Diabetes and Kidney Disease

Edgar V. Lerma
Vecihi Batuman
Editors

Second Edition

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To all my mentors and friends, at the University of Santo Tomas Faculty of Medicine and Surgery in Manila, Philippines, and Northwestern University Feinberg School of Medicine in Chicago, IL, who have in one way or another, influenced and guided me to become the physician that I am...
To all the medical students, interns, and residents at Advocate Christ Medical Center, whom I have taught or learned from, especially those who eventually decided to pursue Nephrology as a career...
To my parents and my brothers, without whose unwavering love and support through the good and bad times, I would not have persevered and reached my goals in life …
Most especially, to my two lovely and precious daughters Anastasia Zofia and Isabella Ann, whose smiles and laughter constantly provide me unparalleled joy and happiness; and my very loving and understanding wife Michelle, who has always been supportive of my endeavors both personally and professionally, and who sacrificed a lot of time and exhibited unwavering patience as I devoted a

significant amount of time and effort to this project. Truly, they provide me with motivation and inspiration.

—Edgar V. Lerma

To my former mentors, colleagues, residents, fellows, and nurses – too many to name individually. They made a career in nephrology an exciting and fulfilling journey. And to my family for their loving support and encouragement.

—Vecihi Batuman

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Chapter 1
Historical Background of Diabetic Kidney Disease

Vivian Fonseca, Arezu Bhatnagar, and Govind Datta Chamarthi

Introduction

Symptoms of diabetes are recorded as far back as 400 BC; the Indian physician Sushruta describes diabetes in an ancient Hindi document as "madhumeha" or the honeyed-urine disease [1]. Around 150 AD, the Greek physician Aretaeus of Cappadocia wrote:

> Diabetes is a remarkable disorder, and not one very common to man. It consists of a moist and cold wasting of the flesh and limbs into urine... the secretion passes in the usual way, by the kidneys and the bladder. It is of improbable, also, that something pernicious, derived from other disease which attack the bladder and kidneys may sometimes prove the cause of this affliction. The patients never cease making water, but the discharge is as incessant as a sluice let off. This disease is chronic in character, and is slowly engendered, though the patient does not survive long when it is completely established for the marasmus produced is rapid and death is speedy [2].

For many centuries thereafter, diabetes mellitus was regarded as a disease of the kidney.

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The Discovery of Diabetic Kidney Disease

Following the now famous paper published by Paul Kimmelstiel and Clifford Wilson in 1936, many incorrectly assume that diabetic renal disease was recently recognized. However, the discovery of diabetic kidney disease has been a gradual process, and the meaning of diabetic renal disease has changed over time [3].

Erasmus Darwin [4] described it as urine that could be coagulated by heat, confirming the observations of Cotunnius [5] and Rollo [6] that the urine of some diabetics contained protein [7]. In the 1830s, research conducted by the "father of nephrology" Richard Bright into the causes of kidney disease led to what became known as Bright's disease. Pierre-François Olive Rayer [8] and Wilhelm Griesinger [9] were the first to hypothesize that diabetes might cause a form of Bright's disease.

In the 1850s, much data on renal histology in patients with diabetes were published. Lionel Beale examined the histology of enlarged diabetic kidneys and analyzed them chemically, showing an excess of fat present in the tubules. Luciano Armanni (1875, cited by Ebstein) and Wilhelm Ebstein [10] described vacuolization of renal tubular epithelium.

The concept of diabetic kidney disease continued to develop, and in 1883, Ehrlich confirmed glycogen infiltration—a common postmortem finding in the pre-insulin era. For the next 50 years, these tubular deposits of glycogen were the only lesion believed to be specifically associated with diabetes, later called "nephropathia diabetic" by Aschoff in 1911.

Kenzo Waku [11] published a description of diffuse capillary wall thickening studied by silver staining in 8 of 13 diabetic patients, in a Japanese journal written in German. No clinical details of the patients were provided, and the study gained little attention. It was not until 1936, when Kimmelstiel and Wilson published their paper "Intercapillary lesions in glomeruli of kidney" in *The American Journal of Pathology*, that interest intensified in the study of diabetic vascular complications.

The Pathology of Diabetic Renal Disease

Paul Kimmelstiel (1900–1970), a native of Hamburg, Germany, came to the USA in 1933. Clifford Wilson (1906–1997), a relatively unknown British clinician, went to Harvard University as a Rockefeller travelling fellow and met Kimmelstiel. Their first paper [12] described glomerular lesions in eight patients who died of renal failure. The lesions were attributed to diabetes mellitus because seven of the eight patients were known to have the disease. Most of the patients had hypertension, heavy albuminuria, and edema and were aged 48–68 years. The diabetic patients had diabetes from a range of 10 months to 10 years. Their glomeruli showed uniform lesions involving large expansion of the intercapillary space. This expansion

was shown to be continuous with the hyaline lesions of the afferent glomerular arteriole. Kimmelstiel and Wilson did not emphasize the association of these lesions with diabetes but suggested that the appearance was an acceleration of senile glomerulosclerosis. They noted that it was a rare finding and that it could complicate glomerulonephritis.

Although Kimmelstiel and Wilson's observations were received initially with uncertainty, they stimulated interest in diabetic vascular pathology. After their publication, the eponym "Kimmelstiel–Wilson nodules" began to be applied to diabetic renal lesions. However, it was Arthur Allen (1941) who clarified the link with diabetes [13]. He studied autopsies of 105 patients with diabetes (all of which were over age 40), 100 patients with hypertension, 100 patients without hypertension or diabetes, and 34 patients with glomerulonephritis. Thirty-four percent of the diabetics showed the lesion, but otherwise it was seen in only three other patients.

Type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes are etiologically and epidemiologically distinct conditions and affect different divisions of the population. However, there has been no major difference identified between the nephropathies seen in both conditions, either pathophysiologically or in terms of their management. They can thus be conveniently considered together. It should be remembered, however, that patients with type 2 diabetes tend to be older and more hypertensive and so more likely to have concomitant hypertensive and renovascular disease [14].

Initial Studies of Renal Biopsies

Before 1950, renal histology samples were mostly obtained from autopsied patients. The only way of analyzing kidney tissue from a live person was through an open operation. In 1951, Danish physicians Poul Iversen and Claus Brun described a method involving needle biopsy [15]. It became possible to obtain renal specimens of diabetic patients in all stages of disease. By the end of the 1950s, there were a large amount of data collected such as those published by Robert Kark in Chicago [16]. These data revealed that patients with mild glomerular disease may have heavy proteinuria and patients with less renal involvement may have complex lesions of nodular glomerulosclerosis.

In 1957 the electron microscope [16] and in 1959 immunofluorescent protein tracing [17] were used to study glomerular lesions in patients with diabetes mellitus. Using these techniques, the hypothesis of a diffuse thickening of the basement membrane in diabetics was proven. In 1956, Ruth Østerby-Hansen published a study, [18] which showed that there was no thickening of the peripheral glomerular basement membrane in early diabetic patients. This finding brought forth the possibility of treatment through modifying whatever was causing subsequent changes.

Radioimmunoassay and the Concept of Microalbuminuria

In New York, in the 1950s, Rosalyn Yalow[1] and Solomon Aaron Berson developed the technique of radioimmunoassay, and they later published their findings [19]. The technique allowed for the precise measurement of minute amounts of proteins and hormones. In 1960, Harry Keen and associates from Guy's Hospital used the technique to detect small amounts of albumin in the urine of diabetics. Their paper [20] was published in *The Lancet* in 1963. Keen studied diabetics at all stages of disease, including those who had no proteinuria on conventional testing. Keen realized that elevated albumin excretion below the proteinuric level might be important in the natural history of diabetic kidney disease, and the concept of microalbuminuria was developed.

In 1982, GianCarlo Viberti published findings that confirmed that microalbuminuria could predict the subsequent evolution of overt nephropathy with proteinuria in type 1 diabetics, [21] and in 1984, Carl Erik Mogensen showed the same finding in type 2 diabetics [22]. Concurrently, it became apparent that the reduction of blood pressure could postpone renal failure [23].

The Renin–Angiotensin–Aldosterone System and Diabetic Kidney Disease

In the 1950s, Mann et al. documented the natural history of diabetic renal disease. Death from renal failure that resulted from diabetic kidney disease usually occurred in patients who had long-standing type 1 diabetes. However, after the 1970s with improved treatments, much larger number of patients with type 2 diabetes began to survive and develop end-stage renal disease. Attention began to shift from the treatment to the prevention of diabetic kidney disease.

Pharmacologic blockade of the renin–angiotensin–aldosterone system (RAAS) has become the standard of care for patients with type 2 diabetes mellitus and renal involvement [24]. The history of the discovery of the RAAS began in 1898 with the studies by Tigerstedt and Bergman, who reported the pressor effect of renal extracts; they named the renal substance renin based on its origin [25]. Angiotensin-converting enzyme inhibitors (ACE-i) were the first class of clinically applicable drugs that specifically block the RAAS. Originally, ACE-i were developed as antihypertensives, in particular aimed at the treatment of high-renin hypertension. The first proposals [26, 27] that the outcome of diabetic kidney disease could be improved using RAAS blockade with ACE-i drugs began in the early 1980s. Brenner and Zatz showed that rats with diabetes that were treated with ACE-i were protected against nephropathy; however, conventional blood pressure lowering agents did not

[1] By injecting radioactive iodine, they were able to track insulin and prove that type 2 diabetes is due to an inefficient use of insulin. This discovery awarded them a Nobel Prize.

[28]. The first controlled trial [29] of ACE-i in humans with diabetes appeared in 1987.

In 1993, the landmark study using captopril was published [30]. The trial demonstrated that captopril protected against deterioration of renal function in patients with type 1 diabetes and diabetic kidney disease and was significantly more effective than blood pressure control alone. Captopril reduced the risk of doubling of the serum creatinine by 48% when compared with standard antihypertensive therapy. Both treatment groups had similar blood pressures; thus, the effect of captopril on progression was determined to be independent of its antihypertensive properties, an effect termed "renoprotection."

In 2001, the Irbesartan diabetic kidney disease Trial, [31] designed to ascertain whether the use of the angiotensin II receptor blocker irbesartan or the calcium channel blocker amlodipine provided similar renoprotection in overt nephropathy associated with type 2 diabetes, was published. Irbesartan was shown to reduce the risk of doubling the serum creatinine by 33% when compared with standard antihypertensive therapy and by 37% when compared with treatment with amlodipine. Blood pressures were again similar across groups, indicating that these salutary effects were a result of renoprotection. Similar results were reported using losartan in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial [32].

Results of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA 2) trial were also published in 2001. IRMA 2 studied the effects of the use of irbesartan (300 or 150 mg/day versus placebo) to prevent progression from the earlier stage of microalbuminuria to the later stage of overt nephropathy in patients with hypertension and type 2 diabetes. The study demonstrated that patients receiving irbesartan (300 mg/day) had about one third the risk of developing overt nephropathy compared with the patients not receiving (adjusted risk reduction 68% at 300 mg/day) [33].

Value of Glycemic Control

Diabetes is the most common cause of ESRD in Western countries, and glycemic control is correlated with the development and progression of diabetic kidney disease. Epidemiologic studies have demonstrated that diabetic kidney disease risk is higher in patients with poor metabolic control [27, 34, 35]. Although genetic factors modulate DN risk and some patients do not develop this complication despite several years of poor glycemic control, there is evidence that hyperglycemia is a necessary precondition for DN lesions. Two major early glomerular lesions, glomerular basement membrane thickening and mesangial expansion, are not present at diagnosis of diabetes but are found 2–5 years after onset of hyperglycemia [34].

Studies in identical twins who are discordant for type 1 diabetes support the concept that hyperglycemia is necessary for the development of diabetic glomerulopathy. Twin studies show that the nondiabetic siblings had structurally normal

kidneys, while their diabetic twin pair had glomerular lesions [36]. Moreover, normal kidneys from nondiabetic donors that are transplanted into patients with diabetes develop lesions of DN [37, 38].

A number of articles now suggest a long-term survival advantage with simultaneous pancreas kidney (SPK) transplantation, compared with kidney transplantation alone for patients with end-stage renal disease caused by diabetic kidney disease [39]. SPK offers the opportunity to test the ability of pancreas transplantation to prevent the development of diabetic glomerular lesions, because the renal graft has never been exposed to hyperglycemia. Patients who have dual-organ transplants almost always normalize their glycemic values afterward, and this is partly why these patients live longer than those who get a kidney alone. In 1985, Bohman et al. were the first to demonstrate that the development of diabetic glomerulopathy was prevented in the recipients of SPK [40]. In 1993, the same group confirmed prior observations when they reported data on a cohort of 20 SPK patients who were followed for up to 6 years, compared with a group of 34 kidney transplant recipients with diabetes [41]. More recent studies support the same observation [42, 43].

Treatment of Hyperglycemia

Almost 4000 years ago, "diabetes" or a disease describing it was well documented in ancient records from Egypt, India, and across China. Interestingly, all recognized that sweet copious amounts of urine and sweet-scented sweat were associated with obesity and may have a hereditary component to it. They also noted that these phenotypic traits may possibly be occurring due to overindulgence of rich foods such as milk which contains a lot of sugar in it.

With very limited resources in regard to the pathophysiology of diabetes, an array of ancient medicines were used. These included oil of roses, dates, raw quinces and gruel, jelly of viper's flesh, broken red coral, sweet almonds, and fresh flowers of blind nettles [44].

For the most part, diabetes was considered incurable at that time. Knowing now that there are microvascular complications such as diabetic kidney disease, there is much doubt as to whether people survived for that long, whether physicians of that time stopped treatment or tailored treatment to best suit the various stages of this dismal disease [45].

In type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) Research Group demonstrated that intensive treatment was associated with decreased incidence of microalbuminuria and reduced progression to macroalbuminuria as compared with conventional treatment [46]. In type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) Group trial demonstrated a reduced incidence of microalbuminuria in the intensively treated group as compared with conventional treatment, but a parallel finding in macroalbuminuria was not significant [47].

However, the Kumamoto study [48] and the Veterans Affairs Cooperative study [49] both showed that intensive treatment was effective for primary prevention (decreased incidence of microalbuminuria) and secondary prevention (reduced progression to macroalbuminuria).

The Epidemiology of Diabetes Interventions and Complications (EDIC)/DCCT follow-up study [50] and the UKPDS study also found that lowering HbA1c reduced decline in GFR in type 1 and type 2 diabetes, respectively.

Intensive Glycemic Control

The benefit of intensive glycemic control for nephropathy is currently under debate. Intensive treatment of hyperglycemia may prevent DN, including development of microalbuminuria, but there is little evidence that it slows the progression of chronic kidney disease [51].

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, assignment of the treatment group to an HbA1c goal of less than 6% led to increased mortality and cessation of the trial [52]. Furthermore, in one analysis of data from the ACCORD study, combined intensive glycemic and blood pressure control did not produce an additive benefit on microvascular outcomes in patients with type 2 diabetes. This differs from the findings of the ADVANCE study, [53] which showed that intensive glucose and BP controls were independently beneficial and their combination produced synergistic benefits in nephropathy, new-onset microalbuminuria, and new-onset macroalbuminuria.

The Impact of Glucose-Lowering Drugs on Diabetic Kidney Disease Progression

While the impact of good glycemic control on nephropathy progression is generally well accepted, none of the medications for hyperglycemia were shown to have a specific beneficial effect on the kidney in the past. However, recently data has emerged demonstrating that some drugs developed for lowering blood glucose can decrease proteinuria and significantly slow the progression of chronic kidney disease (CKD). While some minor benefits have been seen with DPP-4 inhibitors and thiazolidinediones, the effects of SGLT2 inhibitors and, to a lesser extent, GLP-1 receptor agonists are clinically impactful, and the use of the former has now been incorporated into several clinical guidelines, [54] including the specific treatment of diabetic kidney disease. Figure 1.1 [76] shows the evolution of treatment and management for diabetes.

