly for GFR values >60 ml/min/1.73m^2, but because of the cost, this measurement is not routinely available.

It has recently become clear, however, that albuminuria or proteinuria is more powerful than eGFR for predicting CKD progression as well as CV events [11, 12]. The easiest procedure to measure urine albumin or protein is testing a first-void morning urine specimen. Twenty-four-hour urine collections are suitable mainly for scientific purposes. Complete assessment of CKD patients for evaluating both CKD progression and CVD risk should therefore comprise both eGFR and urinary examination for albumin and/or protein.

27.3 Pathomechanisms

Although traditional risk factors definitely play an important role in CKD, many additional pathogenetic factors have been identified that are thought to explain the extremely high CV complication rate in CKD. CVD risk is elevated in patients with primary kidney disease even before GFR has decreased. It is important to mention that when glomeruli are lost by a pathological process, the "whole kidney GFR" may remain completely normal for some time because of hyperfiltration of the remaining glomeruli. Even at that stage of incipient CKD, early CVD risk markers include:

- Elevated asymmetric dimethylarginine (ADMA) and the associated endothelial cell dysfunction
- Sympathetic nervous system overactivity (because of afferent signals emanating from the diseased kidneys ascending to the central nervous system and activating hypothalamic centers)
- Insulin resistance, including the frequently associated metabolic syndrome
- Dyslipidemia
- Blood pressure (BP) elevation within the normal range (particularly elevation of nighttime BP) and the associated cardiac remodeling and hypertrophy
- Proinflammatory and prothrombotic states
- Oxidative stress, and many others

27.4 Interventions: The Dilemma of Incomplete Evidence

A major problem for managing CKD patients with high CVD risk is that in CKD, prospective controlled evidence is extremely scarce [13] so that recommendations are mainly based on observational data (correlations) or opinion (based on pathogenetic mechanisms). The potential fallacy of this approach is illustrated by the recent discussion concerning homocysteine: whereas homocysteine is strongly predictive of CVD risk in CKD patients [14], interventions to lower serum homocysteine concentration proved to be futile [15]. A further example is the powerful correlation between low hemoglobin concentration and CVD risk; yet there is no evidence that administration of epoetin (EPO) to raise hemoglobin (Hb) concentrations to near-normal levels improves outcome [16].

27.5 Preventive Strategies

With these caveats in mind [17], the currently recommended preventive strategies to reduce CVD risk in CKD patients include:

- Target blood pressure
- Sodium restriction
- Selection of antihypertensive agents
- Reduction of sympathetic nervous system (SNS) overactivity (beta-blockers or central antisympathetic agents)
- Statins
- Aspirin
- Smoking cessation
- Phosphate control
- Vitamin D

As important as active intervention is avoiding injurious factors, for instance, administration of nonsteroidal anti-inflammatory medication, administration of radiocontrast, and – in CKD 4 and 5 – administration of gadolinium for magnetic resonance imaging (MRI) examination.

27.5.1 Target Blood Pressure

Lowering BP has two aims:

- To reduce progressive loss of renal function, and
- To reduce CVD risk

The evidence that lowering BP reduces the rate of progressive renal function loss

is limited. In the MDRD study, ordinary BP control [target 107 mmHg mean arterial pressure (MAP)] compared with intensified control (target 91 mmHg MAP) reduced GFR loss from 3.4 to 1.9 ml/min per year [relative risk (RR) 0.85, confidence interval (CI) 0.6–1.22], but overall, the difference was not statistically significant [18], and only after 10 years did a significant but minor difference emerge. In proteinuric patients, however, achieving BP values <140/90 mmHg caused significantly reduced progression [19]. In patients with type 2 diabetes, it has also been shown that intensified (target <130/80 mmHg) compared with conventional therapy (target 140/90 mmHg) reduced the risk of transition from microalbuminuria to overt proteinuria [20] .

The current consensus is to lower BP to at least 130 mmHg systolic, and there is debate as to whether lowering it further is safe in patients with preexisting CVD. If proteinuria >1g/day persists despite lowering BP to target levels, and if no serious CVD is present, BP should be lowered further and renin–angiotensin system (RAS) blockade should be intensified. The European Society of Hypertension and European Society of Cardiology (ESH-ESC) guidelines [2] recommend two main goals:

- BP control (<130/80 mmHg) and
- Reduction of proteinuria (<1g/day)

If despite strict BP control (<130/80 mmHg) proteinuria >1 g/day persists, further reduction of proteinuria (preferably to values <1 g per day or even 0.5 g/day) should be tried by escalating antihypertensive medication, particularly RAS blockade. Lowering proteinuria is a treatment target because proteinuria increases renal as well as CVD risk. Achieving this treatment target is complicated, however, by the fact that in a substantial proportion of patients, a so-called “escape” occurs with time, i.e., a secondary increase of proteinuria despite continuing RAS blockade. This complication is the result of a secondary increase of aldosterone production. It responds to administration of spironolactone or eplerenone on top of RAS blockade – with appropriate precautions to prevent hyperkalemia.

One most neglected aspect is the effect of sodium intake on BP. Only a minority of renal patients reduces sodium chloride intake to the recommended target of 7g/day. The issue is rendered particularly difficult by the fact that the consumer can control only 15% of the sodium intake, whereas 85% of salt is already contained in commercial food items. Apart from reduced salt intake, coadministration of diuretics is mandatory (in early stages, mostly thiazides); K+ sparing diuretics are contraindicated. If serum creatinine concentration is >2.5 mg/dl, then loop diuretics are required. Diuretic dosage must be increased in proteinuric patients because protein-bound diuretics within the tubular lumen fail to inhibit sodium reabsorption.

There is consensus that educating the patient to measure his or her own BP is a most effective strategy. In the Kidney Early Evaluation Program (KEEP) study, although 70.2% of CKD patients received antihypertensive treatment, only 13.2% reached target BP. For this reason, hypertension had been made the topic this year of World Kidney Day, with patient education as a major target [21]. Self-measurement of BP causes a substantial increase in compliance.

