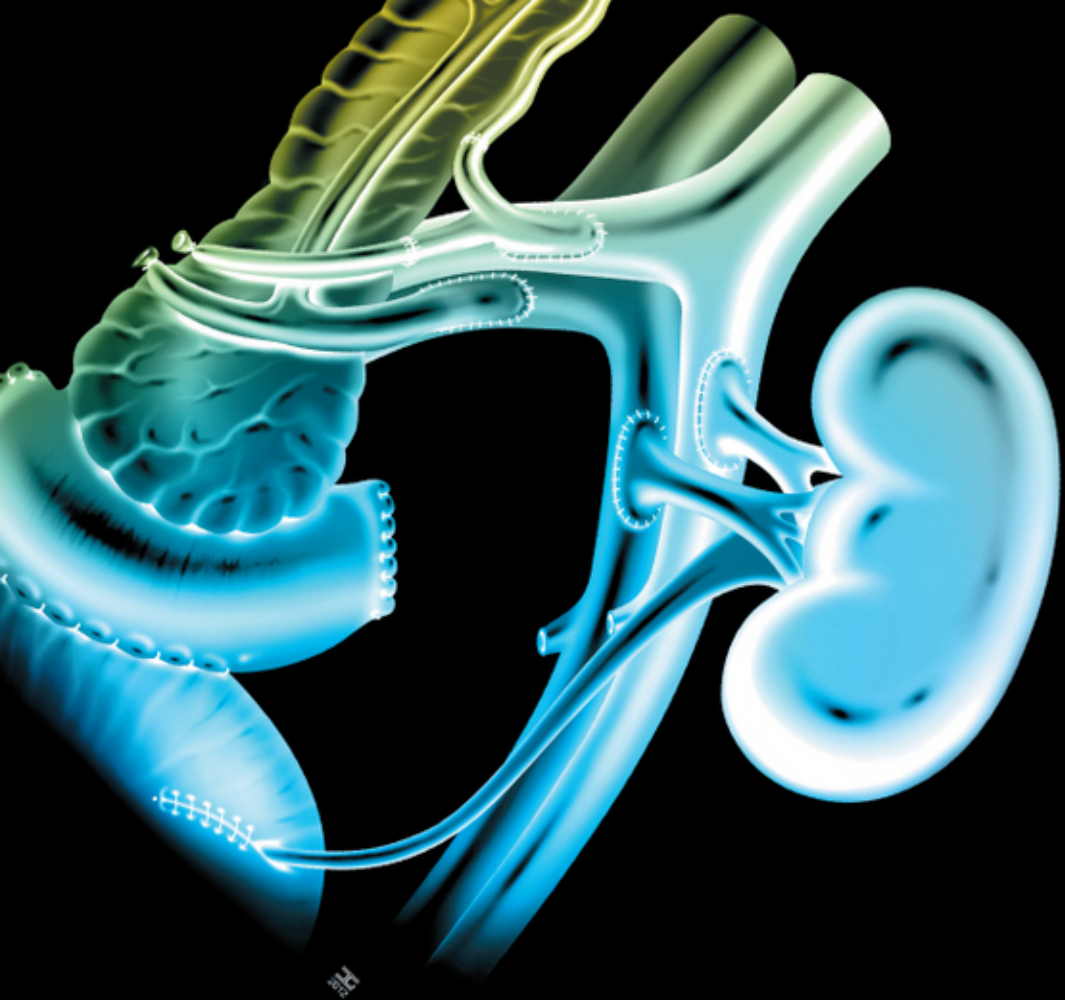

Diabetes and Kidney Disease

Edited by **Gunter Wolf**

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Preface

In 1801 the English physician Erasmus Darwin (1731–1802) recognized some patient with diabetes whose urine could be coagulated by heat, indicating proteinuria, and associated this finding with dropsy and general swelling. In 1936, the seminal discovery by Kimmelstiel and Wilson showed the morphologic changes by the description of glomerular lesions in diabetics with nephropathy. Today, diabetic renal disease is now worldwide the major cause of end-stage renal failure. Besides the uncountable individual suffering of patients with diabetic nephropathy, there is an increasing economical burden for such patients. Patients with diabetic renal disease have a very high cardiovascular morbidity and mortality. The spectrum of patients with diabetes and renal disease has completely been changed: 25 year ago diabetic nephropathy was a feature of patients with type 1 diabetes, type 2 diabetes was considered a relatively rare even a "normal" process of aging. Now, the increasing pandemic of patients with type 2 diabetes makes this group the largest suffering from diabetic nephropathy, albeit the incidence of patients with type 1 diabetes has also increased in recent years. The current book provides an up-to-date review of many aspects, not only of diabetic nephropathy but of the more complex relationship between the kidney and diabetes. All the contributors to this book are experts in their fields. It covers a wide range of topics from epidemiology, pathophysiology and genetics to concrete treatment recommendations and algorithms for the practicing physician. Furthermore, the reader will also find chapters on topics normally not found in standard books on diabetic nephropathy, such as diabetic nephropathy in children, the relationship between retinal and renal diabetic complications and diabetes, bone, and the kidney. Therefore, the book is not only for the expert nephrologists and diabetologists, but also for general internists and primary care physicians. The authors have put an enormous amount of work into this book. They would be happy if this contribution could help to better care for patients with diabetes and renal affections. Many thanks to Wiley-Blackwell (especially Jennifer Seward) for agreeing to start this ambiguous projects and for the continuous help while carrying it out.

