Diabetic nephropathy is a common complication of diabetes and the leading cause of chronic kidney disease in the developed world. Approximately 40% of persons with diabetes develop diabetic nephropathy, manifested as albuminuria and/or decreased glomerular filtration rate. Even mild degrees of albuminuria and decrease in glomerular filtration rate are associated with significantly increased risks of cardiovascular disease, end-stage renal disease, and premature deaths.

Epidemiology of Diabetic Nephropathy

Prevalence of diabetes has reached epidemic proportions in the world. According to the International Diabetes Federation, there were 366 million people with diabetes in 2011, and this is expected to rise to 552 million by 2030 [1]. Most people with diabetes live in low- and middle-income countries, and these countries are anticipated the greatest increase in diabetes over the next decades. In the USA, 11.3% or 25.6 million adults aged 20 years or older had diabetes in 2011, with prevalence increasing in older age groups (26.9% of people aged ≥65 years) [2].

With the global epidemic of diabetes, diabetic nephropathy has become an important clinical and public health challenge. IH de Boer and colleagues estimated the disease burden of diabetic nephropathy in the US adult population aged 20 years or older using data from the National Health and Nutrition Examination Survey [3]. Diabetic nephropathy was defined as diabetes with the presence of albuminuria, impaired glomerular filtration rate, or both. The prevalence of diabetic nephropathy in the US adult population aged 20 years and older was 3.3% (95% confidence interval, 2.8–3.7%) (Table 2.1). The estimated number of persons with diabetic nephropathy in the USA was 6.9 million (95% CI, 6.0–7.9 million) during 2005–2008 [3]. Among the US adults with diabetes, the prevalence of any diabetic nephropathy was 34.5%, the prevalence of albuminuria (with or without impaired glomerular filtration rate) was 23.7%, and the prevalence of impaired glomerular filtration rate (with or without albuminuria) was 17.7% in 2005–2008 (Table 2.1).

The prevalence of diabetic nephropathy in the general population was not available from other countries. However, the prevalence of albuminuria in diabetes patients was reported in various populations. Parving HH et al. reported the prevalence of micro-/macroalbuminuria in a cross-sectional study among 32,208 type 2 diabetes patients from 33 countries [4]. The overall prevalence of microalbuminuria and macroalbuminuria was 38.8% and 9.8%, respectively, in the study population. Asian and Hispanic patients had the highest prevalence of microalbuminuria (43.2% and 43.8%) and macroalbuminuria (12.3% and 10.3%) while Caucasians had the lowest microalbuminuria (33.3%) and macroalbuminuria (7.6%). Twenty-two percent of patients had impaired renal function (glomerular filtration rate <60 mL/min/1.73 m²). Unnikrishnan RI and colleagues reported that the prevalence of overt nephropathy and microalbuminuria was 2.2% and 26.9%, respectively, among type 2 diabetes patients in urban Asian Indians [5]. Among 8,897 Japanese type 2 diabetes patients from 29 medical clinics (i.e., general practitioners) or general/university-affiliated hospitals from different areas, the prevalence of microalbuminuria and decreased glomerular filtration rate (<60 mL/min per 1.73 m²) was 31.6% and 10.5%, respectively [6].

The prevalence of diabetic nephropathy varied among ethnic groups in the US population. The Pathways Study, a cross-sectional analysis among 2,969 primary care diabetic patients of a large regional health maintenance organization observed the racial/ethnic differences in early diabetic nephropathy despite comparable access to diabetes care [7]. Among those without hypertension, microalbuminuria was two-fold greater (odds ratio 2.01; 95% confidence interval 1.14–3.53).
and macroalbuminuria was threefold greater (odds ratio 3.17; 95 % confidence interval 1.09–9.26) for Asians as compared with whites. Among those with hypertension, adjusted odds of microalbuminuria were greater for Hispanics (odds ratio 3.82; 95 % confidence interval 1.16–12.57) than whites, whereas adjusted odds of macroalbuminuria were threefold greater for blacks (odds ratio 3.32; 95 % confidence interval 1.26–8.76) than for whites [7].