The safety of BP lowering has recently become a complex issue. Results of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

(ONTARGET) [22] indicate that in high-risk CVD patients, lowering BP <130 mmHg might – counterintuitively – increases CVD risk. This finding in nonrenal patients is in line with observations in the Irbesartan Diabetic Nephropathy Trial (IDNT) on diabetic patients with nephropathy, in which lowering BP to levels <121 mmHg systolic lowered renal endpoints but increased overall mortality by a factor of 3 [23]. Certainly, in nonrenal patients with preexisting coronary heart disease, lowering diastolic BP to values <70 mmHg increases the risk of myocardial infarction (MI) – a finding easily explained by the fact that coronary perfusion of the heart occurs only in diastole and may therefore become compromised by lowering the diastolic pressure below this threshold [24].

There is consensus that office BP measurements alone are insufficient to manage a patient with CKD. As mentioned above, self-measurement of BP should be recommended for all patients. Nighttime elevation of BP is found even before GFR decreases [25]. Therefore, 24-h BP measurements should be performed if proteinuria persists and/or loss of GFR continues, despite adequate office BP measurements. A specific problem in CKD patients is the finding that central BP in the aorta (to which kidney and heart are exposed) is often strikingly higher than peripheral BP.

27.5.1.1 Type of Antihypertensive Medication

Mainly the following classes of antihypertensive agents are necessary or useful for treating patients with renal disease:

- Angiotensin-converting enzyme inhibitors (ACEIs)
- Angiotensin receptor blockers (ARB), versus
- Combination of ACEI plus ARB
- Diuretics (see above)
- Different calcium-channel blockers
- Beta-blockers or central antisympathetic agents
- Currently under investigation: renin inhibitor, aliskiren
- Endothelin receptor A blockers

Angiotensin-converting enzyme inhibitors: The rationale for the use of ACEIs is documentation by the metaanalysis of Jafar et al. [26] that ACEIs are superior to other antihypertensive agents with respect to lowering renal endpoints in patients with elevated baseline urinary protein excretion. Evidence for a specific superiority of ACEIs on progression of renal disease in nonproteinuric renal disease is not available. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study [27], reducing albuminuria in the first 3 months was a powerful predictor of both renal and CVD prognosis. Therefore, it is sensible to measure proteinuria after 1–3 months after the start of ACEI treatment and to uptitrate RAS inhibitors beyond the doses licensed for BP lowering if proteinuria is not lowered to the target of 1g/day [2].

Angiotensin receptor blocker: ARBs are equally effective and have fewer side effects (no cough, no angioneurotic edema). The combination of ACEIs and ARBs, which had been proposed by one fraudulent paper [28], provides no further benefit. More intense blockade of the RAS increases the risk of acute renal failure [29] because sodium retention by compensatory upregulation of the RAS is no longer possible in situations of sodium loss (diarrhea, sweating, vomiting). It is therefore important to inform the patient that in such cases, RAS blockade should temporarily be interrupted and medical consultation obtained.

Aliskiren: In proteinuric type 2 diabetic patients, the direct renin blocker aliskiren has been shown to cause significantly further reduction of proteinuria when administered on top of ARBs [30]. Studies documenting effects on hard renal endpoints are not yet available.

Spironolactone or eplerenone: In coronary patients with marginally reduced GFR, plasma aldosterone concentration is a powerful predictor of CV events [31]. Whether aldosterone blockade, e.g., by spironolactone or eplerenone, is beneficial (and safe) in patients with more advanced CKD is unclear, although proposals in this direction have recently been advanced [32] .

Calcium-channel blockers: The renal effects of CCBs are not uniform. Dihydropyridine CCBs cause dilatation of the preglomerular vessel, increased glomerular capillary pressure, and increased proteinuria – at least unless BP targets are reached and unless the RAS system is blocked. In contrast to the conventional L-type CCBs, novel CCB blocking both T and L calcium channels in the glomerulus avoids adverse effects on glomerular capillary pressure and proteinuria and also reduces SNS activation.

Beta blockers: Because of their adverse metabolic effects, there was great hesitation in the past to use beta-blockers in CKD patients, particularly in diabetic patients with CKD. Such hesitation is no longer justified for the novel beta blockers carvedilol and nebivolol, which are devoid of adverse metabolic side effects [33] . The use of beta-blockers appears to be particularly indicated in dialyzed patients, because sudden death is the major cause of death. Beta-blocker treatment has been shown to lower mortality rates in hemodialyzed patients in an observational study, and in an interventional study, it reduced mortality in hemodialyzed patients with heart failure.

Reasonable alternatives are central sympathoplegic agents, e.g. moxonidine, which have been shown to interfere with kidney disease progression [34].

While fighting metabolic syndrome by reducing body weight is a sensible strategy in the nonrenal patient, matters are more complex in the patient with CKD. In patients with incipient CKD, arbitrarily defined as serum creatinine <2.5 mg/dl, the recommendation to lose weight will do more harm than good. More advanced CKD is a catabolic state with an inflammatory component [35]. In such patients, weight loss is associated with a high risk of death. Whereas advising physical exercise is appropriate, advice to lose weight is counterproductive at this stage.

27.6 Statins

In the absence of a nephrotic syndrome, abnormalities of the lipid pattern of CKD patients appear to be deceivingly minor, i.e., elevated triglycerides and most frequently low total and high-density-lipoprotein (HDL) cholesterol. Behind this unobtrusive pattern hides a spectrum of abnormalities comprising elevated small, dense low-density lipoprotein (LDL), very-low-dense lipoprotein (VLDL) remnants, and intermediate density lipoproteins, chylomicron remnants, apolipoproteins modified by glycation, oxidation or carbamylation, high Lp(a) and acute-phase HDL. A grasp of some of these abnormalities is provided by calculating the concentration of non-HDL cholesterol, i.e., LDL+VLDL, the normal value being 130 mg/dl [36]. Counterintuitively, low total cholesterol is correlated with high mortality. The explanation is confounded by microinflammation: when C-reactive protein (CRP) is normal in CKD patients, the mortality rate increases with increasing plasma concentrations of cholesterol.