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Part I

Introduction and Pathophysiology

Chapter 1

History of diabetic nephropathy: a personal account

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Introduction

Type 2 diabetes and diabetes-associated nephropathy have currently become worldwide epidemics, but they are by no means completely novel diseases. No unequivocal description of diabetes mellitus is found in the *Corpus Hippocraticum* or in the subsequent European medical literature; in Europe it was centuries before the sweet taste of urine in subjects with diabetes was described by Thomas Willis in 1674, and for sugar as the responsible chemical compound to be identified in the urine by Matthew Dobson in 1776.

In contrast, an impressive body of evidence documents the common presence of diabetes, presumably the result of genetics and lifestyle, in ancient India and China, and later in Arabia and Iran, pointing to the diagnostic acumen of the physicians of these countries in the distant past.

The characteristic "sweet urine" in diabetes was mentioned in the Indian Sanskrit literature covering medicine and presumably written between 300 BC and AD 600 [1]. These ancient physicians mentioned "sugar cane urine" (*Iksumeha*) or "honey urine" (*Madhumeha* and *Hastimeha*) as well as "urine flow like elephant in heat". They noted that ants and insects would rush to such honey urine—strongly suggesting that this observation was the consequence of glycosuria and diabetes. This condition was correctly ascribed to excessive food intake and insufficient exercise; the authors also mentioned the cardinal symptoms: polyphagia, polyuria, and polydipsia; even the secondary sequelae of diabetes, such as abscess formation, carbuncles, lassitude, and floppiness, were reported. Proposed interventions included the very rational advice of active physical exercise and long marches. In China, the oldest description of diabetes as "Xiaoke" (wasting thirst or emaciation and thirst) syndrome can be traced back more than 2000 years to the *Yellow Emperor's Classic of Internal Medicine*. Ancient Chinese physicians had

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noted that "sweet" urine was a manifestation of a disease characterized by hunger and polyphagia, by thirst and polydipsia as well as by polyuria. In addition, Chinese literature has described the characteristic complications of skin abscesses, infections, blindness, turbid urine, and edema. The pathogenesis of this condition was ascribed to improper fatty, sweet, and excessively rich diet. Interventions with diet therapy, exercise, herbal medicine, and acupuncture were proposed.

In Arabian (and Persian) literature diabetes, called "Aldulab" (water wheel), as a disease characterized by polydipsia, polyuria, and marasm was described by the scholar Abū Alī al-Husain ibn Abdullāh ibn Sīnā (Avicenna AD 980–1037) [2]. It is also of interest that Maimonides, a Jewish physician who emigrated from Toledo to Egypt commented on a disease in Egypt of fat, elderly men characterized by polyuria and rapid physical decay; he stated that he had never seen this condition in his native Toledo, illustrating the apparent rarity of diabetes in Europe at that time. Subsequently, in medieval Europe diabetes definitely existed, at least in the upper class, as suggested by the available descriptions of the terminal diseases of Henry VIII of England, Louis XIV of France, August der Starke of Saxony, and others. However, it was centuries before the sweet taste of urine in diabetes was described by Thomas Willis (in 1674) and before sugar in the urine was identified as a distinct chemical substance by Matthew Dobson (in 1776).

Nevertheless some key observations had been made very early. Domenico Cotugno (*De Ischiade Nervosa*, Commentarius Gräffer, Vienna, 1770) described what in retrospect presumably was proteinuria in a nephrotic patient with coagulable urine; later proteinuria was described in diabetic patients on many occasions.

In the 19th century, with increasing wealth and an increasing prevalence of obesity, a progressive increase in the frequency of type 2 diabetes was noted. In type 2 diabetes, proteinuria was repeatedly described in the 19th century, but end-stage renal disease (ESRD) was apparently uncommon in type 2 diabetic patients, presumably because most patients died from cardiovascular events or other (mostly infectious) complications before the manifestations of advanced kidney disease appeared. The failure to recognize renal disease as a sequela of diabetes is illustrated by the fact that Friedrich Theodor von Frerichs had written a brilliant description on the pathophysiology underlying proteinuria and kidney disease [3]; yet, disappointingly, in his encyclopedic book on diabetes (*Über den Diabetes*, Berlin, 1884, Verlag August Hirschwald), the standard book on diabetes in the German literature, he mentioned only tubular and interstitial lesions of the kidney, and did not mention the glomeruli at all. Surprisingly, he states that the kidneys of diabetic patients are usually small and that interstitial tissue is increased.

Later, Armanni described vacuolization in proximal tubular epithelial cells with subnuclear deposits of glycogen and fat in the kidneys of diabetic patients (Armanni–Ebstein lesion) [4].