The prevalence of diabetic nephropathy has been increasing in the US population. For example, de Boer and colleagues reported that the diabetic nephropathy prevalence increased 18 % from 1988–1994 to 1999–2004 and 34 % from 1988–1994 to 2005–2008 (p=0.003 for trend). Increase in the prevalence of diabetic nephropathy was directly related to the increased prevalence of diabetes, without a change in the prevalence of diabetic nephropathy among those with diabetes [3]. Increases in diabetic nephropathy prevalence were largest for persons aged 65 years or older among whom diabetic nephropathy was most common.

Diabetic nephropathy is the single leading cause of end-stage renal disease, accounting for nearly half of all end-stage renal disease cases [8]. The US Renal Data System reported that the incidence rates (per million population) of end-stage renal disease due to diabetes, hypertension, glomerulonephritis, and cystic kidney disease in 2010 were 152, 99, 22.7, and 8.1, respectively [8]. The prevalence of end-stage renal disease due to diabetes, hypertension, glomerulonephritis, and cystic kidney disease in 2010 were 656, 437, 263, and 85, respectively. Diabetic nephropathy is also the major cause of end-stage renal disease in other western populations [9, 10].

The costs for diabetic nephropathy to individual and society are considerable [8, 11, 12]. In the USA, total Medicare spending in 2010 was $522.8 billion and expenditure for end-stage renal disease was $32.9 billion [8]. This number did not include expenditure for non-Medicare patients, which was additionally estimated to be $14.5 billion [8]. In 2010, overall per person per year costs for patients with chronic kidney disease reached $22,323 for Medicare patients aged 65 and older and $13,395 for non-Medicare patients aged 50–64 in the MarketScan database [8]. Among Medicare patients with both chronic kidney disease and diabetes, per person per year costs for African-Americans reached $28,651 and $24,593 in whites in 2010 [8]. The cost of diabetic nephropathy progression was recently analyzed using information from the Kaiser Permanente Northwest health maintenance organization [12]. Among patients who progressed, annual medical costs were 37 % higher following progression from normoalbuminuria to microalbuminuria ($10,188 vs. $7,424) and 41 % higher following progression from microalbuminuria to macroalbuminuria ($12,371 vs. $8,753).

In summary, the prevalence of diabetic nephropathy is high and increasing in the US and other populations. Diabetic nephropathy accounts for nearly half of all incident cases of end-stage renal disease in the USA. In addition, diabetic nephropathy is associated with increased mortality from cardiovascular disease and all causes. Medicare and non-Medicare spending on diabetic nephropathy and consequent end-stage renal disease is substantial in the USA. Therefore, the prevention of diabetic nephropathy is important to improve health outcomes of persons with diabetes and to reduce the societal burden of chronic kidney disease.

### Table 2.1 Prevalence (95 % confidence interval) of diabetic nephropathy in the US population, NHANES 2005–2008

<table>
<thead>
<tr>
<th>Overall US population</th>
<th>Persons with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥20 years</td>
<td>3.3 (2.8, 3.7)</td>
</tr>
<tr>
<td>Age 20–64 years</td>
<td>1.8 (1.4, 2.1)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>10.7 (9.3, 12.2)</td>
</tr>
</tbody>
</table>

Data are adopted from de Boer IH et al. JAMA. 2011;305(24):2532–9

### Obesity, Metabolic Syndrome, and Diabetic Nephropathy

The growing prevalence of obesity and metabolic syndrome (the cluster of risk factors including hypertension, insulin resistance and dyslipidemia) is the major driving force for the continued increase in the prevalence of type 2 diabetes [13]. These disorders likely interact to exacerbate the kidney damage (Fig. 2.1).

Hypertension associated with obesity, metabolic syndrome, and diabetes may play an important role in the pathogenesis of diabetic nephropathy. Previous studies indicate that central obesity, metabolic syndrome, and diabetes lead to increase of blood pressure [14–17]. Clinical trials also indicate that weight loss reduces blood pressure in most hypertensive subjects and is effective in primary prevention of hypertension [15].