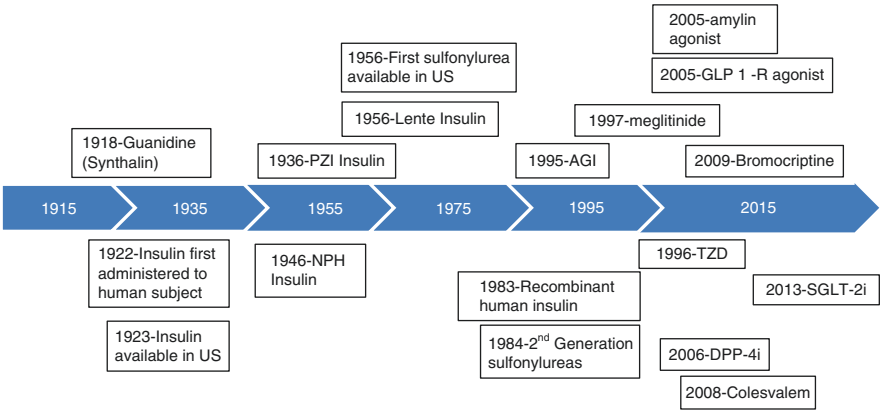

Fig. 1.1 Evolution of treatment and management for diabetes. (NB: *PZI* protamine zinc insulin, *NPH* neutral protamine Hagedorn, *AGI* alpha glucosidase inhibitors, *GLP-1R agonist* glucagon-like peptide-1 receptor agonist, *TZD* thiazolidinediones, *SGLT2i* sodium glucose transporter inhibitors, *DPP-4i* dipeptidyl peptidase-4 inhibitors)

Sodium Glucose Transporter Inhibitors (SGLT2i)

Phlorizin, a molecule from the root bark of apple trees, has been studied for over a century. In 1933, it was discovered to increase renal excretion of glucose, decrease its reabsorption, and lower its overall levels in the body. Phlorizin seemed to be an ideal alternative in managing glucose levels in those with diabetes mellitus (mechanism of action; non-selective inhibitor of both Sodium Glucose Transporters (SGLT) 1 & 2). SGLT1 accounts for the dietary glucose uptake in the intestine and, SGLT2 is responsible for glucose reuptake in the tubular system of the kidney. SGLT1 reabsorbs the remainder of the filtered glucose [55]. Phlorizin's dramatic reduction in glucose reabsorption in the intestines, its negative effects on the body as well as, its inadequate absorbance when taken orally, became quite evident.

For decades, researchers had many concerns about phlorizin and others in the same class due to side effects thought to be related to its nonspecific inhibition of transporters in other organs. Finally, the development and approval of a more specific SGLT2i, canagliflozin, in 2013 by the US Food and Drug Administration (FDA) led to reassurance about such effects. Dapagliflozin and empagliflozin followed in 2014 [56]. Several others in this class are now available worldwide.

Large-scale clinical trials mandated by the FDA, Empagliflozin- regulatory outcome (EMPA-REG OUTCOME) and Cardiovascular Assessment Study (CANVAS), examined SGLT2i's effects in type 2 diabetics. These programs showed an approximate 35% reduction in the incidence of heart failure [55]. Furthermore, there were reductions in mortality and major CV events. These trials also highlighted a

reduction in the progression of nephropathy, a decrease in proteinuria and, a slower decline in eGFR.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial demonstrated canagliflozin's action on inhibiting SGLT2 in advanced CKD due to diabetic kidney disease. The study enrolled patients with significant proteinuria and eGFR as low as 30. Compared to placebo it decreased creatinine levels, preventing progression of CKD, and reduced the rates of mortality secondary to end-stage kidney disease (ESKD) and other cardiovascular effects [57]. Importantly, the drug was continued in people whose eGFR dropped below 30, and no harmful effects were seen, demonstrating possible benefits at a stage where significant reduction in glucosuria was unlikely.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial that commenced in 2017 has recently halted due to its overwhelming positive effects [58]. DAPA-CKD mirrors CREDENCE but on a broader scale. Its population were those suffering from chronic renal disease without diabetes. Dapagliflozin's outcome also proved to delay further kidney damage and decrease cardiovascular effects in those suffering with diabetes mellitus.

Interestingly, the beneficial effects on eGFR occurs despite an initial drop in eGFR, possibly related to dehydration, which may be associated with incidences of acute kidney injury in a few patients. In addition, and more likely, the effects are due to a corrective action of SGLT2i on the impaired tubulo-glomerular feedback. However, a meta-analysis by Menne et al. concluded that there was no increased risk of AKI in patients taking SGLT2 inhibitors. In addition, they advise physicians that the possibility of AKI should not deter them from prescribing them [59].

Thus, novel approach to treating hyperglycemia by working on the kidneys and reducing the risks of associated macrovascular complications such as cardiovascular disease was established. The results of these trials have spawned many others as well as mechanistic studies to understand the findings. Mechanisms proposed include a reduction in BP, improved energetics in the renal cells, improved blood flow through normalization of juxtaglomerular feedback, and a suppression of activation of intrarenal angiotensin production [60].

Glucagon-like Peptide-1 Receptor (GLP-1R) Agonists

Over 100 years ago, Moore et al. [61] discovered that gut extracts contain hormones that regulate the function of the pancreas and administration of these hormones lowers glucose levels in urine. In 1932 Le Barre purified these extracts and called it incretins. The invention of radioimmunoassay (RIA) by Berson and Yalow in 1960 which led to the ability to reliably measure insulin with RIA soon reopened the *incretin* question. In 1964, [62] McIntyre showed that there was a higher plasma insulin response to glucose given orally than to glucose given intravenously, hence proving the incretin mechanism exists. This report proved a stimulus to studies aimed at identifying and isolating these incretins.

In 1973 John Brown [63] isolated GIP as an inhibitor of gastric acid secretions but in subsequent studies showed that it is a commanding releaser of insulin during hyperglycemia but could not explain the effect of GIP on insulin secretion after oral glucose. Therefore, the search for other incretins continued. In 1983, Graeme Bell [64] identified two glucagon-like peptides during the cloning and sequencing of mammalian pre-proglucagon and named them GLP-1 and GLP-2, both of which were expressed in the gut. But GLP-1 as such didn't show a significant insulinotropic effect. In 1987, Habener [65] and Holst [66] independently discovered that GLP-1 was also synthesized in truncated form, which showed an even greater insulinotropic effect, and this led to the birth of GLP-1 drugs based on the incretin concept. The results of the 1993 clinical study by M A Nauck showed that exogenous GLP-1 [7-36 amide] caused normalization of fasting hypoglycemia, without the stimulation of insulin secretion. The first GLP-1RA drug was exenatide and was approved in 2005 [67, 68].

In recent years the efficacy of GLP-1 drugs in lowering blood glucose has been very well established, and also many trials have shown that it has a consistent association in lowering systolic blood pressure and weight [69]. In 2016, the LEADER trial [70] compared cardiovascular event outcomes in 9340 patients with type 2 diabetes with cardiovascular disease or cardiovascular risk factors randomly assigned to subcutaneous liraglutide or placebo. After a median follow-up of 3.84 years, the study showed a significant difference between the groups, in death from cardiovascular events (HR, 0.87), glycemic control (−0.4%), weight loss (2.3 kg), and systolic blood pressure (−1.2 mmHg). In addition to these, the study also showed a significant reduction in nephropathy events (HR, 0.78).

This result was driven by the significant reduction in new-onset microalbuminuria (HR, 0.74) in the liraglutide group. A short time after the LEADER trial, the SUSTAIN-6 trial [71] showed very similar results with subcutaneous semaglutide. There was a significant reduction in new or worsening nephropathy in the semaglutide group compared to the placebo group (HR, 0.64). As seen in the LEADER trial, this was driven by a reduction in new-onset microalbuminuria.

These studies have shown, when added to usual care, GLP-1RA results in lower rates of development and progression of diabetic kidney disease. On the flip side, some of the studies have shown patients to develop acute kidney injury as a side effect of GLP-1RA treatment. However, this is thought to be due to nausea and vomiting leading to dehydration, rather than a specific toxic effect on the kidney. Some GLP-1RAs such as exenatide have this in their package insert suggesting that they must be used with caution in patients with CKD. In 2019, oral semaglutide became the first FDA-approved oral GLP-1RA drug, and already there are studies looking for its impact in the clinical settings.

Bardoxolone

Bardoxolone was initially developed as an anticancer drug. However, as clinical studies progressed, data consistently showed that bardoxolone had a positive impact on the estimated glomerular filtration rate (eGFR) of these patients [72]. Multiple global trials have assessed its capabilities in alleviating or limiting the progression of chronic kidney disease (CKD) in patients suffering with diabetic kidney disease.

The Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus (BEACON) trial was a multicenter, international, phase 3 randomized, double-blind clinical trial that administered bardoxolone once daily to one group and placebo to another group. Their aim was to see if bardoxolone would increase the eGFR in those suffering with stage 4 chronic kidney disease. In total, 2185 patients were randomized into the study.

Among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes. It in fact increased early-onset fluid overloading, especially in those suffering from heart failure or had prior history/hospitalization of heart failure. A higher rate of cardiovascular events with bardoxolone methyl than with placebo prompted immediate termination of the trial, [73] which was disappointing in light of benefits seen in phase 2 trials.

The Phase 2 Study of Bardoxolone Methyl in Patients with Chronic Kidney Disease and Type 2 Diabetes (TSUBAKI) study took place in Japan after BEACON was terminated. This trial aimed to determine if patients without risk factors can mitigate the risk for fluid overload and whether changes in eGFR with bardoxolone methyl reflect true increases in GFR [74].

The outcome of this trial was extremely interesting to note, factoring in that the incidence of cardiovascular events was deemed lower in CKD patients in Japan versus in clinical trials in the USA. Additionally, the trial found no significant safety concerns, such as fluid overloading and heart failure as were seen in BEACON [75].

Despite an early halt to the study, the BEACON trial did attest to the fact that bardoxolone could preserve kidney function by delaying the progression of CKD and thus end-stage renal disease. Patients who were randomly assigned to placebo had a significant mean decline in eGFR from their baseline value (−0.9 ml per minute per 1.73 m^2; 95% CI, −1.2 to −0.5) as compared to those randomly assigned to bardoxolone methyl, who were noted to have had a significant mean increase from their baseline value (5.5 ml per minute per 1.73 m^2; 95% CI, 5.2 to 5.9). The difference between the two groups was 6.4 ml per minute per 1.73 m^2 (95% CI, 5.9 to 6.9; $P < 0.001$) [73].

Recent Updates

There seems to be widespread acceptance of SGLT2 inhibitors as an important class of medications to slow the progression of CKD; indeed this benefit appears to occur independent of glucose excretions. As discussed above multiple potential mechanisms have been implicated. There has also been interest in the role of aldosterone in progression of CKD. Although not approved for the indication and often associated with hyperkalemia, spironolactone has been used in the management of the condition, though limited by side effects. A recent clinical trial with a novel nonsteroidal mineralocorticoid receptor antagonist finerenone demonstrated significant efficacy in slowing progression of CKD without large effects on BP reduction or hyperkalemia [78].

Table 1.1 [77] highlights some of the major randomized clinical research trials (RCT) throughout the years and their outcomes. Many of these trials resulted in favorable outcomes including reductions in albuminuria and general kidney

Table 1.1 Landmark clinical trials in diabetes

Study trial, year	Diabetes type	Follow-up (years)	Design (RCT)	Outcome
Diabetes control and complications trial **(DCCT)**, **1993**	Type 1 diabetes mellitus	6.5 years	Intensive vs. standard glycemic control	Intensive glycemic control (HbA1c 7.3% vs. 9.1%) reduced the incidence of micro- and macroalbuminuria by 39% and 54%, respectively
The Captopril Trial, **1993**	Insulin-dependent diabetes mellitus (IDDM)	4 years	Captopril vs. placebo	Captopril slowed down the progression of kidney disease in IDDM
UK prospective diabetes study **(UKPDS)**, **1998**	Type 2 diabetes mellitus	10 years	Intensive vs. standard glycemic control	Intensive vs. standard glycemic control (HbA1c 7.0% vs. 7.9%) reduced risk of microalbuminuria by 33%
Reduction of endpoints in NIDDM with the angiotensin II antagonist losartan **(RENAAL)**, **2001**	Type 2 diabetes mellitus	3.4 years	Losartan vs. placebo	Every 10 mmHg of systolic blood pressure rise increased the risk of end-stage kidney disease or death by 6.7%. Losartan decreased proteinuria by 35% ($p < 0.001$). Serum creatinine doubling risk was reduced by 25% ($p = 0.006$) and end-stage kidney disease by 28% ($p = 0.002$)

Table 1.1 (continued)

Study trial, year	Diabetes type	Follow-up (years)	Design (RCT)	Outcome
Randomized Olmesartan and diabetes microalbuminuria prevention study **(ROADMAP)**, **2001**	Type 2 diabetes mellitus	3.2 years	Olmesartan vs. placebo	Olmesartan reduced the time to microalbuminuria onset. Blood pressure control was similar in both treatment arms
Irbesartan diabetic kidney disease trial **(IDNT)**, **2001**	Type 2 diabetes mellitus	2.6 years	Irbesartan vs. amlodipine vs. placebo	Irbesartan was Reno-protective with a lower risk of serum creatinine doubling (33%; $p = 0.003$) and end-stage kidney disease (23%; $p = 0.07$) compared with amlodipine and placebo
Ongoing Telmisartan alone and in combination with Ramipril global endpoint trial **(ONTARGET)**, **2008**	Type 2 diabetes mellitus	4.5 years	Telmisartan/ lisinopril combination vs. losartan alone	Combination therapy was associated with an increased composite outcome of dialysis. Serum creatinine doubling and death (hazard ratio [HR] of 1.09; 95% confidence interval 1.01–1.18; $p \leq 0.037$)
Action to control cardiovascular risk in diabetes **(ACCORD)**, **2008**	Type 2 diabetes mellitus	Terminated at 3.5 years	Intensive vs. standard glycemic control	Targeting HbA1c 6.0 vs. 7.0%–7.9% resulted in excess mortality
A study of cardiovascular events in diabetes **(ASCEND)**, **2010**	Type 2 diabetes mellitus	Terminated at 4 months	Avosentan vs. placebo	Avosentan reduced proteinuria compared with placebo group. However, it had excess adverse cardiovascular events
Bardoxolone methyl evaluation in patients with chronic kidney disease and type 2 diabetes **(BEACON)**, **2011**	Type 2 diabetes mellitus	Terminated at 9 months	Bardoxolone vs. placebo	Bardoxolone methyl led to a significant increase in cardiovascular morbidity (HR 1.83, $0 < 0.001$)
Aliskiren trial in type 2 diabetes using cardiovascular and renal disease endpoints **(ALTITUDE)**, **2012**	Type 2 diabetes mellitus	Terminated at 2.7 years	RAS blockade plus aliskiren vs. placebo	The addition of aliskiren to maximal angiotensin receptor blockers (ARBs) offered no additional benefit. In addition, hyperkalemia and hypotension were significantly increased in the treatment arm

(continued)

Table 1.1 (continued)

Study trial, year	Diabetes type	Follow-up (years)	Design (RCT)	Outcome
Action in diabetes and vascular disease **(ADVANCE)**, **2013**	Type 2 diabetes mellitus	5 years	Intensive vs. standard glycemic control	Intensive glycemic control (HbA1c 6.5% vs. 7.3%) reduced risk of microalbuminuria, macroalbuminuria, and end-stage kidney disease by 9%, 30%, and 65%, respectively
Veterans affairs nephropathy in diabetes (VA NEPHRON-D), **2013**	Type 2 diabetes mellitus	Terminated at 2.2 years	Losartan/ lisinopril combination vs. losartan alone	The combination therapy offered no real benefit and resulted in an excessive risk of hyperkalemia and acute renal failure
Epidemiology of diabetes interventions and complications **(EDIC/DCCT)**, **2014**	Type 1 diabetes mellitus	18 years	Intensive vs. standard glycemic control	Reno-protective effect of intensive control persisted and resulted in a 45% reduction risk of microalbuminuria at 18 years
Canagliflozin on renal and cardiovascular outcomes in participants with diabetic kidney disease **(CREDENCE)**, **2019**	Type 2 diabetes mellitus	Terminated at 2.6 years	Canagliflozin vs. placebo	The relative risk for renal events (doubling of creatinine or end-stage kidney disease) was significantly lower in the treatment arm
The Dapagliflozin and prevention of adverse outcomes in chronic kidney disease **(DAPA-CKD)**, 2**017**	With/ without type 2 diabetes mellitus	Terminated at 3 years	Dapagliflozin vs. placebo in patients taking ACE-I or ARBs	HR for the primary endpoint was 0.61 (95% confidence interval [CI) 0.51–0.72; p = 0.000000028). The benefit of dapagliflozin on the primary endpoint was consistent in patients with and without diabetes HR for secondary endpoints were as follows: (a) worsening renal function or death from kidney failure, 0.56 (95% CI 0.45–0.68; p < 0.0001); (b) hospitalization for heart failure or cardiovascular death, 0.71 (95% CI 0.55–0.92; p = 0.0089); and (c) all-cause mortality, 0.69 (95% CI 0.53–0.88; p = 0.0035)

Table 1.1 (continued)

Study trial, year	Diabetes type	Follow-up (years)	Design (RCT)	Outcome
Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes **(FIDELIO-DKD), 2020**	5734 type 2 DM with CKD	2.6 years	Finerenone vs. placebo All patients on RAS blockers	During a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P = 0.001). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively). In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo

function. However, with such stringent control of sugar levels with these types of reno-protective medications, it also leads to serious adverse events countervailing the benefits found. Awareness of treating diabetes and associated renal disease must still be made when treating this cohort.