It was Griesinger who first provided a systematic analysis of kidney morphology [5] describing, 64 autopsies of diabetic individuals. This analysis was based on the available literature and included seven of his own patients whom he had treated up to this point in Tübingen, reflecting the relative rarity of diabetes at that time. Fifty-eight per cent of the patients were between 20 and 40 years, and he stated that diabetes was rare elderly people. He stated,

> the opinion that the kidneys are infrequently affected in this disease and changes of the kidneys, if any, would consist only in true hypertrophy is wrong. In any case, these diseases of the kidneys complicate diabetes in a remarkable fashion and are the trigger for

> a series of pathological processes in many advanced cases. The frequency of these renal lesions is in line with the frequent finding that many diabetic patients have protein in their urine, mostly not constantly, but often at times copiously. . . . there are, however, cases where – with the onset of albuminuria – sugar disappears from the urine. In these cases usually morbus Brightii takes its known course with generalized hydrops etc. In the majority of cases, moderate albuminuria coexists with glycosuria . . . .

Another description of kidney lesions was provided by Abeille [6], who stated,

> most frequently one finds only simple hypertrophy of the kidney at autopsy . . . in some cases these organs were the seat of Bright's disease, i.e. albuminuria associated with glucosuria . . . it has been stated that albuminuria documents regression of the disease . . . to the contrary it is the result of functional trouble or evidence of structural lesions as a result of Bright's disease.

What had been widely known in the 19th century was the high prevalence of albuminuria in diabetes; characteristic is the observation of Schmitz, who stated that in 1200 diabetics he found different amounts of urinary protein in 824 cases; he stated "I never saw uremia to occur in an albuminuric diabetic patient, presumably because they died beforehand from cardiovascular causes" [7]. Naunyn [8] had an interest in diabetes, and the pancreatic secretion of a glycemia-lowering substance had been discovered by Mehring and Minkowski at his clinic in Strasburg. Naunyn found albuminuria in 34 of 134 young diabetic patients, of whom six patients excreted >1 g of albumin per day. He also confirmed the above-mentioned observation that glycosuria disappeared when proteinuria increased. The same observation was also made by van Noorden [9].

At this time, a key finding for the understanding of diabetic nephropathy was the discovery by Etienne Lancereaux in 1880 that there are two types of diabetes, i.e. type 1 (diabete maigre) and type 2 (diabetes obese).

It is of interest that in the 19th century and even in the first decades of the 20th century, chronic kidney disease in diabete patients is not mentioned at all in major textbooks on kidney disease, e.g., by Volhard or Fishberg. Franz Volhard in his ground-breaking description of kidney disease [10] completely ignored diabetes as a cause of kidney disease in this seminal work. Even later in Fishberg's book [11], the reference to diabetes is limited to diabetic coma and to prerenal azotemia; he stated "nephritis is extremely rare in diabetes and if it occurs, it is not the result of excessive 'work' of the kidney, but is caused by accompanying problems, e.g., tuberculosis, cardiac disease, arteriosclerosis." In summary, apart from recognizing diabetes as a cause of proteinuria, diabetes was not on the radar of most physicians with an interest in nephrology. Even among diabetologists, nephropathy was not at the forefront of interest until approximately 20 years after the introduction of insulin treatment—the latency until severe renal problems arise.

Étienne Lancereaux (1829–1910) in his paper "Le diabete maigre: ses symptomes, son evolution, son prognostie et son traitement" had introduced the concept of "diabète maigre" and "diabète obese" in 1880. In retrospect, it is of interest to note that the breakthroughs achieved by the early descriptions of Kimmelstiel [12] and of Allen [13] almost all concerned patients with type 2 diabetes with a relatively long duration of the disease, presumably because type 1 diabetic patients had often succumbed before they had time to develop glomerulosclerosis. After insulin became available, it usually took up to two decades for terminal kidney disease to develop. Subsequently, however, in the 1960s and 1970s, the focus of

attention in clinical and anatomical studies on diabetic nephropathy was on type 1 diabetic patients who had at this point in time lived long enough to develop advanced diabetic nephropathy, which takes more than 10 to 20 years to develop.

All this started with the brilliant description of intercapillary lesions in diabetic patients by Paul Kimmelstiel and Clifford Wilson in 1936 [12]. Kimmelstiel was born to a Jewish merchant family in Hamburg and was associate professor at the Department of Pathology in Hamburg–Eppendorf. In 1933 he emigrated to the USA and worked at the Harvard Institute of Pathology, where he met Clifford Wilson with whom he described the intercapillary changes of the glomerulus in diabetes mellitus in a landmark publication. He studied the kidneys of eight patients who had presented with massive edema (out of proportion to existing cardiac failure) with hypertension of the "benign" type and with a history of long-standing diabetes. The glomeruli were regularly hyalinized (staining for fat, but only exceptionally yielding double refraction) and the number of capillaries was reduced. Often a ring of open capillaries surrounded central hyaline masses. A very high degree of "arteriosclerosis" with fatty degeneration was seen in the arterioles. Although the basement membrane of the capillaries was preserved for a long time, it eventually changed and the capillary walls thickened homogeneously near the central hyaline masses; the capillaries collapsed and finally merged with the central hyaline. There was no definite proof of an inflammatory process. He gave a very detailed account of the differences between this novel lesion and intercapillary glomerulonephritis as described by Fahr, an extracapillary glomerulonephritis emphasizing the striking hyaline thickening of the intercapillary connective tissue of the glomerulus. The non-inflammatory degenerative nature of the lesion suggested to him that both arteriosclerosis and diabetes were involved in its causation, and prompted him to coin the novel term "intercapillary glomerulosclerosis". Interestingly, in 1934, MacCallum had described glomerular lesions resembling Kimmelstiel–Wilson lesions; however, he failed to make the connection to diabetes and ascribed this to "the ageing process of the glomerulus".