Central obesity induces hypertension initially by increasing renal tubular reabsorption of sodium and causing a hypertensive shift of renal-pressure natriuresis through multiple mechanisms including activation of the sympathetic nervous system and renin–angiotensin–aldosterone system, as well as physical compression of the kidneys [18, 19]. The hypertension, as well as the increases in intraglomerular capillary
pressure, and the metabolic abnormalities (e.g., dyslipidemia, hyperglycemia) likely interact to accelerate renal injury. Similar to obesity-associated glomerular hyperfiltration, renal vasodilation and increases in glomerular filtration rate and intraglomerular capillary pressure, and increased blood pressure also are characteristics of diabetic nephropathy [20]. Increased systolic blood pressure further exacerbates the disease progression to proteinuria and a decline in glomerular filtration rate leading to end-stage renal disease [21]. Multiple studies have clearly shown the protective effect on the kidneys of reducing blood pressure in diabetes. Furthermore, tight blood pressure control in diabetic patients may slow progression of nephropathy to a greater extent than tight control of blood glucose [22].

Hyperfiltration and increased glomerular filtration rate are the common early renal changes associated obesity and diabetes [20, 23]. The underlying mechanism may include increased salt reabsorption by the proximal tubule or loop of Henle, leading to tubuloglomerular feedback-mediated reduction in afferent arteriolar resistance, increased intraglomerular capillary pressure, and increased glomerular filtration rate [24]. The increased glomerular filtration rate initially serves as a compensatory response that permits restoration of salt balance but eventually contributes to renal injury, especially when blood pressure is elevated. Tubuloglomerular feedback-mediated dilation of afferent arterioles and attendant impairment of renal autoregulation permit increases in blood pressure to be transmitted to the glomerular capillaries causing even greater increases in intraglomerular capillary pressure and glomerular injury than would occur with comparable increases in blood pressure in kidneys of non-obese, nondiabetic subjects [25]. In addition, hyperglycemia may also contribute to the development of glomerular hyperfiltration through mechanisms similar to those occurring in obesity. Reduced delivery of salt to the macula densa, as a consequence of increased proximal reabsorption of glucose and sodium, may reduce afferent arteriolar resistance and increase intraglomerular capillary pressure and glomerular filtration rate via attenuated tubuloglomerular feedback [26–28]. Also, afferent vasodilation and efferent vasoconstriction in response to circulating or locally formed vasoactive factors (e.g., angiotensin II) produced in response to hyperglycemia or shear stress may promote diabetic glomerular hyperfiltration [29, 30]. Even though the mechanisms explaining the increase in glomerular filtration rate in diabetes and obesity uncomplicated by diabetes may be similar, the factors that trigger tubuloglomerular feedback-mediated renal vasodilation and glomerular hyperfiltration are different. Some studies suggest that hyperglycemia, obesity, and hypertension may have at least partially additive effects on glomerular hemodynamics [25]. For example, mice lacking the gene for the melanocortin-4 receptor are obese, hyperinsulinemic, and hyperleptinemic but normotensive at 55 weeks of age [32]. These animals have moderately increased glomerular filtration rate and only modest albuminuria compared with WT mice; however, their glomerular filtration rate and albuminuria increased further when rendered hypertensive following treatment with N(G)-nitro-L-arginine methyl ester. These data suggest that elevations in blood pressure exacerbate obesity-related glomerular hyperfiltration and albuminuria, further supporting the concept of an additive, or perhaps synergistic, effect of various components of obesity, metabolic syndrome, diabetes, and hypertension on glomerular hemodynamics. In addition, obesity, metabolic syndrome and diabetes are states of low-grade inflammation and oxidative stress, all of which may lead to kidney damage, progressive loss of nephrons, and decline in glomerular filtration rate over time. Another element of the
metabolic syndrome, hyperlipidemia, has been linked to reductions in glomerular filtration rate in diabetic nephropathy, especially in the latter stages of the disease. Numerous clinical trials have pointed to the importance of lipid control in preserving glomerular filtration rate in patients with diabetes [33]. However, further studies are needed to determine if the beneficial effects of lipid-lowering agents in diabetic nephropathy are due to improvement in the lipid profile or if there are other renoprotective effects.