Conclusion

Over the last several decades we have accumulated substantial knowledge on the natural history, pathophysiology, and progression of diabetic kidney disease. Through data from worldwide clinical trials, innovative medical treatments have been established to slow the progression of this disease. The advancement of modern medicine has certainly provided a much better prognosis and quality of life in individuals suffering from this epidemic, diabetic kidney disease.

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Chapter 2
Diabetes and Kidney Disease: A Review of the Clinical Practice Guidelines

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Introduction

Chronic kidney disease (CKD) among those with diabetes includes both diabetic and nondiabetic kidney disease. Diabetes causes microvascular changes in the kidney, leading to diabetic kidney disease (DKD). Diabetic kidney disease occurs in approximately 30% of patients with type 1 diabetes (T1DM) and 40% of patients with type 2 diabetes (T2DM). It is the leading cause of end-stage kidney disease (ESKD) in the Western populations, contributing to almost 50% of all cases. Several societies, such as the Kidney Disease: Improving Global Outcomes (KDIGO), European Association for the Study of Diabetes in collaboration with the European Society of Cardiology (ESC/EASD), and American Diabetes Association (ADA), have issued clinical practice guidelines to guide clinicians manage diabetes in those with CKD [1–3]. KDIGO clinical practice guidelines provide an assessment of the strength of recommendation (strong, *level 1*; weak, *level 2*) and the quality of the evidence (*A*, *B*, *C*, *D*). ESC/EASD guidelines are graded according to the strength of recommendation *(Class I*, *IIa*, *IIb*, *and III)* and level of evidence *(A*, *B*, *and C).* ADA publishes "Standards of Medical Care in Diabetes," referred to as the *Standards of Care*, in which recommendations are assigned ratings of *A*, *B*, or *C* (depending on the quality of evidence in support of the recommendation) and *E* (based on expert opinion) [3]. For these clinical practice guidelines, extensive literature search (such as MEDLINE, SCOPUS, CENTRAL, etc.) using formal search criteria has been adopted. In this chapter, we will discuss the following aspects of diagnosis and treatment in patients with diabetes and CKD based on the evidence-based clinical

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practice guidelines of these societies: (a) glycemic monitoring and targets, (b) use of antihyperglycemic therapies, (c) blood pressure control and comprehensive management, (d) lifestyle interventions, and (e) the importance of self-management and team-based care.

Glycemic Management

Given the significant role that hyperglycemia plays in the development of DKD, adequate glycemic management is one of the most important and most challenging aspects of diabetes management, especially in patients with CKD. Hemoglobin A1c (HbA1c) may be inaccurate in patients with advanced kidney disease, especially in dialysis patients. Insulin, which has significant metabolism and clearance by the kidneys, may last longer in the body. Oral antihyperglycemic agents, which are metabolized or cleared by the kidneys, may accumulate and lead to hypoglycemic episodes. Many agents need dose adjustments or discontinuation with changes in kidney function.

Glycemic Monitoring and Targets

Glycemic control in diabetics can be assessed by HbA1c measurement, self-monitoring of blood glucose (SMBG), and/or continuous glucose monitoring (CGM). Early intensive diabetes control, as evidenced by lower HbA1c targets, is associated with a lower risk of long-term diabetic microvascular complications and mortality, both in T1DM and T2DM [4, 5]. The Diabetes Control and Complications Trial (DCCT) showed that when compared to conventional diabetes therapy, intensive therapy in T1DM was associated with a reduction in the incidence of microalbuminuria and albuminuria. Long-term follow-up of DCCT treatment groups showed a significant decrease in the development of impaired GFR and hypertension [4]. Meta-analysis of four large randomized controlled trials in T2DM (ACCORD, ADVANCE, UKPDS, and VADT) showed beneficial effects of intensive glycemic control with reduced incidence of microvascular complications including microalbuminuria and macroalbuminuria [6].

All major societies recommend using HbA1c to monitor glycemic control (Table 2.1). ADA recommends checking HbA1c at least twice a year in patients meeting treatment goals and stable glycemic control, and quarterly in those not meeting goals and/or in who the treatment has been modified (*E*) [7]. HbA1c goal of <7% is recommended by ADA for most patients *(A)*, with lower goals (<6.5%) based on provider judgment and patient preference in those with no significant hypoglycemia *(C)*. Higher targets (<8%) are recommended for those with advanced CKD, established macrovascular complications, limited life expectancy, hypoglycemic unawareness, risk of medication-induced hypoglycemia, and presence of other comorbidities, or in

Table 2.1 Guidelines recommendations for management of patients with diabetes and CKD

Topic	ADA (2021)	KDIGO (2020)	ESC and EASD (2019)
HbA1c target	<7.0% *(A)* <8%[a] *(B)*	6.5–8.0% *(1C)*	<7% *(IA)*
First-line hypoglycemic agent	Metformin *(A)* + SGLT2i[b] *(A)* GLP1-RA[c] *(A)*	Metformin *(1B)* SGLT2i *(1A)* GLP1-RA[d] *(1B)*	SGLT2i [e] *(IB)* or GLP1-RA[f] *(IIaB)*
Physical activity level	200–300 min/week (A)	150 min/week *(1D)*	≥150 min/week *(IA)*
Protein intake	0.8 g/kg/day *(A)*	0.8 g/kg/day *(2C)*	*Less protein is recommended*
Sodium intake	<2300 mg/day *(B)*	<2000 mg/day *(2C)*	<2300 mg/day *(IA)*
Blood pressure target	<140/90 mm hg *(A)*	–	Systolic blood pressure < 130 mm hg *(IA)* Diastolic blood pressure < 80 mm hg *(IC)*
Albuminuria reduction	RAAS blocker for UACR ≥300 mg/g *(A)* or 30–299 mg/g *(B)* SGLT2i for UACR >300 mg/g *(A)*	RAAS blocker *(1B)*	RAAS blocker *(IA)*

HbA1c hemoglobin A1c, *SGLT2i* sodium-glucose cotransporter 2 inhibitors, *GLP-1RA* glucagon-like peptide-1 receptor agonists; *RAAS blocker* renin-angiotensin-aldosterone system blocker, *UACR* urine albumin-to-creatinine ratio

[a]For those with history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve

[b]For those with eGFR ≥30 ml/min/1.73 m^2 and albuminuria ≥30 mg/g creatinine

[c]For those with CKD with increased risk of MACE

[d]For those who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications

[e]For those with eGFR 30–90 ml/min/1.73 m^2

[f]For those with eGFR ≥30 ml/min/1.73 m^2

those who the goal is difficult to achieve despite the use of multiple agents *(B)*. Similar recommendations for an individualized target ranging from <6.5% to <8% are made by KDIGO *(1C)*. ESC/EASD also recommends a target of <7% to reduce microvascular *(1A)* and macrovascular complications *(IIa/C)*. HbA1c assessment may be inaccurate in certain conditions, such as in the presence of hemoglobin variants, as well as conditions that affect red blood cell turnover (hemolytic and other anemias, recent blood transfusion, glucose-6-phosphate dehydrogenase deficiency, use of erythropoietin-stimulating agents, advanced CKD including ESKD, and pregnancy). Another limitation of this test is that it does not provide a measure of glycemic variability or hypoglycemia**.** KDIGO guidelines recommend that clinical judgment should be exercised when using HgbA1c in such conditions.

Diabetic patients with markedly labile blood glucose values who are more prone to hypoglycemic events, such as T1DM and T2DM with severe insulin deficiency, need daily glucose monitoring. In such situations, SMBG by the patient is a useful tool that aids in self-management and medication titration. CGM can play an important role in assessing the safety and efficacy of treatment in patients who require intensive insulin regimens. ESC/EASD *(IIa/A)* and KDIGO suggest using SMBG or CGM to facilitate optimal glycemic control and avoid the risk of hypoglycemia, and a glucose management indicator derived from CGM to assess glycemic control for patients in whom HbA1c is not concordant with their clinical symptoms or measured glucose levels [1, 2]. For certain patient population, CGM metrics like "Time in Range (TIR)" and "Time in Hypoglycemia" may be used in place of HbA1c as glycemic targets and parameters for the reevaluation of the treatment regimen. With the use of CGM, ADA recommends a goal TIR of >70% with a time below the range of 4% as a parallel goal to HbA1c *(B)*.

Medical Therapy for Hyperglycemia

The goal of therapy in diabetes is to manage hyperglycemia and prevent and treat its associated microvascular and macrovascular complications. While drug therapy in T1DM is essentially centered around insulin, more options are available to patients with T2DM.

Older Agents

Apart from lifestyle modification, multiple oral and injectable antihyperglycemic drugs are available for glycemic management in patients with T2DM. When selecting glucose-lowering medications for patients with T2DM and CKD, due consideration should be given to a particular agent's risk of hypoglycemia and limitations of use in reduced GFR. Since DKD is a risk factor for developing cardiovascular disease (CVD), medication safety and efficacy in the prevention and treatment of CVD should also be considered. Cost and patient preference will also guide the use of one agent over the other.

For a long time, sulfonylureas and metformin were the primary oral agents. In 1998, the UK Prospective Diabetes Study showed the benefit of metformin in reducing the risk of mortality in overweight patients with T2DM by 36% compared to conventional therapy. Also, metformin prevents weight gain, helps achieve weight loss, and reduces cardiovascular events [8]. Compared with sulfonylureas, metformin is associated with less risk of hypoglycemia, and in comparison to thiazolidinediones, it has reduced incidences of edema, congestive heart failure, and weight gain. Metformin is recommended as the first-line agent for treating T2DM patients with CKD with eGFR ≥30 ml/min/1.73m^2 by ADA *(A)* and KDIGO *(1B)*. Based on

ESC/EASD guidelines, metformin should be considered in T2DM patients without CVD and for those at moderate CVD risk *(IIa)*. In patients with reduced eGFR (<45 ml/min/1.73m^2), the US Food and Drug Administration recommends that metformin should not be initiated and an existing dose should be reduced. Metformin should be temporarily discontinued before the use of iodinated contrast in those with eGFR between 30 and 60 ml/min/1.73m^2. Its use is contraindicated in patients when eGFR is <30 ml/min/1.73 m^2 due to increased risk of lactic acidosis, which is endorsed by clinical practice guidelines.

If the glycemic target is not achieved after about 3 months of treatment with metformin, ADA recommends adding one of the six classes of antihyperglycemic drugs: sulfonylureas, thiazolidinediones (TZD), sodium-glucose cotransporter 2 inhibitor (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), or basal insulin**.** The choice of this additional drug will be based on the specific effects of each class of medication, their side-effect profile, cost, level of kidney function, and patient factors *(E)*. Medications cleared by the kidneys such as sulfonylureas accumulate with reduced GFR and, thus, increase the risk of hypoglycemia. Thiazolidinediones (pioglitazone and rosiglitazone) as well as saxagliptin (a DPP4i) are associated with an increased risk of incident heart failure and are, therefore, not recommended for use in patients with or at increased risk of heart failure (ESC/EASD, *III*).

Newer Agents

Several newer antihyperglycemic agents, including SGLT2i and GLP-1RA, have been tested in large trials and have become available for clinical use in recent years.

Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

The most important of the newer classes of antihyperglycemic drugs are the SGLT2i. SGLT2i directly affect the sodium-glucose cotransporter 2 in the proximal tubule of the kidneys and thereby inhibit tubular glucose and sodium reabsorption and reduce intraglomerular pressure albuminuria, oxidative stress, and inflammation in the kidney and, ultimately, reduce risk of CKD progression and CVD events [9]. Besides, they cause modest volume contraction, systemic blood pressure reduction, and weight loss. Major adverse effects are diabetic ketoacidosis, lower extremity amputations, and genital mycotic infections. They can cause an initial decrease in GFR due to hemodynamic effects, but this is usually reversible and rarely needs therapy discontinuation. Long-term use of SGLT2i is associated with the preservation of GFR. Several large cardiovascular outcomes trials with SGLT2i in patients with T2DM at high risk of CVD or existing CVD (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58) have examined kidney effects as secondary outcomes [10–12]. Recent trials, focused on primary kidney outcomes using SGLT2i (CREDENCE

and DAPA-CKD), have shown beneficial results with these medications and have established SGLT2i as an important class of medications in the management of DKD [13, 14]. Canagliflozin can be used in patients with reduced GFR (above 30 ml/min/1.73m^2). Dapagliflozin has been studied in populations with eGFR down to 25 ml/min/1.73m^2 and has also shown efficacy in nondiabetic CKD [14].

Based on the results of these trials, the use of an SGLT2i is recommended by KDIGO *(1A)*, ADA *(A)*, and ESC/EASD *(IB)* for patients with T2DM and DKD with eGFR ≥30 ml/min/1.73m^2 and urinary albumin/creatinine of >300 mg/g [1, 2, 15]. ADA guidelines recommend that when an additional agent required to be added to metformin or metformin cannot be used or tolerated, an SGLT2i or GLP-1RA should be considered. Unless contraindicated, KDIGO recommends using metformin along with an SGLT2i as the first-line therapy in patients with T2DM and CKD *(1A)*. For patients not meeting their glycemic targets despite using other antihyperglycemic agents and who can tolerate further lowering of HbA1c, KDIGO suggests adding an SGLT2i. For patients meeting their glycemic target or at risk of hypoglycemia with further lowering of A1c, agents other than metformin can be reduced to allow the addition of SGLT2i.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA)

GLP-1RA stimulate the incretin hormone pathway and thereby enhance the glucose-dependent insulin secretion, suppress postprandial glucagon release, slow the gastric emptying, and improve satiety through effects on the central regulation of feeding. These actions assist in improving glycemic control, weight loss, and reducing blood pressure. Independent of the glucose-lowering effects, GLP-1RA also have direct nephro-protective effects. These agents inactivate sodium hydrogen exchanger 3 in the brush border of the proximal tubular cells of kidneys and promote secretion of atrial natriuretic peptide, thereby inducing natriuresis and diuresis and thus improving blood pressure.