Kimmelstiel's concept of a diabetes-specific glomerular disease was confirmed and more firmly identified as a sequela of diabetes by Allen in New York [13]. He popularized the concept of a specific glomerular lesion caused by diabetes, based on autopsies of a much larger cohort of 105 diabetic patients, 34% of whom showed this specific lesion. He noted that it was virtually specific for diabetes (which is no longer absolutely true today, e.g., it may be seen in κ-light chain nephropathy etc.).

In the early 1970s, more and more diabetic patients were started on hemodialysis; these were initially almost exclusively young patients with type 1 diabetes (interestingly the first type 1 diabetic patient who started hemodialysis in Downstate Medical Center Brooklyn as a compassionate case was the husband of a dialysis nurse). The initial outcomes were most unsatisfactory [14], and in these days it was stated "Diabetic nephropathy is irreversible in humans; no case of recovery or cure has been reported in the literature; once the clinical signs of nephropathy have become manifest, the natural course is inexorable progressive to death" [15]. The helpless situation of the physician at this time was illustrated by the statement ". . . the renal failure will progress in spite of all forms of therapy. In the terminal stage the physician's role will mostly be of psychological nature, attempting to maintain a reasonable degree of optimism in the patient . . ." [16]. It was only later on that the major proportion of patients with advanced diabetic nephropathy developing terminal renal failure suffered from type 2 diabetes. In retrospect it is amusing that we [17] had great

difficulty to get our paper published which indicated a "similar risks of nephropathy in patients with type 1 or 2 diabetes mellitus"—this statement was based on the finding that the cumulative risk of proteinuria after 25 years of diabetes mellitus was 57% in type 2 diabetes and 46% in type 1 diabetes. Obviously it was felt that renal complications were mostly restricted to patients with type 1 diabetes. In the early 1970s, when diabetics first started on dialysis, it was mainly relatively young type 1 diabetic patients. Today this has become a small minority (2.2% of diabetic patients on hemodialysis in Germany [18] while type 1 plus type 2 diabetes currently accounts for 49.6% of all hemodialysis patients in Germany [18].

The progress in understanding the underlying pathophysiology of diabetic nephropathy, the introduction of treatments to prevent, stop, or at least retard progression of diabetic nephropathy, and the progressively better outcomes of the treatment of end-stage diabetic nephropathy by dialysis or transplantation has been an impressive success story in recent decades. For reasons of space we focus on interventions that interfere with the progression of diabetic nephropathy.

A major initial step forward was the introduction of quantitative morphology by Osterby in Aarhus. She showed that in the early stage of diabetes the basement membranes were normal (thus excluding the then popular hypothesis of a pre-existing capillary defect predisposing to diabetic nephropathy). She concluded that such changes of the capillary membrane were the consequence of hyperglycemia—thus opening the window to prevention by achieving near-normal glycemia [19]

In those days, the notion prevailed that diabetic nephropathy was a unidirectional process with continuous downhill deterioration. The observation of Fioretto [20] provided evidence that the lesions of diabetic nephropathy are potentially reversible after pancreas transplantation. Using quantitative methods to evaluate glomerular morphology, she studied at baseline and after 5 and 10 years eight microalbuminuric type 1 diabetic patients who had received a pancreas transplant. Before transplantation median albuminuria was 103 mg/day; it had decreased to 20 mg/day 10 years after pancreas transplantation. Although 5 years after pancreas transplantation the thickness of the glomerular and tubular basement membranes had not changed, after 10 years the thickness of the glomerular basement membrane had significantly decreased from 570 ± 64 nm to 404 ± 38 nm; the mesangial fractional volume had decreased as well (baseline 0.33 ± 0.007; at 10 years 0.27 ± 0.02 $p = 0.05$), thus documenting that in principle the lesions of diabetic nephropathy are even reversible with longstanding normoglycemia.

In an important later study on the morphology underlying progression, Osterby showed that the onset of proteinuria is associated with widespread disconnection of the junction between the proximal tubuli and the associated glomerulus, leading to atubular glomeruli and loss of glomerular function [21]. She also showed that in type 2 diabetes, the lesions are more heterogeneous and resemble the typical histological pattern of type 1 diabetic lesions only in a minority of cases [22].

In the clinical arena, the door for early diagnosis of glomerulopathy was opened with the availability of an immunoassay for urinary albumin in low concentrations [23]. The establishment of this novel methodology permitted Keen's collaborator Giancarlo Viberti [24] to examine 87 patients with insulin-dependent diabetes mellitus in whom the urinary albumin excretion rate (AER) was measured in 1966/67; at follow-up after 15 years, 63 of the original cohort were alive and were restudied; the others had died in between. The development of albustix-positive proteinuria was related to past AER values in 1966/67: the advanced stage of proteinuria had developed in only two of 55 patients with an initial AER <30 mg/min, but in

seven of eight patients with AER 30–140 mg/min—illustrating the power of "microalbuminuria" to predict the evolution of clinical diabetic nephropathy. With foresight he postulated that such levels of AER are potentially reversible, pointing to the possibility of the prevention of diabetic kidney disease. This key observation was quickly confirmed by other authors, specifically Mogensen [25] and Parving [26].