In view of such confounding findings, the question arises as to whether lowering cholesterol creates a benefit. Several post hoc analyses examined the effect of statins in patients with CVD disease who also happened to have reduced GFR and were included in studies on statins. These analyses documented less CKD progression and fewer CV events in CKD patients treated with statins [37], and statins reduced indicators of microinflammation [38] .

The situation is unresolved, however, for patients on dialysis. Whereas an observational study found better survival of patients on statin treatment, two major trials on diabetic patients [6] and another on mostly nondiabetic patients on hemodialysis [39] failed to document significant benefit from statins on composite CVD endpoints. On the basis of post hoc analysis, it has been argued, however, that in this population, patients will benefit from statins by a selective reduction of coronary death [40], but the final answer is not yet in, and the outcome of the Study of Heart and Renal Protection (SHARP) trial must be awaited.

27.7 Vitamin D and Phosphate–Calcium Metabolism

In patients with cardiological disease but with normal renal function, it has recently been shown that concentrations of the vitamin D metabolites 25(OH)D and $1,25(OH)_2D_3$ were strongly correlated with CVD outcome [41].Whereas interventional data assessing vitamin D metabolite administration to nonrenal patients with cardiac disease are not yet available, the finding is of considerable interest for the nephrologist, because several observational studies documented reduced mortality rates in dialyzed patients with administration of active vitamin D compared with patients without vitamin D treatment [42]. Furthermore, both the concentration of the

precursor molecule 25(OH)D and $1,25(OH)_2D_3$ are predictors of death from CVD and increased risk of CV events in dialysis patients [43]. It has been shown abundantly in experimental studies that active vitamin D has a beneficial effect on cardiac morphology and performance [44], in part because $1,25[OH)_2D_3$ inhibits renin release from the juxtaglomerular apparatus [45]. The outcome of ongoing interventional trials in renal patients is expected with great interest, but recent recommendations argue for normalizing the concentration of the precursor molecule $25(OH)D_3$ if the concentration is <30 mg/ml.

Another area in which observations in renal patients appear to be relevant for nonrenal patients concerns plasma phosphate concentration. Plasma phosphate is a strong predictor of overall mortality and specifically of death from coronary disease and sudden death in dialysis patients [46]. The same has recently been found in nondialyzed patients with CKD and even in cardiac patients without kidney disease [47]. Managing abnormal phosphate metabolism in CKD, e.g., reduced dietary intake, oral phosphate binders, or inhibitors of intestinal phosphate transport, have recently been reviewed [48].

One controversial issue is management of atrial fibrillation, the frequency of which is 10–20% in end-stage kidney disease. The dilemma is that uremia is a state with both procoagulatory and prohemorrhagic tendency. The risk of bleeding is massively increased, and the indication for anticoagulation must therefore be individualized according to recent recommendations [49].

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Trends in the Management of Cardiac Patients with Renal Functional Impairment

28

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Abstract Treatment of acute decompensated heart failure is challenging, especially in that traditional diuretic approaches can worsen the cardiorenal syndrome, with activation of the renin–angiotensin–aldosterone and sympathetic nervous systems. A variety of alternative pharmacologic therapies have been used with limited success, including inotropes, natriuretics, aquaretics, and erythropoiesis-stimulating agents, and trials with adenosine receptor antagonists are ongoing. It has been proposed that salt and water removal by nonrenal or extracorporeal means would avoid maladaptive tubuloglomerular feedback neurohumoral mechanisms induced by diuretics. This has been the rationale for a growing literature supporting the use of paracentesis, ultrafiltration by peritoneal dialysis modalities, and extracorporeal therapies such as slow continuous ultrafiltration. The latter are appealing in that there is existing technology as well as newly developed machines dedicated to this technique. Use of these mechanical fluid removal therapies, however, warrants caution because of the risks of excess fluid removal, hypotension, acute kidney injury, and blood or air leaks inherent in blood–pumped modalities.

Keywords: Ultrafiltration • Diuretics • Renin–angiotensin–aldosterone system • Sympathetic nervous system • Tubuloglomerular feedback • Aquaretics • Natriuretics • Adenosine receptor antagonists • Air embolus • Erythropoiesis stimulating agents

28.1 Introduction

Whereas a number of established therapeutic strategies for heart failure (HF) have been used for many decades (e.g., diuretics and beta-blockers), novel therapeutic strategies have also recently emerged with promising preliminary results (e.g., extracorporeal ultrafiltration). The currently available therapeutic strategies for patients

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Cardiorenal Syndrome. Adel E. Berbari, Giuseppe Mancia (Eds.)

Table 28.1 Treatment Options for Cardiorenal Syndrome

Conventional:
Diuretics (e.g., loop diuretics and long-acting thiazides)
Rhythm and rate control (e.g., for atrial fibrillation)
Digoxin
ACEi and ARBs
Vasodilators
Electromechanical (e.g., biventricular pacing)
Recently Introduced Medications:
Inotropes (i.e., milrinone and dobutamine)
Aquaretics (i.e., vasopressin antagonists)
Erythropoiesis-stimulating agents
Adenosine receptor blockers (investigational)
Ultrafiltration:
Peritoneal dialysis
Extracorporeal therapies:
Intermittent ultrafiltration
Slow continuous ultrafiltration (SCUF)

ACEi, angiotensin-converting enzyme inhibitors; *ARB*, angiotensin receptor blocker

with HF and concomitant renal dysfunction can be divided into two large categories: pharmacologic and nonpharmacologic (Table 28.1).

28.1.1 Pharmacologic Therapeutic Strategies

A thorough cardiology evaluation is essential for patients with cardiorenal syndrome, as some will have cardiac output benefits from control of tachyarrhythmias, placement of pacemakers (e.g., biventricular pacing in the setting of dyssynchrony), or medications to reduce afterload. Inotropes are conceptually attractive, but many have limited benefit (i.e., digoxin) or require inpatient continuous intravenous infusions (i.e., dobutamine and milrinone). Studies using the Acute Decompensated Heart Failure National Registry (ADHERE) registry have highlighted the difficulty in achieving an adequate diuresis using conventional medications in patients admitted with acute heart failure [1]: 16% even gained weight during the course of therapy. Currently available specific pharmacologic agents include.