In large cardiovascular outcomes trials (ELIXA, LEADER, SUSTAIN-6, REWIND) in patients with or at high risk of CVD, GLP1-RAs such as lixisenatide [16], liraglutide [17, 18], semaglutide [19], and dulaglutide [20] have shown beneficial kidney effects as secondary outcomes (preservation of eGFR and prevention of worsening albuminuria). Based on the data from these trials, and independent of the glycemic targets, ADA recommends using an SGLT2i or GLP-1RA with cardiovascular benefit in patients with established atherosclerotic CVD, established kidney disease, or heart failure *(A)* [21]. KDIGO also recommends using a long-acting GLP-1RA as an agent of choice in patients who cannot achieve glycemic target despite the use of metformin and SGLT2i *(1B)*. Efficacy of SGLT2i in improving glycemic control is reduced at eGFR <45 ml/min/1.73m^2. To achieve additional glycemic control at that level, a long-acting GLP-1RA should be considered [1]. Liraglutide, semaglutide, and dulaglutide are minimally cleared by kidneys and, therefore, do not require any dose adjustment even with eGFR as low as 15 ml/

min/1.73m^2. For T2DM patients who need the addition of an injectable agent on top of oral agents to achieve glycemic target, ADA recommends preferred use of GLP-1RA over insulin *(B)*.

Insulin Use in Type 2 DM

Insulin use in T2DM is recommended by ADA (*E*) for those patients who present with significantly elevated blood glucose levels (≥300 mg/dl), or HbA1c levels of >10%, or symptoms of hyperglycemia (polyuria, polydipsia), or those with catabolic features (weight loss, hypertriglyceridemia, ketosis) [21]. Many patients with long-standing T2DM may eventually require insulin therapy in addition or instead of other agents. Basal long-acting insulin can be added to metformin or other oral drugs to improve glycemic control. It helps to reduce hepatic glucose production and controls hyperglycemia overnight and between meals. Some patients may also require the addition of doses of prandial short-acting insulin. In patients with a substantial reduction of kidney function, insulin doses can be titrated by patients based on self-monitoring of glucose levels to avoid hypoglycemia.

Hypertension Control in DKD

Hypertension is common comorbidity among patients that have both diabetes and CKD. Approximately 58–70% of patients that are diagnosed with diabetes also have a diagnosis of hypertension. Additionally, many patients have been known to develop hypertension before displaying signs of kidney disease [22]. Alternatively, with declining eGFR, the incidence of developing hypertension increases. Thus, optimal control of hypertension in patients with DKD is crucial to CVD risk reduction and slowing the progression of kidney disease.

Hypertension Management

Treatment of hypertension in patients with DKD involves both pharmacologic and non-pharmacologic measures to reduce cardiovascular risk and delay complications. Non-pharmacologic interventions include lifestyle and dietary modifications, physical activity, and lipid control, which have been discussed in other sections of this chapter.

Managing hypertension via RAAS inhibition in patients with DKD remains the cornerstone of pharmacological therapy. RAAS inhibition is achieved using ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) to improve albuminuria, cardiovascular risk reduction, and reduction of DKD progression [23–25]. KDIGO

clinical practice guidelines recommend using either ACEi or ARB in their maximally tolerated doses in patients with DKD and hypertension *(1B)*. After initiation of therapy with either agent, kidney function is to be monitored. Unless an increase in serum creatinine by >30% is observed within 4 weeks, the agent is to be continued [1]. ESC/EASD guidelines also recommend using either ACEi or ARB in their maximally tolerated doses for treatment of hypertension to achieve a blood pressure target of 120/80 mm Hg or at least targeting 130/80 mm Hg in patients with diabetes *(IA)* [2]. ADA guidelines encourage lifestyle intervention for patients with blood pressure ≥ 120/80 mm Hg with initiation of antihypertensive therapy once blood pressure is ≥140/90 *(A)*. Initial antihypertensive therapy is recommended with ACEi or ARB, at its maximum tolerated dose *(C)* [26].

Given the advantages of RAAS inhibition with monotherapy, treatment of DKD and hypertension with dual agents has also been studied. However, long-term studies including the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) have failed to show an improvement in cardiovascular outcomes with dual agents. Rather they have shown an increased risk of acute kidney injury and hyperkalemia [27, 28]. If optimal hypertension control is not achieved with single agent RAAS blocker, other agents including diuretics, calcium channel blockers (CCB), and/or beta-blockers may be used. CCB in combination with ACEi or ARB may help improve BP in addition to albuminuria [29]. If hypertension persists, despite management with three antihypertensive agents, the use of mineralocorticoid receptor antagonist may be considered as they have also been shown to help reduce BP and improve albuminuria [30].

Albuminuria Management

Proteinuria is a hallmark finding in patients with DKD and has been independently associated with increased cardiovascular risk and kidney disease progression. Consequently, in patients with DKD that are normotensive, ACEi or ARB may be considered if albuminuria is present to minimize this risk as suggested in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and INNOVATION (The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy) trials [25, 31]. Conversely, if non-albuminuria and normotension is present, RAAS inhibition is not likely to help and has not been shown to reduce the incidence of either CKD progression or albuminuria [32]. ADA recommends ACEi or ARB for albuminuria ≥300 mg/g *(A)* or 30–299 mg/g *(B)* [26]. SGLT2i is another agent to be considered per ADA clinical practice for urinary albumin creatinine >300 mg/g *(A)* [15]. KDIGO guidelines also recommend treatment with an ACEi or ARB for patients with diabetes, hypertension, and albuminuria *(1B)* [1]. ESC and EASD guidelines recommend treatment with ACEi or ARB for patients with hypertension and diabetes, especially with albuminuria or left ventricular hypertrophy *(IA)* [2]. If

albuminuria is <30 mg/24 h, other agents including diuretics and dihydropyridine calcium channel blockers may be considered, which have also demonstrated a reduction in cardiovascular risk.

Lifestyle Management

Tobacco Cessation

Tobacco use is a risk factor for developing CKD and CVD and is one of the leading causes of mortality worldwide [33, 34]. Avoiding tobacco products may provide health benefits and reduce the incidence of these disease processes and mortality. Although no randomized control trials have examined the effects of tobacco cessation on patients with diabetes and kidney disease, a small randomized trial did show increased BP values and DKD progression in smokers [35]. Additionally, a prospective cohort study reported a higher cardiovascular risk in current or prior smokers with diabetes and kidney disease [36]. Numerous other studies have shown an association between tobacco cessation and decreased albuminuria in patients with CKD, and retardation of diabetic kidney disease [37, 38]. Hence, recently released KDIGO clinical practice guidelines recommend tobacco cessation for those with diabetes and kidney disease *(1D)* [1, 2].

Dietary Modifications

A well-balanced diet is an essential factor in maintaining optimal health. ADA recommends weight loss and the Dietary Approaches to Stop Hypertension (DASH) diet in patients with BP > 120/80 and DM *(A)* [26]. This diet focuses on low sodium and increased potassium intake. However, as a patient's kidney disease progresses, the importance of limiting certain foods that may lead to various electrolyte abnormalities and volume imbalances increases. Limiting foods rich in potassium or phosphorus is often necessary in CKD to prevent hyperkalemia or hyperphosphatemia. Additionally, increased protein intake can lead to increased acid load, which can be associated with worsening metabolic acidosis in patients with advanced kidney disease. ADA recommends protein intake of approximately 0.8 g/kg body weight per day in patients with CKD and diabetes *(A)* [15]. KDIGO also recommends restricting dietary protein intake in patients with diabetes and CKD to 0.8 g/kg/day *(2C)* to help limit glomerular hyperfiltration and reduce kidney disease progression [1, 39]. For patients that are on kidney replacement therapy, ADA recommends increasing protein intake to avoid malnutrition *(B)* [15]. KDIGO recommends a protein intake of 1–1.2 g/kg/day to counteract their high catabolic state and negative nitrogen balance [1]. KDIGO and ESC/EASD guidelines recommend patients with DKD to have a diet rich in vegetables, fruits, whole grains, fibers, legumes,

plant-based proteins, unsaturated fats, and nuts *(IA)*. On the other hand, processed foods, carbohydrates, and alcohol consumption should be limited [1, 2].

Another risk factor that leads to increased blood pressure, worsening CV function, and kidney disease progression is sodium [40]. Increased sodium intake promotes water reabsorption contributing to hypervolemia. Consequently, sodium restriction has been studied considerably in many trials over recent years [41, 42]. Restricting sodium in the diet improves the effect of RAAS blockade and improves blood pressure, which is associated with decreased CV events, reduced stroke risk, and decreased CKD progression [43, 44]. Additionally, limiting sodium intake may improve hypervolemia in addition to proteinuria [45]. KDIGO recommends limiting sodium intake to less than 2 g per day in patients with diabetes and CKD *(2C)* [1]. ADA recommends sodium restriction to 2.3 g per day in patients with prediabetes and diabetes *(B)* [46]. ESC/EASD guidelines recommend limiting sodium intake to <2.3 g per day in patients with DKD *(IA)* [2].

Physical Activity and Exercise

Exercise and physical activity have a positive correlation with a healthy lifestyle. However, many of the patients with CKD and DM are sedentary or have low levels of physical activity, which places them at an even higher risk of CVD and mortality. Many studies have shown a benefit of physical activity in CKD patients, including improved blood pressure, increased capacity, cognitive benefits, CV function, and improved quality of life [47, 48]. Although there is limited data on physical activity in patients with diabetes and CKD, increased physical activity likely brings similar advantages in this population in addition to reducing HbA1c levels [49, 50]. ADA clinical practice encourages 200–300 min of physical activity per week *(A)* [51]. ESC/EASD guidelines recommend aerobic and resistance training for at least 150 min per week *(IA)* to improve glycemic control, lipid levels, and hypertension [2]. In line with the 2019 American College of Cardiology/American Heart Association guidelines, KDIGO clinical practice guidelines also recommend at least 150 min per week of accumulated moderate-intensity physical activity in patients with DKD *(1D)* [1, 52].

Self-management Programs and Team-Based Care

Self-management skills are critical for those with diabetes and kidney disease. Several diabetes self-management educational programs have been developed to empower and enable individuals to build self-management knowledge and skills. Overall goals of these programs are to reduce long-term microvascular and macrovascular complications, severe hypoglycemia, and diabetic ketoacidosis and to optimize well-being, quality of life, and treatment satisfaction. These programs can be

delivered face-to-face as one-to-one or group-based programs or via technology platforms by different members of health-care teams. Systematic reviews in the general population with diabetes have shown that reducing clinical risk factors in self-management education programs is likely to offer cost savings in the long-term. Therefore, KDIGO clinical practice guidelines recommend a structured self-management educational program be implemented for the care of people with diabetes and CKD *(1C)* [1]. These guidelines also recognize the importance of team-based care and suggest that policymakers and institutional decision-makers should implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD.

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Part I
Natural Course, Pathogenesis, Morphology and Genetics

Chapter 3
Diabetic Kidney Disease: Scope of the Problem

Jing Chen

Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the United States and worldwide [1, 2]. Approximately 30–40% of persons with diabetes develop diabetic nephropathy, manifested as albuminuria and/or decreased glomerular filtration rate [3]. Higher levels of albuminuria and lower levels of estimated glomerular filtration rate (eGFR) independently increase the risk for cardiovascular events, ESKD, and death [4, 5].

Epidemiology of Diabetic Kidney Disease

Prevalence of diabetes has reached epidemic proportions in the world. According to the International Diabetes Federation, the global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence is higher in urban (10.8%) than rural (7.2%) areas and in high-income (10.4%) than low-income countries (4.0%). The prevalence of diabetes in women in 2019 is estimated to be 9.0% and 9.6% in men.

The increase of diabetes prevalence with age leads to a prevalence of 19.9% (111.2 million) in people aged 65–79 years. The global prevalence of impaired glucose tolerance is estimated to be 7.5% (374 million) in 2019 and projected to reach 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045 [6]. In the United States, 31 million adults aged 20–79 years had diabetes in 2019, and the number is expected to rise to 34.4 million by 2030 and 36.0 million by 2045 [6].

With the global epidemic of diabetes, diabetic kidney disease has become an important clinical and public health challenge. In 2017, the age-standardized global

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Table 3.1 Prevalence (95% confidence interval) of diabetic versus nondiabetic kidney disease versus in the US population, NHANES 2009–2014

	CKD	UACR ≥300 mg/g	eGFR <60 ml/min per 1.73 m^2
Diabetes, %	25 (21 to 28)	4.6 (3.4 to 5.8)	12 (9 to 15)
No diabetes, %	5.3 (4.6 to 5.9)	0.3 (0.2 to 0.5)	2.5 (2.0 to 3.0)

Data are adopted from Zelnick et al. [8]
NHANES National Health and Nutrition Examination Survey, *CKD* chronic kidney disease, *UACR* urine albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate

prevalence of diabetic kidney disease (DKD) in men and women was 15.48/1000 and 16.50/1000, respectively [7]; and there were an estimated 219,451 deaths that were attributed to DKD among men and women, respectively. These deaths accounted for about 34% of all CKD deaths among men in 2017 and 36% in women. These proportions have increased since 1990, where DKD deaths were 29% of all CKD deaths in men and 32% of all CKD deaths in women [7]. According to data from National Health and Nutrition Examination Survey from 2009 to 2014, the estimated prevalence of CKD (eGFR <60 ml/min per 1.73 m2; albumin-to-creatinine ratio ≥ 30 mg/g, or both) for those with diabetes versus without diabetes was 25% versus 5.3% in the United States, respectively; albumin-to-creatinine ratio ≥ 30 mg/g was 16% versus 3.0%, respectively; and eGFR <60 ml/min per 1.73 m^2 was 12% versus 2.5%, respectively (Table 3.1). Approximately 24% of CKD among all US adults was attributable to diabetes after adjusting for demographics [8].

Despite that the prevalence of diabetes in the United States has increased over the last 20 years from 6% to 10%, the proportion of people with diabetes who also have CKD has remained relatively stable (approximately 25% to 30%) [8, 9]. However, the distribution of clinical manifestations of diabetic kidney disease has changed [9]. The prevalence of persistent moderately to severely increased albuminuria in diabetic patients decreased from approximately 21% during the period from 1988 to 1994 to 16% during the period from 2009 to 2014. By contrast, the prevalence of decreased eGFR (<60 mL/min/1.73 m2) increased from 9% to 14%. The lower prevalence of albuminuria over time was observed only among adults younger than 65 years and non-Hispanic whites, whereas the prevalence of reduced eGFR appeared to increase without significant differences by age or race/ethnicity [9]. The lack of decline in albuminuria prevalence among blacks and Mexican Americans may be attributable in part to less frequent use of proven diabetes therapies [10].

The CKD awareness remains extremely poor. Only 10% of people with stage 3 CKD (eGFR 30 to 59 mL/min/1.73 m^2) are aware of their diagnosis in the United States; although this proportion is higher among people with stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m2), less than 60% of patients overall are aware of their disease [1, 11]. One in two (50.1%) people living with diabetes do not know that they have diabetes in the world [6].

The costs for diabetic nephropathy to individual and society are considerable. In the United States, the total Medicare spending on both chronic kidney disease and ESRD patients was in excess of $120 billion in 2017. For identified CKD (not

ESRD), the total Medicare expenditure was $84 billion. Spending for ESRD patients totaled $35.9 billion, accounting for 7.2% of the overall Medicare-paid claims in the fee-for-service system [12]. The cost of diabetic kidney disease was recently analyzed using information from 5968 studies in French or English published between January 1, 2000, and October 23, 2015; an average cost per patient and per year ranged from US $1095 to US $16,384 [13]. The cost of diabetic nephropathy progression using information from the Kaiser Permanente Northwest health maintenance organization suggested that annual medical costs were 37% higher following progression from normoalbuminuria to microalbuminuria ($10,188 vs. $7424) and 41% higher following progression from microalbuminuria to macroalbuminuria ($12,371 vs. $8753) [14].

In summary, the prevalence of diabetic kidney disease is high. Diabetic nephropathy accounts for nearly half of all incident cases of end-stage renal disease in the United States. In addition, diabetic kidney disease 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 United States. 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.

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. These disorders likely interact to exacerbate the kidney damage (Fig. 3.1).