Furthermore, Mogensen [27] provided the evidence that in type 2 diabetic patients microalbuminuria was predictive of renal and cardiovascular risk and stated that "screening for microalbuminuria in such population will identify high risk patients with abnormalities that are potentially treatable." Today, monitoring of urine albumin excretion is part and parcel of the standard of care for diabetes and has done much to increase awareness of the renal (and cardiovascular) complications of diabetes.

The potential significance of albuminuria soon broadened beyond the issue of kidney disease with the proposal of the "Steno hypothesis" that "albuminuria in type 1 diabetes is not only an indication of renal disease, but a new independent risk marker of proliferative retinopathy and macroangiopathy as a result of a generalized abnormality ("leakiness") of vascular beds [28].

It has recently been argued that the concept of "micro"-albuminuria should be abandoned and that urine albumin concentration should be treated as a continuous variable which reflects the progressive increase in both renal and cardiovascular risks in patients with progressively higher concentrations of urinary albumin [29], but because of the inertia of medical nomenclature the term microalbuminuria persists to this day.

Despite the early documentation of Mogensen that microalbuminuria predicts clinical proteinuria and early mortality, the common view was that the risk of developing nephropathy and uremia was very high in type 1 diabetes, but substantially less elevated in type 2 diabetes. Since in those days type 2 diabetes occurred mostly in elderly individuals with limited life expectancy and high cardiovascular mortality, the true renal risk in type 2 diabetes had been underestimated, because most patients did not survive to experience advanced renal complications. The study of Hasslacher [17] addressed this issue by evaluating all patients with type 2 and type 1 diabetes without severe secondary disease who were followed in the university hospital in Heidelberg between 1970 and 1985. After 25 years it was found that the cumulative risk of proteinuria was virtually identical, i.e., 57% in type 2 and 47% in type 1 diabetes; the cumulative risk of renal failure 5 years after the onset of proteinuria was 63% and 59% respectively. This finding documented that in patients with type 2 and type 1 diabetes the renal risk is similar.

Apart from progress in the understanding of the diagnostic value of albuminuria and of the underlying renal pathology, enormous progress had also been made in the prevention and treatment of diabetic nephropathy. One major step concerned glycemic control. This was first evaluated in type 1 diabetes by the landmark prospective controlled Diabetes Control and Complications study [30, 31] and by the subsequent observational Epidemiology of Diabetes Interventions and Complications follow-up study [32]. Young type 1 diabetic patients with no or mild retinopathy had been randomized to conventional or intensified glycemic control (insulin pump or three daily injections). The study clearly documented the benefit of intensive control: the onset of albuminuria >40 mg/day was lower by 39% and onset of proteinuria by 54% [22]. The detailed analysis of the progression of diabetic nephropathy showed that the beneficial effect on albuminuria was independent of blood pressure, age, diabetes duration, baseline glycosylated hemoglobin (HbA1c), and retinopathy [33]. The controlled

trial was followed by an observational follow-up in which glycemic control was no longer significantly different between the two arms of the study population. Nevertheless, 22 years after the start of the study a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 was observed in 24 patients in the group with initially intensified versus 46 patients with initially standard treatment [32]. Indeed today, given better glycemic control and more efficient blood pressure-lowering agents including renin–angiotensin system (RAS) blockade, type 1 diabetic patients in most countries have become a small minority of the total number of diabetic patients requiring treatment for end-stage kidney disease.

A second quantum leap forward was the introduction of antihypertensive treatment. In the past it was thought that blood pressure elevation was necessary to guarantee adequate renal perfusion. I couldn't find a reference to this in the literature, but I learned from Carl Erik Mogensen that as a young physician he tried to lower blood pressure in a type 1 diabetic patient with the newly introduced beta-blockers, although this had been strictly forbidden by the chief of department—obviously because of the then frequent side effects. Against the advice of the authorities, he gave antihypertensive treatment and some years later he could show that this had reduced the progressive loss of GFR in type 1 diabetic patients. This prompted him to carry out a short-term study and a long-term study [34, 35] in six young male diabetic patients with intermittent albustix-positive proteinuria and in 10 young male diabetics with constant proteinuria—a ridiculously small group compared with today's mega trials; he measured glomerular filtration and plasma flow as well as urinary albumin excretion using exact techniques. In the patients without constant proteinuria, no deterioration in renal function was noted during a mean control period of 32 months. In contrast, in patients with constant proteinuria, the decrease in GFR and renal plasma flow (RPF) was 0.91 mL/min/month ± 0.68 and 4.38 mL/min/month ± 3.23 respectively. A positive correlation was found between the rate of decrease in GFR on the one hand and diastolic pressure and albuminuria on the other. After this pioneer study, Mogensen performed an interventional uncontrolled study [35] in six insulin-dependent, juvenile-onset diabetic patients. Blood pressure was lowered from an average of 162/103 mmHg to a mean level of 144/95 mmHg for 73 months. The diastolic pressure was lowered to 95 mmHg, the GFR loss was 1.23 mL/min/month in the run-in period and reduced to 0.49 mL/min/month on antihypertensive treatment; finally a dramatic 95% decrease in albuminuria was seen. This led Mogensen to firmly conclude that antihypertensive treatment slows the decline in renal function in diabetic nephropathy. Based on this finding, which was also reported by Parving [26, 36] at the same time, antihypertensive treatment has become a bedrock of today's management of diabetic nephropathy.