28.1.1.1 Diuretics

Despite the risk of increased renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) activation, a subset of patients do respond to escalat-

ing doses of diuretics and the addition of a long-acting thiazide diuretic to maintain natriuresis. There are risks to high doses of loop diuretics (i.e., ototoxicity and post-diuretic salt retention), and continuous low-dose infusions can be preferable.

RAAS Medications and Interactions

Whereas the use of angiotensin-converting enzyme inhibitors ((ACEi) (and related compounds) has been a mainstay of HF therapy, the resultant hypotension or reduction in glomerular filtration rate (GFR) can be clinical dilemmas, especially for patients with chronic kidney disease (CKD). Those with acute renal dysfunction may benefit from temporarily decreasing or holding doses of the ACEi in an effort to avoid initiation of dialysis. A long-recognized alternative strategy is to attenuate uremia by first decreasing the diuretic doses prior to adjusting that of the ACEi. Hyperkalemia is another potentially serious consequence of RAAS inhibition, as also seen with aldosterone antagonists (i.e., spironolactone), and may complicate or limit use of these agents.

Adenosine Antagonists

Pharmaceutical agents are under development for inhibition of the adenosine pathway. Adenosine A_1 receptor (A_1R) antagonists are proposed to block the maladaptive activation of the RAAS and SNS axes caused by diuretic-induced natriuresis and signaling at the macula densa. There was a 300-patient pilot randomized, placebo-controlled, dose-finding study of the selective intravenous A_1R antagonist rolofylline in patients with acute HF and renal dysfunction [2]. After 3 days of treatment, the outcomes at days 14 and 60 showed some trends for benefit regarding dyspnea, smaller increases in serum creatinine levels, mortality, and readmission rates. Based on these preliminary results, there is now an ongoing 2,000-patient Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT).

Erythropoiesis-stimulating Agents (ESAs)

There is substantial literature regarding small patient series reporting that correction of severe anemia (hemoglobin concentrations <10 g/dl) improves objective measures of HF and clinical outcomes. There is weak but provocative evidence that these may, in turn, lead to improved kidney function in some patients. Anemia therapies have included blood transfusions, iron repletion, or use of ESAs; however, the target hemoglobin level has not yet clearly been established in this population. In a report describing a 48,612-patient registry at 259 hospitals, 25% of individuals were moderately to severely anemic (hemoglobin 5–10.7 g/dl, potential candidates for ESA therapy). Anemia (hemoglobin <12.1 g/dl) was associated with higher in-hospital mortality rates, longer length of stay, and more re-admissions at 90 days [3]. Based on descriptions of some patients appearing to have further benefits from raising blood counts to normal, there are now ongoing prospective multicenter trials studying that higher goal. This is an important subject because of the well-documented increase in cardiovascular mortality of CKD patients when ESAs are administered to achieve values greater than approximately 12 g/dl. Until there is convincing evidence supporting higher hemoglobin goals in the setting of HF, we believe the most prudent

course is to follow renal disease targets and guidelines: not initiating ESA therapy until hemoglobin levels fall below 10.0 g/dl, and titrating the dosage so as not to exceed hemoglobin levels of 12.0 g/dl. These issues are the subject of recent reviews [4–6].

Antidiuretic Hormone (ADH) Antagonists

Nonosmotic release of vasopressin secondary to low cardiac output results in water retention and hyponatremia. There was much enthusiasm that vasopressin antagonists (selective V_1 or nonselective V_1/V_2 agents) could treat HF by inducing aquaresis. In the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT) trials, 225 patients with euvolemic or hypervolemic hyponatremia were treated with escalating doses of the V_2-selective oral tolvaptan, and there was higher urine output with increase in serum sodium levels of up to approximately 8 mEq/L at day 30 [7]. Use of a nonselective oral V_{1A}/V_2 antagonist was also able to achieve aquaresis and increases in serum sodium that reached 8 mEq/L at 5 days [8]. Whereas these studies confirm aquaresis, it has not yet been proven that this results in clinically relevant improvement in HF. The Explaining Variation in RRT through Expert Opinion Secondary Data Sources and Trend Analysis (EVEREST) prospective, randomized, double-blind, placebo-controlled, multicenter, international trial investigated short-term [9] orally administered tolvaptan (with concurrent diuretics) in more than 4,000 patients. There were small improvements in serum sodium, weight, dyspnea, and edema but no difference in global clinical status. Unfortunately, despite some short-term benefits, treatment in 537 patients for a minimum of 60 days had no effect at 10 months on all-cause mortality or HF-related morbidity [10].

Natriuretic Peptides

The physiology of natriuretic peptides suggests that these would be ideal agents to treat HF in that there could be an increase in renal plasma flow, improved GFR, and enhanced natriuresis. Whereas early trials were encouraging for cardiac benefit [11], they could not show any improvement in renal function [12]. These agents should no longer be utilized for HF due to subsequent reports and pooled analyses of larger numbers of patients demonstrating increased short-term mortality in this patient population [13].

28.1.1.2 Nonpharmacological Salt and Water Removal

Historically, there has been a hesitation to treat HF patients with the various ultrafiltration (UF) modalities initially developed as renal replacement therapies (RRT). The attitude was that sodium and water removal achieved by diuretic regimens would be safer, logistically simpler, and much less expensive than identical fluid losses accomplished by hemodialysis, hemofiltration, or peritoneal dialysis (PD) techniques. Now, however, with newer understanding of the pathophysiology of tubuloglomerular feedback (TGF), it is appreciated that those therapeutic options have the theoretical

advantage of avoiding the RAAS and SNS activation induced by diuretics. Furthermore, many patients will fail to achieve a natriuresis despite aggressive treatment with standard therapies, including diuretics and inotropes.