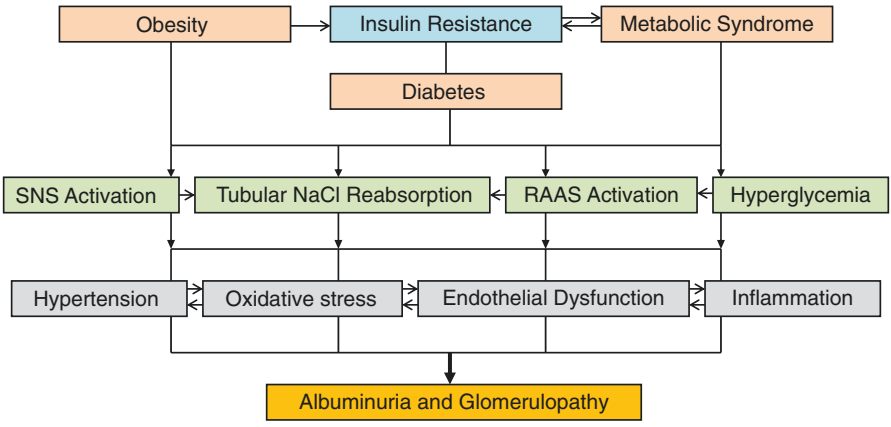

Fig. 3.1 Interaction of obesity-, metabolic syndrome-, and diabetes-related kidney disease
Abbreviations: SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system

According to data from NHANES from 1988 to 1994, 1999 to 2000, and 2015 to 2016, the age-adjusted overall prevalence of obesity in the United States increased progressively from 22.9 to 30.5 to 39.6 percent [15]. In 2015 to 2016, the prevalence of obesity in men was 37.9%, and the prevalence of obesity in women was 41.1%. The age-adjusted prevalence of class III obesity (body mass index [BMI] ≥40 kg/m^2) has risen from 5.7% to 7.7% between 2007 and 2016 [15]. Globally, the proportion of adults with a body mass index (BMI) of 25 or greater increased from 28.8% (95% UI: 28.4–29.3) in 1980 to 36.9% (36.3–37.4) in 2013 for men and from 29.8% (29.3–30.2) to 38.0% (37.5–38.5) for women. Increases were observed in both developed and developing countries. There have been substantial increases in prevalence among children and adolescents in developed countries, with 23.8% (22.9–24.7) of boys and 22.6% (21.7–23.6) of girls being either overweight or obese in 2013. The prevalence of overweight and obesity is also rising among children and adolescents in developing countries as well, rising from 8.1% (7.7–8.6) to 12.9% (12.3–13.5) in 2013 for boys and from 8.4% (8.1–8.8) to 13.4% (13.0–13.9) in girls. Among adults, estimated prevalence of obesity exceeds 50% among men in Tonga and women in Kuwait, Kiribati, Federated States of Micronesia, Libya, Qatar, Tonga, and Samoa [16]. The rising trends in overweight and obesity warrant timely attention from health policy and healthcare system decision.

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 [17–20]. Clinical trials also indicate that weight loss reduces blood pressure in most hypertensive subjects and is effective in primary prevention of hypertension [18].

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 [21, 22]. 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 [23]. Increased systolic blood pressure further exacerbates the disease progression to proteinuria and a decline in glomerular filtration rate leading to end-stage renal disease [24]. 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 [25].

Hyperfiltration and increased glomerular filtration rate are the common early renal changes associated with obesity and diabetes [23, 26]. 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 [27]. 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 nonobese, nondiabetic subjects [28]. 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 [29–31]. 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 [32, 33]. 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 [34]. Some studies suggest that hyperglycemia, obesity, and hypertension may have at least partially additive effects on glomerular hemodynamics [28]. For example, mice lacking the gene for the melanocortin-4 receptor are obese, hyperinsulinemic, and hyperleptinemic but normotensive at 55 weeks of age [35]. 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 [36, 37]. However, further studies are needed to determine if the beneficial effects of lipid-lowering agents in diabetic kidney disease 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, 38]. 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 [39]. Hyperlipidemia is known to be a risk factor for the development of albuminuria in patients with diabetes [40].

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 pro-inflammatory cytokines including tumor necrosis factor-α, interleukin-6, and monocyte chemoattractant protein-1 [41]. 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, cellular events that are important in the development of diabetes and obesity-associated glomerular injury [42]. 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 [28]. 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 may derive directly from the growth in the prevalence of diabetes among individuals aged 65 years and older [6, 8, 9]. Almost half (44%) of the global population with diabetes are more than 65 years of age with a prevalence that peaks (22%) at 75–79 years of age [43]. The

prevalence of CKD in older people (aged ≥65 years) with diabetes increased from 27.3% between 1988 and 1994 to 40.6% between 2009 and 2014 as reported by the National Health and Nutrition Examination Survey [9]. The increase in prevalence of reduced eGFR among individuals aged 65 years and older appeared more significant compared with increase in prevalence in albuminuria in the United States [9]. In a representative sample of outpatients with type 2 diabetes in Italy, DKD prevalence, especially low eGFR, was very high in subjects >65 years old [44]. Renal complications affect 41.3% of this population and more than 60% of those aged >75 years [44].

One of the challenges of managing the elderly with diabetic nephropathy is that they may develop more complications. Older adults with diabetes are at higher risk for both acute and chronic microvascular and macrovascular complications from the disease, including major lower-extremity amputations, myocardial infarctions, visual impairments, and end-stage renal disease, compared to any other age group [45]. Patients who are >75 years of age are more likely to develop complications, have higher rates of death from hyperglycemic crises, and have an increased rate of emergency department visits for hypoglycemia compared to those who are <75 years of age [46]. A recent analysis of the economic cost of diabetes showed that ~61% of all healthcare costs attributed to diabetes are incurred by people with diabetes who are >65 years of age [47]. The average annual expenditure for older adults (≥65 years of age) was $13,239 compared to $6675 for the younger cohort. Thus, older adults with diabetes comprise a growing population posing high health and economic burdens to the society.

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 [48]. 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 [49]. Likewise, tubular atrophy and interstitial fibrosis may be aging-related or due to chronic inflammation or vascular disease [50]. Elderly patients with type 2 diabetes may have renal ischemia due to renal artery stenosis. Sawicki and colleagues [51] 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 Geriatrics Society Panel on Improving Care for Elders with Diabetes recommends that treatment of elderly patients with diabetes focus on specific problems and priorities [52]. (3) The American Geriatrics 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 [53]. (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 [53]. (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, and (6) elderly diabetic patients may be susceptible to nephrotoxic agents such as radiocontrast; thus 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 healthcare 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.

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Chapter 4
Natural Course (Stages/Evidence-Based Discussion)

Dragana Lovre and Tina Kaur Thethi

Introduction

Diabetic kidney disease (DKD) has historically been called diabetic nephropathy if there is macroalbuminuria or proteinuria [1, 2]. DKD is progressive kidney disease as a complication of prolonged hyperglycemia that occurs in both type 1 (T1) and type 2 (T2) diabetes mellitus (DM). Some of the secondary causes of DM include medications, pancreatic disorder, and excess of hormones such as cortisol, catecholamine, or growth hormone, and genetic predisposition [3]. According to the national chronic kidney disease fact sheet of 2017, DM is the most common cause of renal failure in the United States (USA), making about 44% of all new cases [4]. According to the Centers for Disease Control and Prevention morbidity and mortality report from 2017, the overall age-standardized incidence of end-stage renal disease attributed to diabetes (ESRD-D) among adults with diagnosed diabetes decreased by 33% during 2000–2014 [5]. T2DM accounts for about 90–95% of all DM cases and is thus a more common cause of DKD including ESRD [6]. ESRD secondary to T2DM varies among countries and racial group as well as in non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM) patients. In the 1990s incidence in Canada and Japan was in 20% range and Europe and Australia in 10–20% range [7]. The increase in ESRD incidence rates in the USA has leveled off in recent years, but a recent prediction model indicates that population distribution changes, obesity and diabetes prevalence, and ESRD

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survival will result in an 11%–18% increase in the crude incidence rate from 2015 to 2030 [8].

The use of terminology for DKD has been introduced for consistent classification of chronic kidney disease (CKD) by Diabetes and CKD guidelines. The use of the term "DKD" has been reinforced by Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations (CPGCPR) for Diabetes and CKD [9]. It has been suggested to use the term DKD as "presumptive diagnosis of kidney disease caused by diabetes" in place of diabetic nephropathy [9]. KDOQI CPGCPR recommends using the term diabetic glomerulopathy for kidney disease due to diabetes diagnosed by kidney biopsy [9].

Additionally, KDIGO recommends that CKD is classified based on cause (C), GFR category (G), and albuminuria (A) category, that is, it recommends using a CGA classification [10]. GFR category is as shown in Table 4.2, while albumin (A) categories include the following: A1 (ACR <30 mg/g), normal to mildly increased; A2 (ACR 30–300 mg/g), moderately increased; and A3 (ACR >300 mg/g), severely increased [10].

Natural History of DKD in T1DM

Majority of the studies done in the 1960s to 1980s have demonstrated that at the diagnosis of T1DM, the changes occur in kidneys' function, structure, and biochemical profile and have led to identification of natural course of DKD, which occurs in series of five stages [11–16]. As the clinical onset of T1DM is well known compared to that of T2DM, where diagnosis may have been delayed, much of our understanding of DKD has been delineated mainly from experimental animal models and partly from patients with T1DM. However, not all animal models resemble the actual human disease process, and thus the knowledge of the course of kidney disease comes with limitations. Data from the 1980s show that approximately 25–40% of patients with T1DM and 5–40% with T2DM develop diabetic nephropathy [1, 11]. More recent data show that 20–30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy [17]. Numerous other factors have been associated with the development of DKD such as hypertension, cardiovascular disease (CVD), hyperlipidemia, and obesity (body mass index [BMI] ≥ 30) [18]. This chapter will discuss the current understanding of the etiology, disease course, and the different stages of and modification related to DKD.

The associated metabolic abnormalities resulting from diabetes lead to alterations in hemodynamics, structure, and biochemical levels within the kidneys [1, 11]. Many investigative studies have paved the way in identification of the different stages that occur in DKD. Nephropathy is preceded by microalbuminuria. DKD (also been previously known as diabetic nephropathy) can be described in five stages in relation to the changes in function as documented by UAE and GFR, and structure in terms of renal morphology. The majority of changes in the different stages of DKD have been best delineated by Mogensen in 1983 [1, 11, 19]. This chapter discusses the various stages of DKD, which are summarized in Table 4.1 including the unique characteristics seen at different stages.

Table 4.1 Classification and characteristics of diabetic kidney disease stages in T1DM

Stages	UAE values	Characteristics
1: Hypertrophy-hyperfiltration (at diagnosis)	Normal UAE: <20 μg/min < 30 mg/24 h <30 mg mg/g	Kidneys have increased size and weight, hypertrophy of glomerulus, increased intraglomerular pressure, increased TGF-β receptors, hyperfunction, may have normal BM GFR can be normal or increased usually greater than 150 ml/min BP is usually normal but can be increased (especially if there is coexisting essential hypertension) The changes in kidney function are reversible
2: Silent stage (normoalbuminuria)	Normal UAE as above <20 μg/min < 30 mg/24 h <30 mg mg/g UAE can be increased during stressful situation	Kidneys have increased GBM thickness and peripheral GBM thickness, expansion of mesangium, and increased tubular BM width. Possible accumulation of BM-like material and membrane GFR can be normal, decreased, or high (greater than 150 ml/min) BP starting to increase
3: Incipient Diabetic Nephropathy	Microalbuminuria: 20–200 μg/min 30–300 mg/24 h 30–300 mg/g[a] (USA) 2.5–25 mg/mmol (men) and 3.5–35 mg/mmol (women) in Europe and elsewhere	Kidney lesions can range from stage 2 to 4 with some starting from glomerular closure and elevated intraglomerular pressure Renal function is well preserved, but it can have hyperfiltration GFR can be well preserved but can be increased or decreased (from 70 to greater than 150 ml/min) BP is usually higher compared to nondiabetic patients and more prominent during exercise. Loss of nocturnal dip in BP With strict glycemic, BP, and lipid control, this stage can be reversible Without treatment approximately 80% of patients will progress to stage 4 Retinopathy is often present in most T1DM
4: Overt diabetic Nephropathy	Macroalbuminuria: 200 μg/min ≥ 300 mg/24 h >300 mg/g[a]	Kidneys have advanced lesions including diffuse and nodular glomerulosclerosis, increased mesangial volume, additional increase in GBM thickness, mesangial expansion, more frequent glomerular closure, and tubulointerstitial lesions GFR usually starts to decline (can range from 70 to 15 ml/min) but can be normal BP is usually high in majority of patients Renal changes are usually not reversible In a few T1DM UAE can regress
5: End-stage Renal Disease (Uremia)	Decreased UAE as closure of nephron	Kidneys have advanced lesions with hypertrophy of the rest of glomeruli, and generalized closure of glomerulus GFR is usually decreased and typically <15 ml/min requiring renal replacement therapy BP is further increasing Renal lesions can recur after kidney transplant

Modified and adapted from [7, 9, 19, 36, 127, 128]

[a]ACR on spot urine sample; measurement of total proteinuria (≥ 500 mg/24 h or ≥ 430 mg/l in a spot urine sample) can also define this stage; *BM* basement membrane, *UAE* urinary albumin excretion, *GBM* glomerular basement membrane, *BP* blood pressure, *GFR* glomerular filtration rate, *TGF-β* transforming growth factor-beta

The natural history of DKD between T1DM and T2DM is not quite the same, but the stages have more similarities than differences, which will be discussed later in this chapter under the stages for T2DM. The differences can be seen in various ethnicities and age groups between the two types of diabetes. For example, patients with T1DM are younger at diagnosis compared to T2DM [16, 19–22]. In both T1DM and T2DM, the DKD utilizes the same UAE values for classification of microalbuminuria and macroalbuminuria, and GFR value for CKD stages.

The National Kidney Foundation (NKF) classifies CKD based on decreased GFR or other markers of kidney damage [23]. NKF defines CKD as "kidney damage or GFR less than 60 ml/min/1.73 m^2 for 3 or more months" [23]. It also defines "kidney damage" as "pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies" [23]. Also of note, not all CKD is due to DKD in patients with CKD and diabetes; there can be CKD in patients with diabetes that is not DKD or diabetes related [18]. NKF recommends utilizing Modification of Diet in Renal Disease (MDRD) equation for estimation of GFR [18]. The various stages of CKD classified by GFR in relation to UAE value are shown in Table 4.2 and Fig. 4.1. Some cases

Table 4.2 CKD stages by GFR in relation to UAE value

GFR (ml/min/1.73m^2 BSA)	CKD stages	Description
≥ 90	1	GFR may be normal or increased. Changes in kidney function and structure can be detected DKD if UAE is in macroalbuminuria range Possible DKD if UAE is in microalbuminuria range At risk for DKD if UAE is in normoalbuminuria range[a]
60–89	2	GFR is mildly decreased. There are changes in kidney function and structure The rest for possibility of DKD in relation to UAE range is the same as in stage 1
45–59 30–44	3a 3b	GFR is mildly to moderately decreased GFR is moderately to severely decreased DKD if UAE is in macroalbuminuria range Possible DKD if UAE is in microalbuminuria range Less likely DKD if UAE is in normoalbuminuria range[b]
15–29	4	GFR is severely decreased DKD if UAE is in macroalbuminuria range Less likely DKD if UAE is in microalbuminuria range[b] Less likely DKD if UAE is in normoalbuminuria range[b]
< 15 or dialysis	5	End-stage renal failure The rest for possibility of DKD in relation to UAE range is the same as in stage 4

Modified and adapted from [9, 10, 23, 71, 74]

BSA body surface area, *CKD* chronic kidney disease, *DKD* diabetic kidney disease, *GFR* glomerular filtration rate, *UAE* urinary albumin excretion

[a]There may be significant loss of kidney function if GFR is less than 90 ml/min. Risk of DKD includes DM, poor glycemic control, hypertension, CVD, UAE in high normal range, non-white race, family history of hypertension, or CKD, retinopathy, and DM [9, 74]

[b]If kidney biopsy does not show glomerulopathy, consider CKD and diabetes coexistence and require further investigation

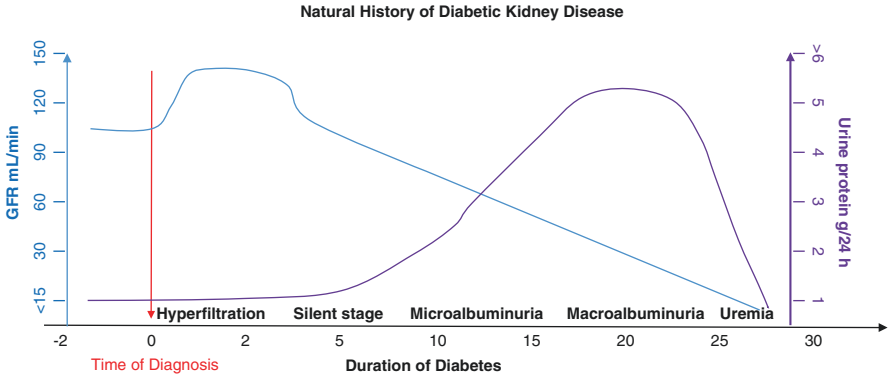

Fig. 4.1 Natural history of diabetic kidney disease by GFR and UAE. (Modified and adapted form ref. [129])

of CKD however may need kidney biopsy to confirm the diagnosis of DKD [18]. Similar to KDOQI, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines state "CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA)" [10].