The third advance in the management of diabetic nephropathy was the introduction of RAS blockade. With the availability of captopril and subsequently of alternative angiotensin-converting enzyme (ACE) inhibitors, in a number of studies different investigators documented the beneficial acute and intermediate-term effect of RAS blockade on lowering albuminuria/proteinuria over and above what was seen with alternative antihypertensive agents [37–42] in relatively small cohorts.

A sufficiently large prospective study on nephropathy of type 1 diabetes was performed by a collaborative study group. The effect of captopril was compared with placebo in 409 patients with proteinuria >500 mg/day and serum creatinine >2.5 mg/dL. Doubling of s-creatinine was significantly less frequent in patients on captopril (n = 25) versus placebo (n = 43); furthermore, a small but significant difference in the rate of decline in creatinine

clearance was found: 11 ± 21% per year in the captopril versus 17 ± 20% in the placebo group, thus documenting that captopril protects against deterioration in renal function in insulin-dependent diabetes with nephropathy significantly more effectively than blood pressure control alone. An impressive 50% reduction in the combined end point of death, dialysis, and transplantation was noted on captopril [43]. Remission of nephrotic-range proteinuria was more frequent in the nephrotic probands of the captopril group (7/42 versus 1/66 in the placebo group; in parallel, GFR by iothalamate clearance declined significantly only in the group which had not achieved remission, thus documenting that captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy significantly more effectively than blood pressure control alone [31]. A further follow-up study compared two levels of target blood pressure [mean arterial pressure (MAP) 92 mmHg versus 100–107 mmHg]; there was no difference in the GFR loss, but proteinuria was significantly less (535 mg/24 hour) in the captopril than in the placebo group [44], which led the authors to suggest that in this population the target MAP should be 92 mmHg.

Because type 2 diabetes is much more frequent than type 1, a major challenge was to document the effect of RAS blockade on nephropathy in type 2 diabetes. In the meantime, angiotensin receptor blockers had become available. The study of Barnett [45] in type 2 diabetic patients at relatively early stages of diabetic nephropathy documented that both ACE inhibitors (enalapril) and angiotensin receptor blockers (irbesartan) were equally effective to achieve a stable plateau of GFR after approximately 4 years following the start of treatment. In type 2 diabetic patients at more advanced stages of diabetic nephropathy, two contemporaneous controlled studies were performed: one with Losartan [46] and the other with Irbesartan [47]. Both came to the same conclusion, i.e., apart from reducing proteinuria, the composite end point of doubling of baseline serum creatinine, development of ESRD or death from any cause was reached in a smaller proportion of patients.

The fourth recent advance was by the Steno Memorial Hospital group in Copenhagen in a controlled study of patients with type 2 diabetes and microalbuminuria. The study provided the proof that intensified multifactorial intervention is more effective than standard treatment according to guidelines (i.e. those valid at the time the study was started). In this study 151 patients were randomly assigned to a group according to the (then) guidelines of the Danish society or to intensified treatment, which consisted of reduction of saturated fat, light to moderate exercise, no smoking (advise which was futile), captopril (irrespective of blood pressure), vitamin C, etc. An effort was made to achieve glycosylated hemoglobin (HbA1c) <6.5%. After a 3.8-year follow-up progression to overt nephropathy was already less (OR 0.27) as was progression of retinopathy (OR 0.45) or autonomic neuropathy (OR 0.32) [48]. After a follow-up of 7.8 years, 47 patients achieved remission to normoalbuminuria. This was associated with less decline in GFR (Δ –2.3 ± 0.4 mL/min/year) compared with patients who progressed to overt nephropathy (GFR Δ ± 0.5 mL/min/year). The start of antihypertensive treatment was also associated with remission to normoalbuminuria (OR 2.32) as was a 1% decrease in HbA1c [49]. In this cohort, the hazard ratio (HR) of a cardiovascular (CV) event was lowered to 0.47, of nephropathy 0.39, and of retinopathy 0.42—globally, approximately 50% risk reduction. The study was followed by an observational follow-up. After no less than 13.3 years a significant effect was also seen on cardiovascular mortality and ESRD: 24 patients in the intensive treatment versus 40 in the conventional treatment group had died (hazard ratio 0.54); both CV death (HR 0.43) and CV events (HR 0.41) were lower

in the intensive treatment group. Only one patient in the intensive versus six patients in the conventional treatment group had developed end-stage kidney disease, suggesting an effect of metabolic memory.

Obviously, compared with the sad state of treatment of diabetic nephropathy 40 years ago [14], the prognosis of diabetic nephropathy has been improved dramatically. But the number of patients, mostly with type 2 diabetes, currently entering end-stage kidney disease, continues to be a challenge and will require novel approaches in the future.