Paracentesis

Avoidance or inefficacy of natriuretic agents would be the rationale for bulk solute and water removal by paracentesis in the subset of HF patients with severe ascites. In a small study, removal of approximately 3 L of ascites resulted in a decrease in intra-abdominal pressure from 13 to 7 mmHg and was associated with improved renal function (serum creatinine decreasing from 3.4 to 2.4 mg/dl) [14]. Repeated intermittent paracentesis, however, is not without risk in that there are significant protein losses, often necessitating albumin repletion, and the possibility of subsequent fluid leakage. Although it is not yet clear how to select patients appropriate for this procedure, the approach has particular appeal in settings where more costly treatments are not available.

28.1.1.3 Peritoneal Ultrafiltration

The physiologic mechanisms of peritoneal electrolyte and fluid transport were first described by Nolph et al. in 1969 [15], with the molecular mechanisms of solute and water transport only recently being elucidated. Peritoneal dialysis solutions of varying dextrose concentrations can be used to osmotically induce UF of plasma across the peritoneal membrane. Depending on the dextrose concentration, exchange dwell time, and membrane transport characteristics, each 2-L exchange might remove up to approximately 800 ml of hypotonic fluid. The number of exchanges and timing (manual or with automated devices) would depend on the degree of the patient's fluid overload rather than being based on urea kinetics, as in the case of end-stage renal disease (ESRD). Whereas conceptually appealing for both home and in-hospital use, peritoneal UF and dialysance of solutes is not without risk (Table 28.2). Diabetic patients often have worsened glucose control because of absorption of the dialysate dextrose. Effluent losses can lead to hypokalemia or hypomagnesemia, which may worsen rhythm control in cardiac patients, necessitating very careful monitoring and repletion. There are also potential problems with placing peritoneal catheters, and their rapid use (often needed for decompensated HF patients) increases the risk of early fluid leaks and peritoneal infection. Large fluid volume in the peritoneal cavity can potentially restrict diaphragmatic excursion and thereby worsen HF-induced respiratory difficulties. This effect can be minimized by more frequent lower-volume exchanges accomplished with the automated cyclers. Lastly, appetite may be impaired by abdominal distention as well as from the calories from the dextrose in the dialysate, which is not desirable in patients prone to cardiac cachexia.

Given these potential benefits and concerns, there have been a number of publications describing successful use of this modality in HF, dating back to the 1960s [16, 17]. Those early reports described intermittent PD, with each session typically

Table 28.2 Risks of Ultrafiltration Therapies

Excess ultrafiltration:
Hypotension
Hemodynamic renal dysfunction
Ischemic acute kidney injury (i.e., acute tubular necrosis)
Extracorporeal blood-pumped techniques:
Air embolus
Blood leaks from tubing disconnections
Bioincompatibility of the extracorporeal circuit and filter
Hemolysis
Complications of systemic anticoagulation
Complications of vascular access catheters:
Infections, local and systemic
Stenoses (i.e., central vein stenosis)
Thromboses
Peritoneal dialysis:
Infections (i.e., peritonitis and catheter-exit site)
Fluid leaks:
Externally draining from exit site
Into abdominal wall
Hydrothorax
Catheter malfunction
Electrolyte abnormalities and arrhythmias
Worsened glycemic control in diabetes mellitus
High intra-abdominal pressure and distended abdomen
Respiratory compromise
Early satiety and decreased appetite
Exacerbations of gastroesophageal reflux

lasting 1–4 days. It was intriguing that in addition to accomplishing UF, investigators also reported that patients had restored diuretic sensitivity. The literature on this subject, however, is difficult to interpret because most studies were small case series, involved heterogeneous groups of patients with varying degrees of parenchymal renal disease, used a variety of PD techniques, and did not have rigorously defined treatment regimens. Also unclear is the potential benefit of the PD regimen coincidentally removing HF-induced ascites and which might have been amenable to paracentesis [14].

Despite the concerns over trial designs, many case reports and small series (fewer than ten patients) have highlighted the safety of catheter placement and efficacy of outpatient PD for fluid removal. Representative of the few studies recruiting somewhat higher numbers of patients are the following three publications: In one of the larger, but nonrandomized, uncontrolled, investigations, Gotloib et al. [18] prospectively studied 20 patients with severe chronic heart failure (CHF). After initial treatment with hemofiltration, the patients underwent PD catheter placement and were transitioned to automated PD for 8 h thrice weekly, using 15–20 L of dialysate per

session. The mean net UF volume was 2.1 ± 0.5 L/session using dialysate that included 4.25% dextrose solutions. At 1-year follow-up, there were improvements in echocardiographic measures of cardiac contractility, bioimpedance findings of intrathoracic fluid, improvement in the New York Heart Association (NYHA) class (IV to I), and a dramatic decrease in hospitalization days (157 to 13 days annually). The patients, however, did have severe baseline renal insufficiency (mean GFR 15 ml/min), so it is not clear how much of the clinical improvement was just due to resolving salt and fluid excesses associated with CKD. Peritonitis occurred at an incidence of 0.27 events/patient per year – not dissimilar to rates observed in the ESRD literature. Improvements in cardiac parameters were similarly described by Ryckelynck et al. [19] in 15 CHF patients, three of whom had ESRD. This study demonstrated the feasibility of long-term PD fluid removal, with mean treatment duration of 12.7 months: The UF volume was 3.74 L/week, with 45 mEq of sodium cleared per day. This represented 57% of the daily amount removed in that only 34 mEq appeared in the urine. Of the ten patients with class IV CHF, four improved to class III and two reached class II. Compared with the historic 6 months prior to the initiation of PD, there was a 67% reduction in the days of hospitalization (from 3.7 to 1.2 days/patient per month). There was a rather high rate of complications over the treatment interval, which extended as long as 28 months: 16% of patients had difficulties such as peritoneal or abdominal-wall infections, difficulty with dialysate effluent drainage, and displaced catheters requiring replacement. Lastly, in the report from Kim et al. [20], the NYHA class similarly improved, but this was observed even in patients who did not manifest increased left ventricular ejection fractions on echocardiography.