Stage 1: Hypertrophy-Hyperfiltration

The initial stage is known as the hypertrophy-hyperfiltration or hyperfunction stage. At the initial diagnosis of T1DM, the changes are seen in function, morphology, and biochemical profile within diabetic kidneys. The initial structural changes of growth in kidney size and function have been demonstrated in both, the animal experimental models and humans with diabetes [19, 24–26]. The functional changes characterized by increase in glomerular filtration rate (GFR) [12, 26, 27], renal plasma flow (RPF) [12, 16, 26, 28], and filtration fraction (FF) [12, 26] can occur in subjects with DM in the initial stage [24]. At the diagnosis and within 1 year of the diagnosis, these changes have been shown to be present [12]. Structural alteration such as increased kidney volume [16, 26, 29] can be seen within days to weeks of T1DM diagnosis and may contribute to increase in GFR [24, 30]. The biochemical or hormonal alterations seen in DM include hyperglycemia, hypoinsulinemia, hyperglucagonemia, normal to elevated growth hormone, and increased urinary albumin excretion (UAE), which may also contribute to increased GFR [15, 24, 26, 31]. The changes occurring in stage 1 may be completely or partially reversible [30].

The increased GFR demonstrated in animal models of T1DM [32] as well as in most human cases of T1DM [26, 29] as a consequence of renal hypertrophy [33] and intrarenal hemodynamic abnormalities due to hyperglycemia are responsible for hyperfiltration [1, 11, 34]. This in turn leads to glomerular hypertension [35].

The streptozotocin-induced DM rat model in the early stage shows kidney hypertrophy [15, 36] and altered renal metabolism of pyrimidine nucleotide metabolism, especially uridine triphosphate (UTP) with greater RNA content in renal cortex and increased transforming growth factor-beta (TGF-β) receptor [36, 37]. As a result of altered UTP metabolism in the diabetic kidney cortex, there is increased glycogen content which leads to formation of Armanni-Ebstein lesion (subnuclear vacuolation in the proximal tubules) and thickening of glomerular basement membrane and deposition of basement membrane-like material in the mesangium [36, 38, 39]. The above early changes including added renal weight and hypertrophy can be prevented or reversed with insulin therapy [15] if the insulin therapy is started at diagnosis of DM and dosed continuously [40]. These changes may not be reversible if insulin is initiated after 3 weeks of onset of DM even if the therapy is continued [15]. However, the diabetic kidneys in humans may return to normal size when hyperglycemia is controlled for 3 months [34].

A short-term study done by Christiansen et al. in nine human subjects with newly diagnosed T1DM evaluated the changes in GFR, RPF, FF, and kidney size before and after 8 days of insulin treatment [26]. The study results indicate that before insulin therapy there are a statistically significant elevation in GFR by 44%, RPF by 18%, and FF and increase in the kidney size by 29% compared to subjects without diabetes [26]. After initiation of insulin therapy, the GFR, RPF, and FF had decreased significantly; however the GFR remained 20% above normal value, and the kidney size did not change compared to subjects in the control group [26]. This study showed that subjects with T1DM have statistically significant larger kidney size and function at diagnosis but there was no significant change in kidney size after insulin treatment [26]. However, with continued therapy as there was improvement in hyperglycemia over 1–2 weeks, other studies report approximately a 20% reduction in GFR [27, 41]. But, in comparison to the control subjects with diabetes, the GFR in T1DM did not decrease to a similar value as complete normalization of glycemic control was not obtained in T1DM group [26, 27, 41]. This study and some of the earlier studies do not mention hemoglobin A1C (HbA1C) level as the glycemic control is certainly an important factor for changes seen in kidney disease. Similar findings as above have been demonstrated by other short-term studies [16, 27, 29, 34].

In another short-term study of six newly diagnosed T1DM, Mogensen et al. evaluated whether reduction in the kidney size and GFR occurs after 3 months of insulin treatment [34]. The mean GFR before insulin therapy was 142.7 ± 9.7 ml/min (range 137–159) which then decreased to 129 ± 10.2 ml/min (range 118–147) after 3 months of insulin therapy. This was a significant decrease in the GFR by 12%, and at the same time, the kidney size as well as the kidney weight decreased by 13% [29]. The degree of enlargement of the kidney size was similar in both newly diagnosed T1DM patients before treatment with insulin as compared to those patients with T1DM who had been on insulin for 1–12 years [29]. This study showed that after strict glycemic control to near normal or normal value, the reversibility of anatomical and functional abnormalities can occur as both GFR and kidney size fall to normal or near normal values [27, 29, 34]. There was no significant change found

in RPF of newly diagnosed T1DM [34] as compared to patients with T1DM of 1–12 years' duration [26] (Table 4.3).

Hyperfiltration secondary to renal hypertrophy occurs as the result of both, glomerular and tubular hypertrophy [1]. Tubular hypertrophy in turn results in increased kidney weight [42]. Proximal tubular hypertrophy is associated with increased salt reabsorption, which can then affect glomerular hyperfiltration [33]. In early diabetes, the increase in GFR is accompanied by glomerular hypertrophy with enlargement of capillary surface area, indicating a positive correlation between the two

Table 4.3 Comparison of stages of diabetic kidney disease in type 1 DM and T2 DM

Stages	Type 1 DM	Type 2 DM
1. Hyperfiltration and hypertrophy	Younger mean age at diagnosis GFR and capillary glomerular pressure are increased BP is usually normal or increased	Older mean age at diagnosis Occur less common than in T1DM and GFR needs careful interpretation as it declines with age BP is often high at diagnosis and requires treatment
2. Silent stage (normoalbuminuria)	GFR is increased or decreased BP is increased (+)	May or may not have hyperfiltration and GFR could be within normal range
3. Microalbuminuria (incipient nephropathy)	GFR is preserved but it can be increased or decreased BP is further increased (++); increased SBP and DBP Hypertension has been used as important prognostic factor for early mortality [16] Occur 5–10 years after diagnosis Increased UAE can be reversible	Microalbuminuria may be present at diagnosis and is not specific indicator for T2DM Hypertension has not been identified as markers for early mortality UAE can regress to normoalbuminuria range
4. Macroalbuminuria or overt nephropathy	GFR is normal or decreased Increased BP (++) Usually occur after 10–15 years of T1DM but can appear after 40–50 years Predict progression to renal failure if untreated and this stage does not disappear, and majority will progress to ESRD	May progress to overt proteinuria Some studies have described both T1DM and T2DM who develop renal impairment without significant proteinuria without known mechanism
5. End-stage renal disease or uremia	GFR is decreased Further rising of BP (+++) Occurs in up to 40% of T1DM and requires RRT	Similar risks for ESRD in T1DM and T2DM T2DM is more common than T1DM, so majority of ESRD patients have T2DM

Adapted from [1, 19]

T1DM type 1 diabetes mellitus; *T2DM* type 2 diabetes mellitus, *GFR* glomerular filtration rate, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *UAE* urinary albumin excretion, *ESRD* end-stage renal failure, *RRT* renal replacement therapy

[13]. The increase in GFR is affected by glycemic control, and thus subjects with near normal glycemic control can reverse GFR to normal level [13].

Early in the course of T1DM, in both human subjects and animal models, hemodynamic changes and elevated GFR are elicited; however, the exact mechanisms of these changes are not fully understood. The GFR is affected by RPF, transglomerular pressure, and the ultrafiltration coefficient (Kf) [26, 43]. The hemodynamic changes seen within the kidney leading to increased GFR have been demonstrated in micropuncture studies of animal models. In the rat model with early stage of DM, studies show that in moderately hyperglycemic rats, there are glomerular hyperfiltration [confirmed by elevated single nephron GFR (SNGFR) measurements], increased effective RPF, and increased intraglomerular capillary pressure [35]. However, in severely hyperglycemic rats, SNGFR was reduced [35]. Other rat models demonstrated increased GFR, RFP, and transglomerular pressure, and normal or increased Kf [44, 45]. The increased intraglomerular capillary pressure results in stimulation of the intrarenal renin-angiotensin system (RAS) [1].

Among the other metabolic changes seen, poorly controlled T1DM is associated with abnormal growth hormone (GH) level. Infusion of GH has shown to result in statistically significant elevation in GFR and RPF but not in FF [43, 46]. Another study by Christensen et al. demonstrated that normal subjects who received human GH to raise the level of growth hormone to the range similar in patients with T1DM showed a statistically significant rise in GFR, and RPF, but not in the change in kidney size, UAE, and beta-2 microglobulin [43]. The conclusion reached by the author was that increased RPF resulting from elevated GH contributes to elevation of the GFR [43].

While some studies show that glycemic control affects GFR and RPF, the results of other studies are contradictory. In two studies, when hyperglycemia was induced by glucose infusion in well-controlled T1DM patients and normal subjects to maintain the blood glucose level greater than 140 mg/dl to 250 mg/dl, it resulted in elevation of the GFR and RPF and decreased sodium excretion [47–49]. Yet, another study in T1DM patients did not find the consistent increase in GFR and RPF after hyperglycemia due to glucose administration [50]. Interestingly, not all the studies have shown a link between early hyperfiltration and later progression to proteinuria stage [2]. However, the interrelation among hemodynamic, structural, and functional changes within the diabetic kidneys has been implicated in the development and progression of nephropathy.

Glomerular hyperfiltration means elevated GFR, and elevated GFR is usually defined as two standard deviations above the mean GFR of a healthy person although there is no definite agreed value. Some studies use GFR greater than 125 ml/min/1.73 m^2 as an elevated GFR [51]. Mogensen et al. conducted a study in subjects with T1DM diagnosed at age 20 or younger and following them up to 14–16 years. Follow-up of these patients shows that those who progressed to diabetic nephropathy had GFR greater than 150 ml/min/1.73 m^2, and renal hyperfiltration was defined as GFR greater than 150 ml/min/1.73m^2 [52]. Those with short duration of diabetes and with GFR greater than 150 ml/min/1.73m^2 with concurrent microalbuminuria have a greater risk of late diabetic nephropathy [2, 53, 54].

The correlation between the duration of T1DM and GFR, RPF, FF, and UAE in DKD is discussed below. In patients with newly diagnosed T1DM, mean GFR before insulin treatment which was 156 ± 25 ml/min decreased to 124 ml/min ± 11, within the first 1–4 weeks of insulin treatment [27]. Similarly, FF was increased before and showed a significant fall after first few weeks of insulin treatment. However, RPF was within normal range before and did not change after treatment with insulin [27]. In terms of duration of diabetes, GFR was shown to be significantly increased in diabetes with duration of 1–6 years and 7–12 years, with mean value of 140 ± 20 ml/min and 137 ± 15 ml/min, respectively. GFR starts to decrease after having diabetes for about 13–18 years and more so after 18 years, with mean values of 123 ± 19 and 110 ± 31 ml/min, respectively [27]. RPF and FF increase significantly with 1–12 years' duration of T1DM, and then both started to decline after 13–18 or more than 18 years of the diabetes [27]. As for UAE, it remained within the normal range even after having T1DM for 19 years or more and was thus independent of duration of diabetes of note, in patients without proteinuria, UAE decreased significantly with insulin treatment [27].

Stage 2: The Silent Stage

The second phase of DKD is known as the silent stage with normoalbuminuria. This stage lacks clinical signs and has normal to near normal UAE regardless of the duration of T1DM [19]. This stage can occur from 1 to more than 15 years of duration of T1DM [19]. The GFR is usually normal to elevated in this stage [1, 11]. The elevated GFR can range between 20% and 30% higher above the baseline in treated and even higher, 30–44%, in those with untreated diabetes [11, 26]. However, in some T1DM patients, there are significant structural changes in the kidney such as thickening of basement membrane and expansion of mesangium, which may develop after 2 years of diabetes [1, 30]. Although the kidney function may be well preserved in many patients with a normal UAE, the structural changes may or may not be detected on renal biopsy [55]. However, once these lesions do develop, the changes may not be reversible and may in fact progress over time [30]. The studies for RPF have not shown consistent data as some studies showed increased RPF [26] while other studies demonstrated normal or depressed flow [50].

Caramori et al. conducted a study in patients with T1DM with normoalbuminuria who had T1DM for at least 10 years. In the study, the parameters compared were differences in renal structures (by renal biopsies) and clinical features. These T1DM patients with normoalbuminuria were compared to subjects with normal and low GFR (<90 ml/min/1.73m^2) [56]. Results of this study showed that patients with low GFR had more advanced diabetic glomerular lesions such as higher glomerular basement membrane (GBM) width, fractional volume of the glomerulus occupied by mesangium, fractional volume of the glomerulus occupied by mesangial cells, and fractional volume of the glomerulus occupied by mesangial matrix but lower surface density of the peripheral GBM per glomerulus compared to those with

normal GFR. Prevalence of low GFR was more common in females than males, especially if retinopathy and/or hypertension were present [56]. Retinopathy was present in 64% of total patients: in 58% of the patients in the normal GFR group and 91% of the patients in the low GFR group. Thus, retinopathy was more common in low GFR group with more of proliferative type. Hypertension was present in 36% of patients, and 20.9% were receiving antihypertensive medications, of which 6% were receiving angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Prevalence of hypertension was similar in both groups, but use of antihypertensive medications was statistically significantly higher in the low GFR group. There was no statistically significant difference between mean HbA1C levels between two groups [56].

However, the study conducted by Hansel et al. did find reduced GFR in normoalbuminuric T1DM patients as well who were not on antihypertensive medications and in microalbuminuric T1DM patients [57]. In patients with T1DM, impaired renal function may be present although the UAE value is in the normal range. These results showed that the normoalbuminuric group had significantly lower HbA1C (mean 7.9%), GFR, and mean arterial blood pressure (BP) as compared to microalbuminuric patients (mean HbA1C was 8.9%) [57]. The BP however in normoalbuminuric subjects was not significantly different from BP of the control group. The author concluded that normal UAE is a reliable indicator of well-preserved renal function. Abnormalities such as glomerular hyperfiltration, elevated BP, and poor metabolic control can be seen in microalbuminuric patients [57, 58].

When kidney function changes are not readily detectible at baseline, use of provocation tests such as the exercise test has been suggested [11]. Vittinghus et al. demonstrated that in normal subjects without diabetes, extreme exercise can lead to protein excretion in urine [59]. As UAE is more common at moderately high work load in patients with 3–17 years of T1DM, it was concluded that glomerular membrane was not able to maintain albumin during higher filtration pressure that occurs during exercise [60]. It has been postulated that the albumin excretion is from the glomerular area in diabetes subjects at high-intensity exercise which resulted in only a small increase in beta-2 microglobulin excretion [11]. The exercise test done by Mogensen et al. showed that patients with those T1DM patients that achieved 55–65% of their maximal heart rate (HR) had higher urinary albumin [11]. The studies by Koivisto et al. [61] and Viberti et al. [62] demonstrated that insulin treatment results in normalization of albuminuria after exercise in patients with T1DM. The postexercise albuminuria was likely a reflection of hemodynamic changes that occur in the kidneys [11, 59].

