

Part I

## **Introduction and Pathophysiology**

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# Chapter 1

## History of diabetic nephropathy: a personal account

Eberhard Ritz

*Carola Ruperto University Hospital, Heidelberg, Germany*

### 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” (*Iksumeḥa*) or “honey urine” (*Madhumeha* and *Hastimeḥa*) 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 “Xiao-ke” (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

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 Abdullah ibn Sinā (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 (*diabète maigre*) and type 2 (*diabète obèse*).

It is of interest that in the 19th century and even in the first decades of the 20th century, chronic kidney disease in diabetes 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 diabète maigre: ses symptômes, son évolution, son pronostic et son traitement" had introduced the concept of "*diabète maigre*" and "*diabète obèse*" 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  $\kappa$ -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  $570 \pm 64$  nm to  $404 \pm 38$  nm; the mesangial fractional volume had decreased as well (baseline  $0.33 \pm 0.007$ ; at 10 years  $0.27 \pm 0.02$   $p = 0.05$ ), 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 albutix-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)  $<60\text{ mL/min/1.73 m}^2$  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 albugin-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 proteinu-

ria, the decrease in GFR and renal plasma flow (RPF) was  $0.91\text{ mL/min/month} \pm 0.68$  and  $4.38\text{ mL/min/month} \pm 3.23$  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  $1.23\text{ mL/min/month}$  in the run-in period and reduced to  $0.49\text{ mL/min/month}$  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  $>500\text{ mg/day}$  and serum creatinine  $>2.5\text{ mg/dL}$ . 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:  $11 \pm 21\%$  per year in the captopril versus  $17 \pm 20\%$  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 (advice 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 ( $\Delta -2.3 \pm 0.4$  mL/min/year) compared with patients who progressed to overt nephropathy (GFR  $\Delta \pm 0.5$  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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