Putting the positive reported results in perspective, of the 16 patients described by Stegmayr et al. [21], five did not have adequate UF and needed to be switched to hemodialysis for further fluid removal. Also, an analysis of national data from 107,922 new ESRD patients also challenged the conventional wisdom that PD is the preferred modality for dialysis patients with a history of HF [22]: compared with hemodialysis, PD had a negative impact on survival that increased with time beyond 6 months (relative risk increasing to 1.37). This study also highlights the complexity of long-term care for these patients, especially with loss of residual renal function.

A number of authors have attempted to reconcile the diverse protocols and patient populations published in the small series [23, 24]. In general, the reviews support the efficacy of PD in appropriate patient populations for fluid removal, improvement in NYHA class of HF [19], bridging to cardiac transplantation, decrease in hospitalization days [24], and improved quality of life [25].

28.1.2 Extracorporeal Ultrafiltration: Equipment and Techniques

There are extensive published reports concerning the use of intermittent hemodialysis techniques for fluid removal in HF. Traditionally, acute catheters are used for vascular access and these devices carry the typical infection concerns as in ESRD

patients. Permanent access, even if justifiable from an HF chronicity perspective, is often contraindicated from a cardiac perspective because these arteriovenous fistulas or grafts shunt a liter or more of blood per minute. Once access is established, it is important to recognize that the extracorporeal tubing, filter, and circuit will be filled with a volume of approximately 200–250 ml of blood at a pumped flow rate typically at least 200 ml/min, both of which carry the risk of hemodynamic instability. When the intention is to solely provide UF (i.e., isolated UF), no dialysate is used, and the machine regulates the transmembrane pressure across the dialyzer to accomplish the desired fluid removal rate. Solutes are convectively removed with the ultrafiltrate depending on their sieving coefficients across the particular filter membrane used. Thus, the ultrafiltrate has essentially the same sodium concentration as that of plasma water.

The major risk from intermittent therapies is hemodynamic instability due to fluid removal over traditional 2- to 4-h treatment times. Ideally, to avoid hypotension with UF, there needs to be ongoing (matched) refilling of the intravascular compartment from the fluid-overloaded interstitial spaces. Even with careful setting of the ultrafiltration rate (UFR), many unstable HF patients will not tolerate removal of 2 L or more over the typical sessions of a few hours. Of paramount importance, episodes of hypotension will not only prevent further fluid removal but can also induce renal hypoperfusion and acute kidney injury, potentially making the patient dialysis dependent.

It is believed that slow UFR allows adequate refill of the intravascular compartment, helping maintain hemodynamic stability. This is the rationale for longer or continuous modalities [e.g., continuous venovenous hemofiltration (CVVH)]. There are a number of case reports and small series of patients treated with extended-time intermittent or continuous techniques. Unfortunately, most series had heterogeneous patient populations and did not have appropriate control groups, predefined outcome measures, or rigorous treatment protocols.

28.1.3 Extracorporeal Ultrafiltration: Recent Advances in Techniques

A major factor limiting more widespread use and study of these modalities is that they are logistically difficult in locations other than intensive care units (ICUs), with most being designed for one-to-one supervision by either critical care nurses or dialysis staff. Additional barriers to performing extended treatments on the wards or in a clinic have included relatively large extracorporeal blood volumes, inability to improve the safety profile by slowing the blood pump speeds to <100 ml/min, high blood flow rates precluding the use of peripheral veins for access, complex user interfaces with minimal automation, complicated tubing and connection setup, and lack of portability or remote monitoring. New technology has overcome most of these problems, and there is a growing literature describing safety and efficacy of each treatment, as well as comparisons to pharmacologic therapies in regard to patient outcomes, cardiovascular endpoints, hospitalization costs, duration, and readmissions.

Commercially available modern devices for isolated UF now include those that have small extracorporeal blood volumes (<100 ml), blood flows low enough (<50 ml/min) to permit use of temporary peripheral vein catheters, tubing sets with one-step loading, user-friendly data and help computer screens, and remote monitoring capabilities. Published protocols range from 6 h daily to continuous over multiple days. For example, a compact UF-dedicated device has been developed for use outside the ICU setting and has been the subject of multiple publications ranging from pilot studies to a multicenter randomized trial, postmarketing series, and post-hoc data analyses. The outcomes investigated included cardiac parameters as well as impact on renal function. The first feasibility study [26] was in 21 patients and demonstrated that 16- to 18-gauge catheters could deliver blood at up to 40 ml/min and resulted in 2,611 ± 1,002 ml (up to 3,725 ml) of UF over approximately 7 h. Similarly, in serial short (8-h) sessions, Liang et al. [27] had technical success in removing fluid in 11 patients with severe HF. Of 32 treatments, 41% resulted in UF of at least 3.5 L. Protocols with extended treatment times were pursued, as reported in an early uncontrolled study [28] of 20 patients with decompensated HF and serum creatinine levels of at least 1.5 mg/dl and/or diuretic resistance. Patients underwent UF until resolution of HF symptoms at rates up to 500 ml/h (decreased to 200 ml/h if hypotension occurred). Fluid removal >8 L led to discharge in just 3.7 days, with improved HF scores and hyponatremia, no changes in blood urea nitrogen (BUN) or creatinine levels, and patients appeared to have a decreased rate of re-admission. The success of extended UF treatment times was also reported in a small series by Dahle et al. [29]. Using peripheral access, seven patients had 7.0 L of UF over 33.3 ± 20.0 h, and this was not associated with any change in renal function. The first randomized controlled study using this particular device was in 40 patients at a single center, comparing an 8-h UF session to usual care [30]. Removal of 4.7 L (vs. 2.8 L in controls) was consistent with a 1-day weight loss of 2.5 kg (vs. 1.9 kg in controls) and occurred without change in renal parameters. These encouraging results led to a large prospective, multicenter, randomized, controlled, unblinded investigation comparing early UF with intravenous diuretics [the Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD) trial] in hospitalized hypervolemic patients with HF (100 patients in each group), systolic blood pressure >90 mmHg, serum creatinine £3 mg/dl, and follow-up for 90 days [31]. The study design permitted UF of up to 500 ml/h for the 48 h in the primary efficacy endpoint interval. UF achieved by the study was 241 ml/h for 12.3 ± 12 h, which led to a weight reduction of 5.0 ± 3.1 kg over the 2 days. This was approximately 2 kg more than in patients in the control diuretic group. Although patients in the UF group had a greater weight loss, there was no difference from the control group for dyspnea, increases in serum creatinine >0.3 mg/dl, BUN and sodium levels, heart failure scores, episodes of hypotension, or length of stay. Interestingly, at 90 days, fewer patients who had undergone UF were re-admitted for HF, resulting in fewer rehospitalizations (18% vs. 32%) and r-hospitalization days (1.4 vs. 3.8 days). The UF group also had fewer unscheduled office and emergency room visits (21% vs. 44%). Although the physiologic mechanisms were not studied and there were potential weaknesses to the study design [32], the investigators