The current understanding is that less than 40% of T1DM patients will progress to microalbuminuria and thus it is prudent to prevent ESRD by early detection in susceptible patients in this second stage [1]. In this stage when there is poor glycemic control, UAE can increase during exercise and at rest. Ambulatory blood pressure (AMBP) monitoring studies have shown a modest rise in BP in this phase up to 5 years before UAE increases [58]. However, there was no significant difference in the increased SBP, and no correlation was demonstrated between increased albuminuria and BP rise [59]. Higher HbA1C (most have mean greater than 9%)

[61–63] and higher DBP initially, more severe retinopathy, male sex, and smoking history in T1DM patients were associated with the progression from normoalbuminuria to microalbuminuria stage [63].

Detection of kidney disease in stage 2 is limited. Investigators have tried to identify specific biomarkers as predictors associated with this stage, but studies are still underway. Some of the studies include plasma markers such as prorenin [64] level, which was shown to be elevated in T1DM patients and may have genetic predisposition among siblings of T1DM people. Another study suggested that detection of immune-unreactive and immune-reactive albumin fragments in urine by high-performance liquid chromatography (HPLC) [63] may provide earlier detection of those who will progress to the next stage, microalbuminuria. An additional study used serum cystatin C to estimate GFR to detect changes in renal function in T1DM [65], while another showed that total renin [66] can be increased up to 5 years before the onset of microalbuminuria. It should be noted that long-standing T1DM patients with normoalbuminuria are at substantial risk of progressing to the diabetic nephropathy stage.

Stage 3: Microalbuminuria or Incipient Diabetic Nephropathy (IDN)

The third stage is known as microalbuminuria or IDN. Depending on the population, the prevalence of microalbuminuria varies from 7% to 22% in T1DM, and the annual incidence is about 1–2% in both T1DM and T2DM [18, 67–69]. In subjects with T1DM, it often occurs 5–15 years after the initial diagnosis, and the UAE rate is increased to microalbuminuria range of 20–200 μg/min or 30–300 mg/24 h [18, 52]. Microalbuminuria is also defined as the albumin to creatinine ratio (ACR) of 30–300 mg/g in the USA and 2.5–25 mg/mmol in Europe and elsewhere and is a biomarker of CKD [52]. The urine should be collected at rest as an outpatient procedure, and two of three urine samples are required to be in the microalbuminuria range within 3–6 months at least 1 month apart to confirm the classification [18, 70, 71]. Excluding other causes for increased UAE is advised, especially if duration of diabetes is less than 6 years [18]. The range of UAE in this category is above normal but below overt diabetic nephropathy (ODN) value. Hyperfiltration can also occur in this stage in T1DM [2]. The GFR is usually preserved in this stage, but it can be increased or decreased. Regression of microalbuminuria [72] or progression to ODN can occur in stage 3 [73]. Uncontrolled or untreated hypertension worsens DKD. On renal biopsy, kidney structural lesions have been observed in this stage.

It is important to note that the UAE measurements can be affected by hydration status, recent vigorous exercise, urinary tract infection, hematuria, fever, and other kidney disease, and prolonged erect posture at the time of collection especially during 24-h urine collections [18, 23, 74]. Current radioimmunoassay methods can detect urinary albumin in the amount of microgram concentration and are sensitive, and thus the American Diabetes Association (ADA) and KDOQI clinical practice

guidelines recommend using spot urine ACR preferably the first morning void to avoid 24-h urine collection and conditions that can cause variability of UAE value [18, 71]. Urine ACR approximates 24-h UAE as it is not affected by the various ways of urine collection and the 24-h and timed urine collections are not as accurate or convenient [18].

Results from a study of 43 T1DM patients by Mogensen et al. [2] showed that 4 of the 43 patients (9.2%) in whom the initial UAE was <15 μg/min and who then progressed to the microalbuminuric range (mean UAE of 41.1 ± 17.4) had their GFR increased to >150 ml/min/1.73 m^2. Of the 12 patients (27.9%) with initial UAE value of <70 μg/min, 9 patients (20%) had statistically significant progression of UAE to 2373 ± 2488 range, and GFR had decreased to 93 ± 47 ml/min/1.73 m^2 at a mean follow-up of 7 years [19]. Those patients that had an increase in the UAE had higher initial mean systolic BP (SBP) and diastolic BP (DBP) and even higher mean SBP and DBP at follow-up. The initial SBP was 10 mmHg higher compared to those that remained normoalbuminuric. Thus, those that progressed to macroalbuminuria range had a tendency to have declining GFR and RPF and higher SBP (means were > 11 mmHg) at follow-up compared to normoalbuminuric or microalbuminuric groups. No difference in BP was noted from initial examination to follow-up in those who remained normoalbuminuric and progressed to microalbuminuria range. The patients who remained in normoalbuminuria (27 patients) at follow-up had stable UAE (their initial UAE was <15 μg/min) and BP and a statistically significant decreased RPF. In short, findings from this study showed that T1DM patients with UAE between 20 and 70 μg/min had higher GFR >150 ml/min/1.73 m^2 on initial exam compared to patients with UAE > 70 μg/min. In those patients with UAE >70 μg/min and less than 200, GFR starts to decline during this stage [19]. This long-term study showed that hyperfiltration contributed to the pathogenesis of late diabetic kidney disease [2, 19].

In the DCCT/EDIC study, the cumulative incidence of persistent microalbuminuria (PMI) in the conventional therapy group at intervals of 10, 20, and 30 years of duration of T1DM was 14%, 33%, and 38%, respectively [20]. PMI occurred more frequently after 20 years of diagnosis of diabetes. In the intensive therapy group, the cumulative incidence of PMI at interval of 10, 20, and 30 years' duration of T1DM was 10%, 21%, and 25%, respectively, and the occurrence of the PMI after 20 years of diagnosis of diabetes was lower than conventional group [20]. Progression to the macroalbuminuric stage, impaired GFR, and ESRD occurred at a 10-year cumulative incidence of 28%, 15%, and 4%, respectively, and regression to normoalbuminuria occurred at 40%. Among patients with regression to normoalbuminuria after 10 years of initial PMI diagnosis, the prevalence of those patients that were on ACE inhibitors and angiotensin receptor blockers (ACEIs and ARBs, respectively) was 47% and on lipid-lowering medications was 12%, mean HbA1C at the time of regression was 7.7%, and mean BP was 121/77 mmHg [20]. Even if the patients do progress to the macroalbuminuria stage, the regression to normoalbuminuria has occurred in a minority of patients if GFR was not impaired [20]. Clinically, in this phase there are an increase in both SBP and DBP and a loss of nocturnal dip in BP

before progressing to microalbuminuria stage [75]. Renal function may be increased, normal, or decreased. Effective intervention in this phase may prevent further decline in renal function.

A study by Mogensen et al. conducted with 28 T1DM patients found that there is a correlation with an increase in BP and albuminuria [11]. Other studies also have similar findings showing that intervention during IDN helps in preserving renal function more effectively than in overt diabetic nephropathy (ODN) [76]. However, there was no increase in urinary beta-2 microglobulin, which implied that tubular function was not affected and the increased UAE indicated progressive glomerular changes [11]. During this stage, the renal function is still preserved, but the GFR was elevated at the entry and during follow-up. There was a significant decline in RPF and significant rise in DBP during this period; thus it is speculated that RPF changes may reflect modifications of glomeruli and possible rise in BP in this stage [11].

There is a significant correlation between rise in exercise-induced albuminuria and SBP during exercise but not heart rate (HR), leading to speculation that microcirculatory changes occur in the glomeruli and structural changes may exist [77]. There is a decline in creatinine excretion noted after insulin treatment in subjects with DM with early nephropathy suggesting impaired renovascular autoregulation contributing to higher SBP during exercise [78]. It has been postulated that elevated BP may worsen diabetic nephropathy after apparent microalbuminuria. Studies with human subjects with T1DM have shown that microalbuminuria can be transient and can regress to normoalbuminuria [72]. A study by Perkins et al. showed that there was 58% of regression of microalbuminuria in subjects with T1DM [72], but the study by Hovind et al. showed lower rates of microalbuminuria regression [73]. Notably, in that study, microalbuminuria of short duration, HbA1c (<8%), low systolic BP (<115 mm Hg), and low levels of both cholesterol and triglycerides were positively associated with the regression of microalbuminuria [72]. Poor metabolic control can also contribute to the escalation of BP. Both poor glycemic and BP management may in turn contribute to progression of the DKD as observed in interventional studies to treat hypertension in diabetes [79]. Early antihypertensive treatment with goal BP of less than 135/85 mmHg can help reverse microalbuminuria and preserve GFR [19, 79, 80]. Improved metabolic control also prevents progression of microalbuminuria [81].

Microalbuminuria is a clinical manifestation of DKD, and renal morphologic studies have demonstrated that the microalbuminuria phase can be associated with advanced glomerular structural changes [82]. However, persistent microalbuminuria if untreated will lead to ODN [2]. Thus, it is beneficial to repeat spot urinary microalbumin if there is isolated elevation in urinary microalbumin to confirm the diagnosis. Current recommendations to screen for diabetic nephropathy in T1DM include at least once per year urinary albumin, assessment of GFR by obtaining creatinine, and appropriate staging of kidney disease [9, 71]. This stage clearly indicates that effective BP, lipid, and glycemic control will help prevent progression to the macroalbuminuria stage and may in fact facilitate regression to the normoalbuminuria stage [18].

Stage 4: Macroalbuminuria

This stage is known as macroalbuminuria or overt diabetic nephropathy (ODN). It is defined by the increased UAE rate of ≥300 mg/24 h or > 200 μg/min, on at least two of the three urine samples collected within 6 months while excluding other causes of elevated UAE [1, 9, 11, 52, 70]. It is also characterized as persistent proteinuria greater than 0.5 g/24 h in total protein excretion [19]. In patients with T1DM, this stage usually occurs 10–15 years after the initial diagnosis of DM, but in some patients it can also appear 40–50 years later [25]. In Denmark, T1DM patients have 31% risk of developing persistent proteinuria with the risk being higher in males than females and with early onset of DM under age 10 [83]. In the same study, 6% developed persistent proteinuria after 10 years of T1DM with prevalence of persistent proteinuria being 18% during the first 20 years of T1DM with most occurring after duration of 12–25 years [83]. The prevalence of persistent proteinuria after 35 or 40 years of T1DM was low, and about 70% of T1DM will not develop ODN [83]. DCCT/EDIC study examined the long-term renal outcomes of persons with T1D who developed incident macroalbuminuria [84]. After 25 years of T1D, macroalbuminuria occurred with a cumulative incidence of 6% in intensive and 17% in the conventional arms. Ten years after the diagnosis of macroalbuminuria, the incidence of a sustained reduction in albumin excretion rate (AER) to <300 mg/d was 52%, mostly under treatment with RAS inhibitors, and the incidence of impaired GFR (sustained eGFR<60 ml/min per 1.73 m2) was 32%, including 16% who developed ESRD [84].

If patients do not receive adequate treatment during the macroalbuminuria phase, there is a high probability that they will develop subsequent renal failure [25].

In the early course of ODN, most patients' GFR and serum creatinine can be within the normal ranges, but some people may have hyperfiltration [19]. As the ODN stage progresses, there is a decline in GFR [7]. Further progression in the structural changes in the kidney can be detected in early and intermediate course of ODN, such as additional increase in thickening of glomerular basement membrane (GBM), expansion of mesangium, and the rate of glomerular closure [19]. In advanced stage 4, the remaining gluomerili hypertrophy [19]. Proteinuria is a clinical sign of future deterioration of renal function and it implies poor prognosis and a shorter life expectancy [85].

There are at least two peaks of incidence in ODN with no definite clear contributors. Though poor glycemic and BP control, genetic, molecular, and environmental factors have been proposed in predisposition [73]. More than two thirds of patients with macroalbuminuria have uncontrolled systemic hypertension, and this has been associated with increase in proteinuria [86, 87]. Untreated macroalbuminuria leads to progressive elevation of BP and decline of GFR with eventual progression to ESRD [73]. In the study by Parving et al. in T1DM patients with persistent proteinuria, before treatment, there is a mean decline in GFR with mean value of 0.9 ml/min/month with further elevation in BP and UAE values. During treatment with antihypertensive medication, the mean GFR decline rate decreased to 0.39 ml/min/

month [88]. Another study by Mogensen et al. during this stage demonstrated that the mean decline in GFR was 1.24 ml/min/month before antihypertensive treatment which then decreased to 0.45 ml/min/month during antihypertensive treatment with decreased yearly urinary albumin excretion to −7% with improved SBP and DBP [76]. Viberti et al. showed that strict glycemic control may have beneficial effect on slowing the progression of GFR decline in this stage [89].

In summary, trials have shown that controlling BP slows the GFR decline rate [76, 90]. Long-term antihypertensive medications during this stage have been shown to decelerate the progression of albuminuria and declining GFR by 60% and significantly reduced both SBP and DBP [11]. However the filtration rate continues to decrease despite treatment in patients with difficulty achieving BP goal of 140/90 or lower during that period [90].

Stage 5: Uremia

This last phase is called the uremic stage or end-stage renal failure. It is common in both T1DM and T2DM and occurs in up to 40% of patients with T1DM [1]. It is characterized by uremia and often has decreasing UAE due to closure of nephron [19]. There are advanced kidney lesions and generalized glomerular obliteration. BP in this stage is usually high. Patients with diabetes and ESRD require renal replacement therapy (RRT), which includes dialysis or renal transplantation, which has better outcomes. Diabetes-associated renal lesions have been shown to recur in the transplanted kidney as well [1]. ESRD is associated with high cardiovascular mortality [9].

Natural History of Diabetic Kidney Disease in T2DM

The natural history of DKD in T2DM patients has been less well delineated compared to T1DM patients. This could be partly because most T2DM patients are older and have unknown duration of diabetes prior to diagnosis and concurrent obesity, hypertension, hyperlipidemia, and high rates of cardiovascular disease (CVD) that limit the expression of DKD [9]. Microalbuminuria occurs in approximately 7% at the time of initial diagnosis and up to 18% within 5 years of T2DM diagnosis, suggesting existence of at least 10 years of undiagnosed T2DM [1]. In UKPDS over a median of 15 years from diagnosis of T2DM, almost 40% of patients developed albuminuria, and almost 30% developed renal impairment [91]. The study in Pima Indians has provided valuable insight about DKD in T2DM. Historically Pima Indians have had the highest prevalence of T2DM, with prevalence of 40–45% in adults over age 35 years, and they had low incidence of T2DM during childhood to peak incidence being at 40 years for males and 50 years for females [92]. Most are obese subjects with diabetes and insulin resistance [7, 93]. A more recent study

showed that the overall incidence of diabetes among Pima Indians remained stable over the past four decades, with a significant rise occurring only in the youth [94]. The kidney structural and functional changes in T1DM are similar in T2DM for most part [9]. Among Pima Indians with kidney disease, the highest mortality occurs in subjects with T2DM on RRT, and mortality rate increases with duration of diabetes and from CVD, infection, and malignancy [95].

Stage 1: Initial Stage in T2DM

At the initial diagnosis of T2DM and early stage 1 of DKD, hyperfiltration may or may not occur. If hyperfiltration does occur in T2DM, it is less frequent, at rates of 15–45% as compared to T1DM [7, 96–98]. In the study of 16 recently diagnosed non-proteinuric T2DM patients, hyperfiltration (elevated GFR) was present in 44% of patients, with median GFR (133 mL/min/1.73 m^2; range, 95–165) in the group with T2DM, which was significantly higher than obese controls without diabetes (median, 118; range, 95–139) [98]. Vora et al. in their study of 110 Caucasian patients newly presenting with T2DM showed significantly elevated GFR, effective RPF, and FF compared to nondiabetic control group [96]. These patients have BP in the normal range and did not have prior treatment for diabetes. The mean age was 52.5 ± 10.1 years, GFR was above 140 ml/min in 16% and above mean ±2 SD of the normal in 45%, and microalbuminuria was noted in 7% of T2DM patients [96]. In a study of 20 Pima Indians with T2DM, the mean GFR (140 ± 6 ml/min) was 15% higher than patients without diabetes (122 ± 5 ml/min) [93]. However, another study found that the GFR was normal in newly diagnosed T2DM individuals [99]. As the GFR typically declines with age, it is possible to have hyperfiltration while the GFR remains within normal adult range [1]. The interpretation of GFR and hyperfiltration must thus be carefully analyzed.