Diabetic nephropathy and elements of the metabolic syndrome including insulin resistance and hyperinsulinemia are associated with the development of microalbuminuria early in the disease process [34, 35]. The development of microalbuminuria in diabetic nephropathy was traditionally thought to stem from damage to the glomerular filtration barrier as a consequence of increases in blood pressure which are transmitted to the glomeruli, raising intraglomerular capillary pressure and glomerular filtration rate, and/or hyperglycemia-associated inflammation and oxidative stress [34]. An alternative explanation is that diabetes also impairs proximal tubular reabsorption of albumin which filters across the glomerular barrier [36]. Hyperlipidemia is known to be a risk factor for the development of albuminuria in patients with diabetes [37].

Diabetes and obesity are both states of low-grade inflammation associated with macrophage infiltration into the adipose tissue and the kidney. The infiltrating macrophages become a source of a whole host of proinflammatory cytokines including tumor necrosis factor-α, interleukin-6, and monocyte chemoattractant protein-1 [38]. Furthermore, increased adiposity triggers the release of adipokines into the circulation that in turn may cause renal injury via production of reactive oxygen species. Persistent hyperglycemia also activates vasoactive hormonal pathways including the renin-angiotensin system and endothelin. These in turn activate common second messenger signaling pathways such as protein kinase C and mitogen-activated protein kinase and transcription factors such as nuclear factor-κB that lead to the alteration in gene expression of a plethora of growth factors and cytokines such as transforming growth factor-β. Transforming growth factor-β is a key player in promoting podocyte apoptosis, mesangial cell proliferation and extracellular matrix synthesis, and cellular events that are important in the development of diabetes and obesity-associated glomerular injury [39]. Hyperglycemia and associated metabolic disturbances also cause mitochondrial dysfunction and enhanced generation of reactive oxygen species, which directly alter the expression of key proteins and cytokines causing renal injury. Kidneys of obese individuals often have glomerular/mesangial lipid deposits (foam cells) present, which supports the concept of lipotoxicity, i.e., lipid-induced renal injury [25]. One of the mechanisms by which hyperlipidemia promotes glomerular injury is through renal upregulation of sterol-regulatory element-binding proteins, which in turn promotes podocyte apoptosis and mesangial cell proliferation and cytokine synthesis.

In summary, data from basic and clinical studies suggest that obesity, hypertension, hyperglycemia, hyperlipidemia, and other elements of the metabolic syndrome are highly interrelated and contribute to the development and progression of diabetic nephropathy. Therefore spontaneously targeting at prevention and treatment of obesity, metabolic syndrome, and diabetes may help to maximize the reduction of associated kidney damage.

**Geriatrics and Diabetic Nephropathy**

Increase in the prevalence of diabetic nephropathy also derives directly from the growth in the prevalence of diabetic nephropathy among individuals aged 65 years and older. Individuals older than 65 years are disproportionately affected by diabetes and related end-stage renal disease. According to data from the National Health and Nutrition Examination Survey, diabetes prevalence was 26.9 % among people aged ≥65 years [2, 40]. The prevalence of diabetic nephropathy was increased from 7.1 % in 1988–1994 to 8.6 % in 1999–2004 and 10.7 % in 2005–2008 among individuals aged 65 years and older [3, 41]. Recent data also revealed that the adjusted point prevalence rates per million population of reported diabetes-related end-stage renal disease for individuals aged 60–69 and ≥70 years were 410.3 and 475.7 in whites and 1439.9 and 1471.5 in African-Americans [8, 42].

Although diabetic nephropathy represents a major health threat for the aging American population, chronic kidney disease care in elderly subjects with diabetes is suboptimal. Patel and colleagues [43] reported that only 7.2 % of 6,033 veterans (mean age 66±11 years) with diabetes and chronic kidney disease underwent evaluation by a nephrologist during a 5-year study period. Furthermore, clinical guidelines developed by the American Geriatrics Society Panel on Improving Care for Elders with Diabetes have not specifically focused on the subject of advanced chronic kidney disease in older patients with diabetes [44].