stressed these long-term medical and resource-utilization UF benefits, which were beyond the initial effect on fluid removal.

28.1.4 Ultrafiltration: Long-term Treatment

Few studies have examined the use of UF beyond short-term therapy in episodes of decompensated HF. Canaud et al. [33] described their 10-year experience using both continuous and slow 4- to 8-h daily UF for 52 NYHA class IV patients, with 31 undergoing long-term treatments for up to a year using tunneled catheters. Although a heterogeneous group, 39 were considered responders: 26 becoming class III and 13 improving to class II. In a small, uncontrolled series [34], 14 patients with severe disease (all NYHA class IV) underwent intermittent outpatient treatments over a year. The HF severity class decreased to 3.1, and inotrope dependency changed from 86.4% to 36.8%. Using the prior year for comparison, the number of hospitalizations decreased to 2.6–0.3/year, which corresponded to a change from 41.8 to 2.4 days/year.

28.1.5 Effect of Ultrafiltration on HF Pathophysiology

Given the theoretical advantages and potential concerns about using intermittent techniques for volume removal, there is substantial published literature using this modality. The report on a series of 24 patients with refractory HF describes success from UF of up to 4 L in a few hours [35]. Plasma volume was monitored optically and remained relatively constant, thereby confirming the matching of UFR and plasma refill rate (PRR). Even 24 h after completion of the procedure, the patients had lower right atrial, pulmonary artery, and wedge pressures; higher stroke volume; unchanged heart rates and systemic vascular resistance; and better diuretic responsiveness. Similarly, in a separate study of ten patients undergoing hemodiafiltration, diuretic sensitivity was restored [36].

Consistent with a reversal in HF pathophysiology, UF has been associated with improvement in neurohumoral markers: decreases in levels of norepinephrine, aldosterone, and renin [37, 38]. This benefit reportedly can last for months but may follow a brief postprocedure interval in which these parameters transiently worsen. Compared with a control group that experienced persistent activation of both the RAAS and SNS systems, Agostoni et al. [39] described eight patients with an initial increase in those hormones for 1 day after UF. Levels then declined, and this persisted for 3 months. Similarly, these authors [40] assessed the neurohumoral axis after UF prescribed to reduce right atrial pressure by 50%: a mean of 3 L at 500 ml/h, resulting in a 20% reduction in plasma volume. The increased sodium and water losses were associated with improved edema and organ congestion. Despite a transient drop in cardiac output and blood pressure, at 48 h, there were persistent decreases in pulmonary wedge and right atrial pressures and large decrements (reaching >50%) in

norepinephrine, plasma renin activity, and aldosterone levels. There have also been reports of significant reductions in circulating levels of inflammatory cytokines (e.g., interleukin-8 and monocyte chemoattractant protein-1), a phenomenon that was not observed in patients treated with just diuretics – cytokine production and reduction (and perhaps clearance) thereby being an intriguing area for future research. Lastly, when interpreting studies that compare UF to diuretics, it is important to appreciate that salt loss is more prominent with UF. Part of the benefit from UF may be due to removal of the isotonic fluid (ultrafiltrate), compared with the hypotonic urine produced by the diuretics.

Ultrafiltration has also been shown to have more than just cardiorenal benefits. In a group of 26 patients who underwent a single UF session, there was exercise capacity improvement at 3 months that was inversely related to their pre-UF physical performance and pulmonary function parameters. The improvement in 16 patients suggested that a low maximum oxygen uptake (VO_2 max) (i.e., <18.5 mL/min per kg) might predict individuals who would benefit from the UF procedure. They had a 28% increase in peak oxygen consumption, with pulmonary vital capacity improving from 80% to 91% of predicted and forced expiratory volume in 1 s (FEV1) from 83% to 92% [41]. At days 4 and 30, nine patients with improved oxygen consumption also demonstrated better lung mechanics and echocardiographic measures of right and left ventricular function [42]. In a similar study of 24 randomized patients [43] (compared with controls), those who underwent one 1.9-L UF session had improved peak VO_2, exercise tolerance time, ventricular filling indices, and right atrial and wedge pulmonary pressures – benefits that persisted at 1- and 3-month follow-up assessments. Pulmonary function in CHF, however, is not fully understood and warrants further investigation. For example, there is evidence that CHF can have a deleterious effect on the lung's ability to clear circulating catecholamines, an abnormality that may be improved by UF [44].