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Chapter 2

Epidemiology of chronic kidney disease in diabetes

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Key points

- Valid epidemiological data regarding diabetes and chronic kidney disease are scarce.
- Diabetes-related kidney disease is the leading cause of renal replacement therapy.
- The risk of developing chronic kidney disease in people with diabetes seems to be declining. Nevertheless, with an aging population and the increasing prevalence of diabetes, the number of affected persons remains high.
- The risk of developing diabetes-related chronic kidney disease and, in particular, renal replacement therapy differs with age, sex, ethnic background, and region.
- Epidemiological studies with standardized methods addressing the diabetic population are warranted to get a more valid insight in the incidence and prevalence and the progression of chronic kidney disease in diabetes, its trends and its differences between regions and subgroups.

Introduction

This chapter gives an overview of the epidemiology of chronic kidney disease (CKD) in diabetes. We will focus on (1) incidences of CKD in different stages and of end-stage renal disease (ESRD) requiring renal replacement therapy, namely maintenance dialysis or transplantation, i.e., new cases in a disease-free defined population during a defined period of observation, and (2) prevalences of these endpoints, i.e., the total number of affected persons in a defined period (often at an index date or within 1 year) in a defined population.

Epidemiological measures and pitfalls

This is not an easy task. Some figures are often reported in review articles or overviews regarding renal disease in diabetes [see, for example, 1–4]. In individuals with in either type 1 or type 2 diabetes, it has been reported that 25–40%

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will develop diabetic nephropathy in a 25-year period. Diabetes is considered to be the leading cause for ESRD: The proportion of diabetes-related ESRD among all cases of ESRD is reported to be about 25–55%. There are some hints that the incidences of CKD and ESRD are declining in both type 1 and type 2 diabetes. There are large differences between regions and ethnic groups; however, the data are controversial. Knowledge remains uncertain, mainly because of methodological issues.

- *The numerator* (cases): The definition of CKD in general and diabetes-related CKD differs. Several studies have investigated albuminuria or proteinuria using several definitions. Others have analyzed renal impairment, which, however, has been defined in different ways, frequently using different formulae to estimate the glomerular filtration rate (eGFR). Diabetes-related ESRD is poorly defined: it may be ESRD in individuals with diabetes, or in individuals when diabetes is the main cause of ESRD, or just ESRD due to diabetic nephropathy. Furthermore, most data stem from ESRD registers. Even when registers are complete, the incidence of ESRD depends on access to or acceptance of ESRD, so that the proportion of individuals classified with ESRD probably differs between regions and time periods.
- *The denominator* (the population at risk): Incidence and prevalence of diabetes-related CKD or ESRD may be estimated in the general population (diabetic as well as non-diabetic), in the estimated diabetic population, or in selected samples, e.g. clinic-based patient cohorts or participants in clinical trials. Incidence and prevalence in the general population are difficult to interpret, since the figures depend largely on the prevalence of diabetes in the population, which differs by region and with time trends because of changing incidences, survival, and detection rates. Studies using clinic-based or primary care-based populations or clinical trials will probably overestimate incidence and prevalence, since participants differ from the general diabetic population, e.g., the selection may be of individuals with more severe illness. Thus, whenever possible we will focus on epidemiological studies within population-based diabetic samples. Even then, several problems occur, in particular in type 2 diabetes. It is well known that a high number of individuals with type 2 diabetes are undiagnosed [5]. It is considered that this proportion has declined during previous years because of higher awareness concerning undetected diabetes and improved screening initiatives. Hence, the population of individuals with diabetes might have increased due to a higher detection of previously unknown cases. These individuals may differ from the previously diagnosed population and may be suffering from milder forms of diabetes. A further point is that the definition of diabetes differs with calendar year and region. Foe example, several Scientific Diabetes Associations have lowered the threshold of fasting glucose from 140 to 126 mg/dL [6].
- *The study design*: Study populations differ with respect to age, gender, ethnic background, and demographic variables, which are all considered to influence CKD. Studies differed with respect to their observation period and epidemiological measures. Prevalence may be assessed as "point prevalence" or period prevalence, e.g., 1 year or even life time prevalence. The same is true for incidence: incidence may be estimated as incidence rates per defined person times, or as cumulative incidences for different observation periods. An important issue is the database. Using data from routine statistics, e.g., social insurance data, will largely underestimate CKD, since only diagnosed cases can be identified, and it is well known that a large proportion of CKD is undiagnosed [7].

When looking for epidemiological data in the following, one has to keep in mind these points, which contribute to problems in interpreting results (Box 2.1).

Box 2.1 Epidemiological factors contributing to variation in the recorded incidence and prevalences of end-stage renal disease (ESRD) in diabetes

Bias
Ascertainment bias (expanding access to ESRD treatment)
Classification bias (insulin-requiring type 2 diabetes coded as type 1 disease; diagnostic preference when more than one cause of ESRD is present
Lead-time/length bias (resulting from starting treatment at an earlier stage of disease)

Changing demography
Aging of the population
Immigration of persons at high risk for diabetes

Rising incidence of diabetes

Longer survival of persons with diabetes

Changing medical management of diabetes
Fewer diabetic patients developing nephropathy
Slower progression of diabetic nephropathy