One of the challenges of managing the elderly with diabetic nephropathy is that they may develop more complications, especially heart, eye, and peripheral vascular diseases. In its 2011 National Diabetes Fact Sheet, the Centers for Disease Control reported that in 2004, heart disease and prior stroke were, respectively, noted on 68 % and 16 % of diabetes-related death certificates among people aged 65 years or older [2]. Moreover, the CDC indicated that, in 2005, 27 % of adults with diabetes who were 75 years or older reported some degree of visual impairment compared with 15 % of diabetic patients who were between 18 and
44 years of age [2]. Individuals aged 65 years or older account for 55% of diabetic subjects who had nontraumatic lower extremity amputations [45]. Caring for elderly patients with diabetic renal disease imposes a huge financial burden on governments and family members. For example, the American Diabetes Association indicated that the total estimated cost of diabetes in 2007 was $174 billion, including $58 billion to treat diabetes-related chronic complications [46].

Diabetic nephropathy in the elderly is mainly due to type 2 diabetes and its distribution is uneven among racial groups. American-Indians, African-Americans, and Mexican-Americans have a greater incidence than Caucasians by as much as three to one depending on the minority cohort selected for comparison [42]. Genetic susceptibility, suboptimal care in minority groups, delayed diagnosis of type 2 diabetes, and environmental factors are reasons proposed to explain such disparity. The histologic diagnosis of diabetic nephropathy in older patients may be challenging because mesangial matrix expansion and thickening of the glomerular basement membrane have also been attributed to kidney senescence [47]. Likewise, tubular atrophy and interstitial fibrosis may be aging related or due to chronic inflammation or vascular disease [48]. Elderly patients with type 2 diabetes may have renal ischemia due to renal artery stenosis. Sawicki and colleagues [49] reported that the prevalence of renal artery stenosis in subjects with type 2 diabetes and hypertension was greater than 10%. Bilateral artery stenosis was found in 43% of these cases.

Nearly all studies demonstrating beneficial effects of metabolic and blood pressure controls on diabetic kidney disease have been performed in young to middle-aged cohorts. Importantly, the management of diabetic kidney disease in older people is frequently based on extrapolations of data gathered in selected and motivated younger people. Moreover, people older than 70 years have been virtually excluded in trials supporting major US practice guidelines for the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in chronic kidney disease. In managing diabetes and diabetic nephropathy in the elderly, clinicians should keep in mind several key points. (1) Elderly diabetic patients constitute a diverse group expressing various clinical and functional situations. (2) The American Geriatric Society Panel on Improving Care for Elders with Diabetes recommends that treatment of elderly patients with diabetes focus on specific problems and priorities [50]. (3) The American Geriatric Society has also introduced the concept of time horizon for the benefits of certain treatments. Glycemic control may take as long as 8 years to have positive results on microvascular complications. Benefits of good blood pressure and lipid control may not be noticeable before 2 or 3 years [51]. (4) Many elderly patients with diabetes are frail and are also at greater risk for developing several common geriatric syndromes, such as depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain. The Assessing Care of Vulnerable Elders (ACOVE) project defines a frail elderly patient as a vulnerable person who is older than 65 years and is at increased risk of death or functional decline within 2 years [51]. (5) In consequence, renoprotection in a geriatric population should be tailored according to patients’ autonomy, degree of frailty, life expectancy, comorbidity index, and the stage of diabetic nephropathy. (6) Elderly diabetic patients may be susceptible to nephrotoxic agents such as radiocontrast; specific caution should be taken in preventing and monitoring radiocontrast-induced nephropathy.

Caring for geriatric patients afflicted by diabetic nephropathy requires a long-term commitment by patients and health care professionals. This care is better accomplished by a team consisting of a primary care physician or geriatrician, an endocrinologist, a nephrologist, a cardiologist, an ophthalmologist, a podiatrist, a nutritionist, and a nurse educator. Much effort should be made to diagnose type 2 diabetes early and educate diabetic subjects and primary care providers about the effectiveness of glycemic control and blood pressure lowering to prevent or delay diabetic nephropathy and end-stage renal disease.

References