28.1.6 Extracorporeal Ultrafiltration and Renal Function

It has been hoped that UF could improve cardiac function, which in turn would ameliorate the cardiorenal syndrome, thereby improving renal perfusion and GFR, with consequent restoration of sensitivity to diuretics. In their study, Marenzi et al. [45] ultrafiltered 32 patients until their right atrial pressures decreased by 50%. There were decreases in plasma renin activity of 39%, aldosterone 50%, and norepinephrine 47%. These improvements only occurred in patients who had a baseline urine output of <1 L/day, which then increased with UF. Canaud et al. [33] were similarly able to demonstrate improvement in natriuresis. In the 35 patients who survived their acute admission, after continuous UF or slow daily UF was administered, there was an increase in urine output from 0.7 to 2.0 L/day, with sodium excretion increasing from 33 to 54 mEq/day. This is important evidence in support of UF reversing the RAAS and SNS activation associated with kidney and other end-organ hypoperfusion in refractory HF. These observations of renal benefits in the setting of low baseline

urine output may explain the results of a more recent study that was unable to demonstrate improvements. Rogers et al. [46] compared the effect of isolated UF with that of intravenous diuretic therapy on the renal function of 19 patients with decompensated UF. GFR and renal plasma flow were measured (using iothalamate and para-aminohippurate clearances, respectively), and filtration was calculated. At baseline, there was a moderate degree of renal dysfunction, with an average serum creatinine of 1.7 mg/dl, GFR of 48 ml/min, and renal plasma flow of 137 ml/min. There were no significant differences in kidney parameters before or after 2 days of treatment with either therapy or between the two modalities. It is somewhat difficult to extrapolate these findings, as there may have been confounding effects due to many patients having high urine output. Indeed, this study's patient population was not typical of other investigations in that they were diuretic responsive: the furosemide group had urine output of 5,786 ± 2,587 ml/48 h, whereas most other publications have included patients who were diuretic tolerant or oliguric.

A close look at the results of studies using the novel portable device shows that whereas renal function does not improve with the use of UF, it does not often deteriorate either. Multiple studies have demonstrated that patients can undergo extracorporeal UF without a significant increase in serum creatinine or detriment to renal hemodynamics [28–31, 33]. Determining a safe rate of UF, however, can be difficult, and excessive fluid removal can unquestionably lead to kidney injury. In a small study [27] (11 patients) in which 75% of treatments achieved at least 2.5-L of UF, 45% of patients had an increase in serum creatinine of at least 0.3 mg/dl. This is difficult to interpret in that these individuals had severe CHF, six had an initial GFR of <30 ml/min, and five later required dialysis. In a recent retrospective study [47] of relatively high-volume UF compared with usual care (diuretics with or without nesiritide), the fluid removal rate of 325 ± 117 ml/h for 37.5 ± 24.7 h resulted in more patients having an increase in serum creatinine of >0.5 mg/dl (44% vs. £24%). This led to the protocol's UF rate being lowered to 100–200 ml/h.

28.1.7 Extracorporeal Ultrafiltration: Rate of Fluid Removal

With the advent of technology that permits UF to be extended from the few hours typical of hemodialysis to days of continuous therapy, it has become a challenge to prescribe a rate of fluid removal appropriate and safe for the treatment duration. Intravascular fluid depletion is prevented when the UF rate is not greater than the rate at which the intravascular compartment is being refilled from interstitium (PRR). The PRR is driven by Starling forces, varying over the course of fluid removal due to changes in plasma oncotic pressure and the gradient between interstitial and vascular hydrostatic pressures. If the UFR is, or subsequently becomes, higher than the PRR, then the mismatch will lead to intravascular volume depletion, hypotension, and impairment of renal perfusion and function. Equipment has been developed for hemodialysis machines that optically monitor plasma loss. The UFR is then manually or automatically adjusted so as not to exceed a predetermined rate of hemoconcen-

tration or absolute hematocrit level [48]. It has been suggested that this approach also be used as a guide for UF in patients with refractory HF. It should be anticipated that UFR will need to be progressively lowered as the patient approaches the endpoint for extracorporeal fluid removal [35, 49].

28.1.8 Safety of Extracorporeal Therapies

Much of the appeal to the newer, simplified devices for isolated UF is that they can be performed outside ICU and even in outpatient settings, and that their simple design precludes the need for specially trained dialysis staff. Whereas widespread adoption of these techniques would require their use by nondialysis personnel, this is not to say that these modalities are risk free. Complications from UF were cited in two deaths out of 14 patients in a 1-year outpatient report [34]. In the larger UNLOAD trial [31], however, UF therapy was reported to be safe, without increased mortality or hemorrhage complications. This may reflect the newer technology's improved monitoring and safety features, as well as the lower blood flow and UF rates. There is, however, no reason to believe that even sophisticated electronic safety systems are foolproof, and thus we believe that appropriate training be mandatory for all users in topics that include (Table 28.2).

28.1.8.1 Errors in Ultrafiltration

Excess UF can be caused by machine malfunction (i.e., errors by the device incorrectly measuring volume of the ultrafiltrate) or human mistakes in setting flow rates. Many of hemofilters used in UF systems have high water permeability characteristics; small errors in transmembrane pressure can lead to multiple liters of excess fluid removal.

28.1.8.2 Air Embolism

Despite sophisticated safety systems, as in any pumped extracorporeal therapy, clinicians need to be aware of this potentially lethal complication, with problems caused by as little as 30 ml of air.

28.1.8.3 Blood Leak

These are of particular concern at the site of venous blood return, as current technology is relatively insensitive at detecting the small decreases in intraluminal pressure

occurring upon tubing disconnection at low blood flow rates (which are common in HF therapies).

28.1.8.4 Bioincompatibility

Most modern hemofilters are very biocompatible, and the polymeric membranes in particular lead to little activation of the alternate complement system, leukocyte agglutination, and cytokine release. However, it is important for the clinician to determine whether the membrane is made of polyacrylonitrile (PAN) or its derivatives, as they can lead to high bradykinin levels and hypotension in patients being treated with ACEi. In that instance, HF patients would need to have that medication held, changed to alternatives, or treated with different membranes.

28.1.8.5 Other Potential Complications

These include vascular access (such as infections and thromboses) and hemolysis (i.e., from the shear forces of improper tubing or due to overheating from malfunctioning blood warmers). Lastly, despite the high degree of biocompatibility of modern hemofilters the low blood flow rates necessitate anticoagulation.

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