Longer survival of persons with ESRD

Chronic kidney disease without end-stage renal disease

Incidence of chronic kidney disease in individuals with diabetes

The population-based incidence of CKD in type 1 diabetes, as defined by persistent microalbuminuria, has been declining for several years. Based on data from a population-based incidence register in Sweden, the cumulative incidence of persistent microalbuminuria after 25 years of diabetes decreased from 30% among patients in whom diabetes developed between 1961 and 1965 to 8.9% among those in whom it developed from 1966 to 1970 [8]. After 20 years of diabetes, the cumulative incidence decreased from 28.0% among the patients in whom diabetes developed from 1961 to 1965 to 5.8% among those in whom it developed from 1971 to 1975. Up to the end of the observation time in 1991, persistent microalbuminuria had not developed in any patient in whom diabetes was diagnosed in the period 1976–1980. The mean glycosylated hemoglobin (HbA1c) was significantly higher in patients with than those without persistent albuminuria [8].

More recent data have been reported by the Epidemiology of Diabetes Interventions and Complications Study, the follow-up to the Diabetes Control and Complications Trial (DCCT) study [see, for example, 9, 10]. However, participants in the DCCT were a selected population with a diabetes duration of 1–5 years; hence, the data are difficult to compare with population-based data.

Data describing the incidence of CKD in type 2 diabetes are not available from population-based samples but from clinic-based studies or clinical trials. The UK Prospective Diabetes Study included individuals with newly diagnosed type 2 diabetes for a randomized study which aimed to evaluate intensive diabetes care. Of 5102 participants, prospective analyses were undertaken in those without albuminuria (n = 4031) or with normal plasma creatinine (n = 5032) at diagnosis. Development of albuminuria (microalbuminuria or macroalbuminuria) or renal impairment

(Cockroft–Gault estimated creatinine clearance <60 mL/min or doubling of plasma creatinine) was estimated. After 15 years of follow-up, 38% had developed albuminuria, 29% renal impairment, and 14% both conditions. Of the people who had developed renal impairment, 51% did not have preceding albuminuria. Men had an increased risk of developing micro- or macroalbuminuria compared with women (18% and 47% increase), but a 45% lower risk of developing renal insufficiency. People with Indian Asian ethnicity had an about twofold higher risk for both conditions than white Caucasians, whereas the risk in Afro-Caribbeans was not significantly higher. Risk factors for both conditions were baseline systolic blood pressure, urinary albumin, and plasma creatinine. Distinct sets of further risk factors were associated with the two outcomes, consistent with the concept that they are not linked inexorably in type 2 diabetes [11].

In a hospital-based study in Italy, 1449 patients with type 2 diabetes without CKD at baseline were followed up for 5 years. The 5-year cumulative incidence of CKD, defined as persistent macroalbuminuria [albumin-to-creatinine ratio (ACR) ≥30 mg/mmol in at least two of three samples] or modification of diet in renal disease (MDRD) eGFR <60 mL/min/1.73 m^2 was 13.4%. Age, sex, body mass index, hypertension, smoking history, diabetes duration, lipids, current use of medication, and baseline albuminuria were significantly associated [12].

Prevalence of chronic kidney disease in individuals with diabetes

The prevalence of CKD in type 1 diabetes was estimated in a population-based sample of 648 adult patients with type 1 diabetes in Germany [13]. Nephropathy, defined as at least microalbuminuria or elevated serum creatinine, was observed in 30% of the patients. The probability of having at least macroalbuminuria was 3.5-fold higher in patients in the lowest socioeconomic group than those in the highest socioeconomic group [13]. In a more recent study, 25.2% of type 1 diabetic individuals had MDRD eGFR <60 mL/min/1.73 m^2 [14].

The prevalence of CKD in general or type 2 diabetes has been estimated in several countries in general, or in primary care-based populations with diabetes (Table 2.1). In Hong Kong the prevalence of renal impairment (defined as MDRD eGFR below 60 mL/min/1.73 m^2) was 11.9% [15]. In a population-based study in Taiwan, using the same definition, the prevalence was 15.1%. The prevalence of proteinuria was 29.4% [16]. In a population-based sample in Shanghai, 32.8% of type 2 diabetic patients had CKD stage 3–5, based on the Cockcroft Gault equation [17]. In Australia, the prevalence of proteinuria (ACR >2.5 or 3.5 mg/mmol in men and women) in a primary care-based study was 34.6%, and the prevalence of renal impairment, using MDRD-based eGFR, was 23.1% [18]. Only a subgroup of patients had both abnormal eGFR and abnormal proteinuria. In another study from Australia, the prevalence of CKD was assessed in individuals with screen-detected diabetes, using an oral glucose tolerance test. The prevalence of proteinuria (protein to creatinine ratio ≥0.2 mg/mg) was 8.7%, fourfold higher than in those without diabetes, which was 1.9%, and the prevalence of Cockcroft–Gault estimated GFR <60 mL/min was 27.6%, threefold higher than in individuals without diabetes, which was 9.8% [19]. Thus, the prevalence of at least proteinuria in the study of Chabdan was much lower than the study of Thomas, probably due to the different diabetic populations (population of individuals with screen-detected diabetes compared with patients with diagnosed diabetes in primary care, a higher proportion of people from Asia and Aborigines or Pacific Islanders in the population of Thomas).

In the USA, based on National Health and Nutrition Examination Survey (NHANES) data,