There may be elevated BP at diagnosis of T2DM and most patients require treatment [19]. This is different from T1DM where most people during normoalbuminuric range have normal BP and elevation in BP is linked to renal disease with higher BP corresponding to greater UAE level [19]. The T2DM patients often display hyperinsulinemia and insulin raises urinary sodium reabsorption. Thus, high insulin may indirectly play a role in hypertension by sodium retention [19, 100]. During the initial stage, not all T2DM patients have increased glomerular volume [94, 101].

Stage 2: Normoalbuminuria

T2DM patients with normoalbuminuria comparable to stage 2 in T1DM may or may not have hyperfiltration and usually have normal renal size and may have diabetic glomerulopathy [19]. The GFR has a positive correlation with UAE,

borderline correlation with renal size, but none with glycated hemoglobin, which is different from the finding in T1DM patients [19].

In the UK Prospective Diabetes Study (UKPDS 64), the annual CVD death risk in patients without nephropathy (urinary albumin concentration (UAC) less than microalbuminuria range) was 0.7%, while the risk for those with microalbuminuria was 2.0%, 3.5% for those with macroalbuminuria, and 12.1% with elevated plasma creatinine or RRT [22].

Schmitz et al. studied 19 normoalbuminuric T2DM with light microscopy to determine the relationship between glomerular morphology and UAE and showed that there were no increase in glomerular volume and no significant frequency in occlusion of glomerulus [101]. These patients were either diet controlled for their diabetes or only on oral hypoglycemic. The volume of fraction of red stain material (periodic acid-Schiff positive substance) was increased in open glomeruli by 14% signifying existence of glomerulopathy in T2DM subjects, but high UAC did not reflect more advanced glomerulopathy [101]. The finding of increased glomerular size in both early and late T1DM was not demonstrated in this study in T2DM. In addition, hyperfiltration was not a precursor to the finding of glomerulopathy as suggested by the same study [101]. Higher DBP was seen in T2DM patients who progress from normoalbuminuria to microalbuminuria without any significant difference in HbA1C, but the mean value was 8.8% [25].

Stage 3: Microalbuminuria or Incipient Diabetic Nephropathy

In patients with T2DM, the prevalence of microalbuminuria varies from 6.5% to 42%, and it may be present at or before diagnosis of T2DM, which is different from T1DM [1, 67–69]. The presence of microalbuminuria in T2DM increases the CVD risks such as MI and stroke, and it may not be as specific an indicator for diabetic renal disease as in T1DM patients as other factors such as incipient or overt cardiac insufficiency, urinary tract infection, and urinary obstruction can contribute to it [9]. In hypertensive T2DM patients, BP levels tend to increase as UAE progress to microalbuminuric range [19]. In T2DM, GFR is reduced especially in patients with microalbuminuria or in older patients with normoalbuminuria [7]. Regression of microalbuminuria or remission to normoalbuminuria can occur in T2DM. Regression is defined as a 50% decrease in UAE value from one 2-year period in this study by Araki et al. of 216 T2DM Japanese patients with microalbuminuria [102]. Six-year cumulative incidence of remission was at 51%, regression was at 54%, and progression to ODN was at 28% [102]. The factors associated with regression or remission was short duration of microalbuminuria, use of ACEIs or ARBs, lower HbA1C (less than 6.95%), and SBP less than 129 mm/Hg [102].

The data from UKPDS of 5097 newly diagnosed T2DM patients describe the progression of DKD through the stages from microalbuminuria, macroalbuminuria (UAC values used in the study were 50–299 mg/L and ≥ 300 mg/L, respectively), persistently elevated plasma creatinine (creatinine ≥175 μmol/L) or RRT, and death [22].

From the time of diagnosis of T2DM development of microalbuminuria occurred at 2.0% per year. The prevalence of microalbuminuria 10 years after diagnosis of DM was 24.9% with increasing annual CVD death risk of 2.0% in microalbuminuria group [22]. Many patients with T2DM with microalbuminuria also progress to overt proteinuria [1]. In UKPDS 74 study, over a median of 15 years from diagnosis of T2DM, almost 40% of patients developed albuminuria [91].

However, substantial renal impairment without significant proteinuria has been described in both T1DM [103] and T2DM [104] patients. As the risk of ESRD in T2DM patients and renal impairment is similar with or without microalbuminuria, it is important to assess estimated GFR and serum creatinine as recommended by ADA and KDOQI guidelines [18, 71].

Stage 4: ODN

This stage in T2DM may appear 5 years earlier compared to T1DM as time to diagnosis in T2DM is delayed [7]. The results from UKPDS showed that progression from microalbuminuria to macroalbuminuria was 2.8% per year [22]. The prevalence of macroalbuminuria was less with 5.3% 10 years after T2DM diagnosis, and these patients had higher annual CVD death risk of 3.5%, which was higher than transitioning to renal failure [22].

In UKPDS 74 study, of the patients that developed albuminuria, only 24% subsequently developed renal impairment during the study [91].

Stage 5: ESRD

Cumulative incidence of ESRD is 10–35% among T2DM patients [7]. Nelson et al. [105] reported the cumulative incidence of ESRD development in Pima Indians with T2DM was 40% after 10 years and 61% after 15 years of proteinuria (protein-to-creatinine ratio $\geq$ 0.5 g/g) being detected [105]. Despite the high rate of macroproteinuria in the Pima population, the incidence of ESRD declined after the 1990s, likely as a response to improved control of blood pressure, hyperglycemia, and other risk factors [106]. GFR decline rate is similar among T2DM patients who develop diabetes at young age (like Pima Indians) as compared to T1DM [7]. From UKPDS study the transition from macroalbuminuria to elevated plasma creatinine (EPC) or RRT was at 2.3% per year with a prevalence of EPC or RRT was at 0.8% 10 years following T2DM diagnosis. The patients in EPC or RRT group have annual risk of cardiovascular death at 12.1% and annual death rate of 19.2%, both of which were much higher than in stages 1–4 [22]. Thus, CVD death risk increases with progressive UAE elevation and DKD stages [22]. This stage has higher CVD risk and patients eventually need RRT for survival. Antihypertensive medications and

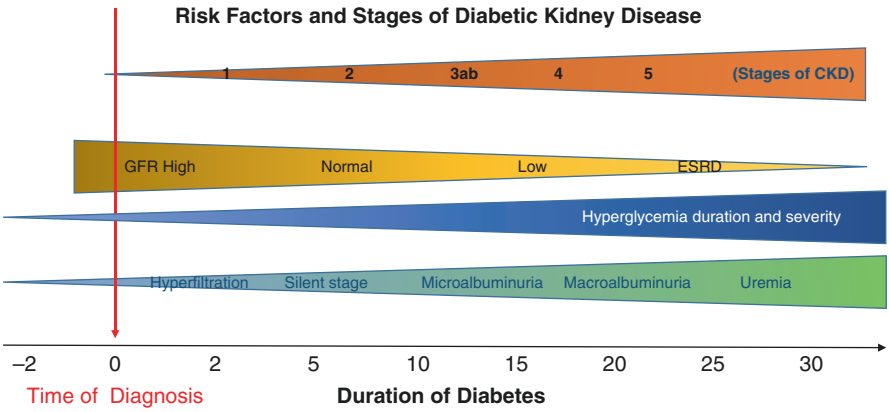

Fig. 4.2 Risk factors and stages of diabetic kidney disease. (Modified and adapted from ref. [130])

improved glycemic control are beneficial in this stage [9]. Patients on RRT had a median life expectancy of 3 years [22] (Fig. 4.2).

Non-albuminuric DKD

Epidemiologic studies have demonstrated an association between poor glycemic control and kidney disease in patients with type 1 and type 2 DM [107, 108]. Studies have also shown that tight glycemic control slows the development of albuminuria [109] and that improved glycemic control slows the rate of decrease in GFR. However, that is not always the case. In the intensive arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [110], there was no reduction in the incident CKD or ESRD despite the tight glycemic control. The third NHANES data demonstrated that albuminuria was absent in 36% of patients who had DM and CKD [111]. After about 15 years of follow-up, in the UK Prospective Diabetes Study (UKPDS), about half of the patients who had developed renal impairment did not show prior albuminuria [112]. In the Diabetes Control and Complications Trials/Epidemiology of Diabetes Interventions and Complication (DCCT/EDIC) follow-up, which had follow-up data over 19 years, 11.4% of the participants had sustained eGFR of <60 ml/min. Among the patients that had sustained eGFR of <60 ml/min, 24% of the patients had normoalbuminuria [113]. These findings support the idea of a phenotype of CKD that is non-albuminuric (or normoalbuminuric), characterized by decline in eGFR without the accompanying increase in albumin-to-creatinine ratio (ACR) [114]. In patients with type 1 DM, the prevalence of non-albuminuric CKD is about 2% in patients; whereas in patients with type 2 DM patients, it is 10% [115]. The National Health and Nutrition Examination Survey (NHANES) [116] data shows that the prevalence of ACR >30 mg/g decreased from 20.8% in

1988–1994 to 15.9% in 2009–2014 whereas the eGFR <60 ml/min^{-1} increased from 9.2% to 14.1% in the same time period.

This raises the question about if there are any specific factors associated with non-albuminuric CKD, on which there are no data. The mortality risk in this phenotype has not been well characterized either. Lee et al. [117] have shown that the cardiovascular outcomes in T2DM patients who had an eGFR of <60 ml/min [1.73m^2] were comparable among those with normoalbuminuria, microalbuminuria, and macroalbuminuria (3.9, 4.21, and 4.10 per 1000 years, respectively). The Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study [118] studied 15,773 patients with T2DM. After adjustment for confounders, their data showed that the mortality risk was similar for those with non-albuminuric DKD [1.58 (1.43, 1.75)] as compared to those with albuminuria but preserved eGFR [1.45 (1.33, 1.58)]. Penno et al. demonstrated in an observational study [119] that renin-angiotensin system (RAS) blockage had no reno-protective effect on non-albuminuric CKD.

There have been numerous studies looking for non-albumin proteins in DM patients without proteinuria since the 1980s. These low-molecular-weight proteins include alpha-1-microglobulin, immunoglobulin light chains, retinol-binding protein, beta-2 microglobulin (b2m), and others [120–123]. Studies evaluating the low-molecular-weight proteins are unable to agree on a single surrogate representative protein and therefore are difficult to compare. Low-molecular-weight proteins are smaller than albumin and thus are relatively less restricted by the glomerular filtration barrier. In healthy individuals, significant quantities of these proteins are estimated to be present in the glomerular ultrafiltrate, but only minute quantities appear in the urine, as they are endocytosed by the proximal tubule cells through the endocytic receptors megalin and cubilin [124–126]. As a result, normal individuals excrete no more than 10–20 mg/day low-molecular-weight proteins in the urine. Thus, low-molecular-weight proteinuria or non-albumin proteinuria (NAP) is a reliable marker of tubular disease in patients without glomerular involvement. Conversely, glomerular involvement disrupting podocyte integrity, i.e., podocytopathy, usually results in massive proteinuria comprising albumin and larger proteins far exceeding the quantity of low-molecular-weight (tubular) proteins as glomerular filtration barrier is impaired. Furthermore, in most studies it appears that non-albumin proteinuria often precedes microalbuminuria [120]. Despite the gaps in knowledge about non-albuminuric DKD, it is imperative for clinicians to assess patients with non-albuminuric DKD, including testing for non-albumin, low molecular proteins, and help address any of the modifiable risk factors to decrease the risk for further decline in eGFR.

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Chapter 5
Pathogenesis: Hemodynamic Alterations

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Introduction

Research on the pathogenesis of diabetic nephropathy started from hyperglycemia, and, indeed, preclinical studies and clinical trials could document that correcting hyperglycemia with intensive glucose control moderately reduces the progression of diabetic nephropathy [1]. Driven by the histomorphological changes of diabetic nephropathy, researchers focused on inflammation and fibrosis as potential mechanisms of disease progression [2–5]. The evolving omics technologies were introduced with great promises to extract the unknown by analyzing large datasets, but many of the studies merely confirmed the known [6], kidney injury involves inflammation and fibrosis as secondary responses only [7]. Consequently, clinical trials testing drugs directed against inflammation and fibrosis either failed or produced relatively low effect sizes on clinically meaningful endpoints [8–11]. In contrast, inhibitors of the renin-angiotensin-aldosterone system (RAAS) demonstrated efficacy to attenuate the progression of diabetic and nondiabetic kidney disease by, at least in part, modulating kidney hemodynamics [12, 13]. By reducing the biological activity of angiotensin II (Ang II), RAAS inhibitors reduced net filtration pressure, probably by increasing glomerular outflow via the efferent arteriole [14]. This way, RAAS inhibitors reduced GFR, which protects the glomerular filtration barrier and attenuates podocyte loss, and progressive glomerulosclerosis [14, 15]. Therefore, RAAS inhibitors reduced proteinuria, which attenuates the metabolic workload of

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hyperreabsorbtion in the proximal tubule [16]. However, the overall effect size of RAAS inhibition to attenuate CKD progression in diabetic nephropathy was limited compared to what could be achieved in nondiabetic kidney disease [14]. In this chapter we discuss (a) the fundamentals of how kidney perfusion determines kidney function, (b) how the RAAS regulates kidney function and how it contributes to diabetic nephropathy, (c) the evolving understanding how sodium-glucose transporters (SGLT) contribute to disease pathogenesis, and (d) the current hierarchical understanding of these and other pathomechanisms of diabetic nephropathy.

Single Nephron GFR Versus Total GFR

The kidney is made of nephrons, the kidneys' independent functional units. Hence, the excretory function of the kidneys, as defined by the glomerular filtration rate (total GFR), represents the sum of all single nephron GFRs (SNGFRs). This implies that nephron number is a critical parameter in kidney function, the progression of CKD, and kidney life span [15]. Nephron number is set at birth and, as mammals cannot replace or regenerate lost nephrons, nephron number declines along life [17]. Aging is associated with a linear loss of nephrons; indeed, at 70 years healthy individuals have a nephron number of around 50% as compared to young adults [17]. In healthy individuals GFR declines accordingly as no compensatory hypertrophy occurs [18], indicating that healthy aging requires less kidney function [19], probably due to less uptake of osmolytes and generation of metabolic waste products (Fig. 5.1). However, during life span nephron loss occurs also from incident injuries such as episodes of acute kidney injury or due to one or several chronic nephropathies (Fig. 5.1). The resulting disequilibrium between the number of remnant nephrons, filtration load, and metabolic waste to excrete induces a compensatory increase in the size of the remnant nephrons associated with an increase in SNGFR [16]. Consequently, total GFR declines less than nephron number; hence, in clinical practice eGFR underestimates the structural damage of the kidney and the true loss of nephrons [15, 16]. For example, a patient with poorly controlled diabetes and CKD stage G2 with a total GFR of 80 ml/min has probably already lost 60% of his nephrons, as with all nephrons GFR should be 150 ml/min or more. These remnant nephrons must have an increased SNGFR as a marker of increased workload and are at risk to succumb soon for single nephron hyperfiltration and tubular hyperreabsorbtion [20]. The condition is worst in a patient with poorly controlled diabetes and CKD stage G3a with a total GFR of 50 ml/min that has probably only 25% of his nephrons left, each of them with massively increased SNGFR, massive single nephron hyperfiltration, and hyperreabsorbtion [20]. Without a robust therapeutic intervention that reduces the workload at the level of the individual nephrons, such nephrons get lost quickly, i.e., progression of DN [20]. Thus, the increased SNGFR is the central pathomechanisms of progression in every form of CKD but in particular in diabetic nephropathy, a disease where single nephron hyperfiltration is the central pathomechanism [16, 20]. While endowment with a

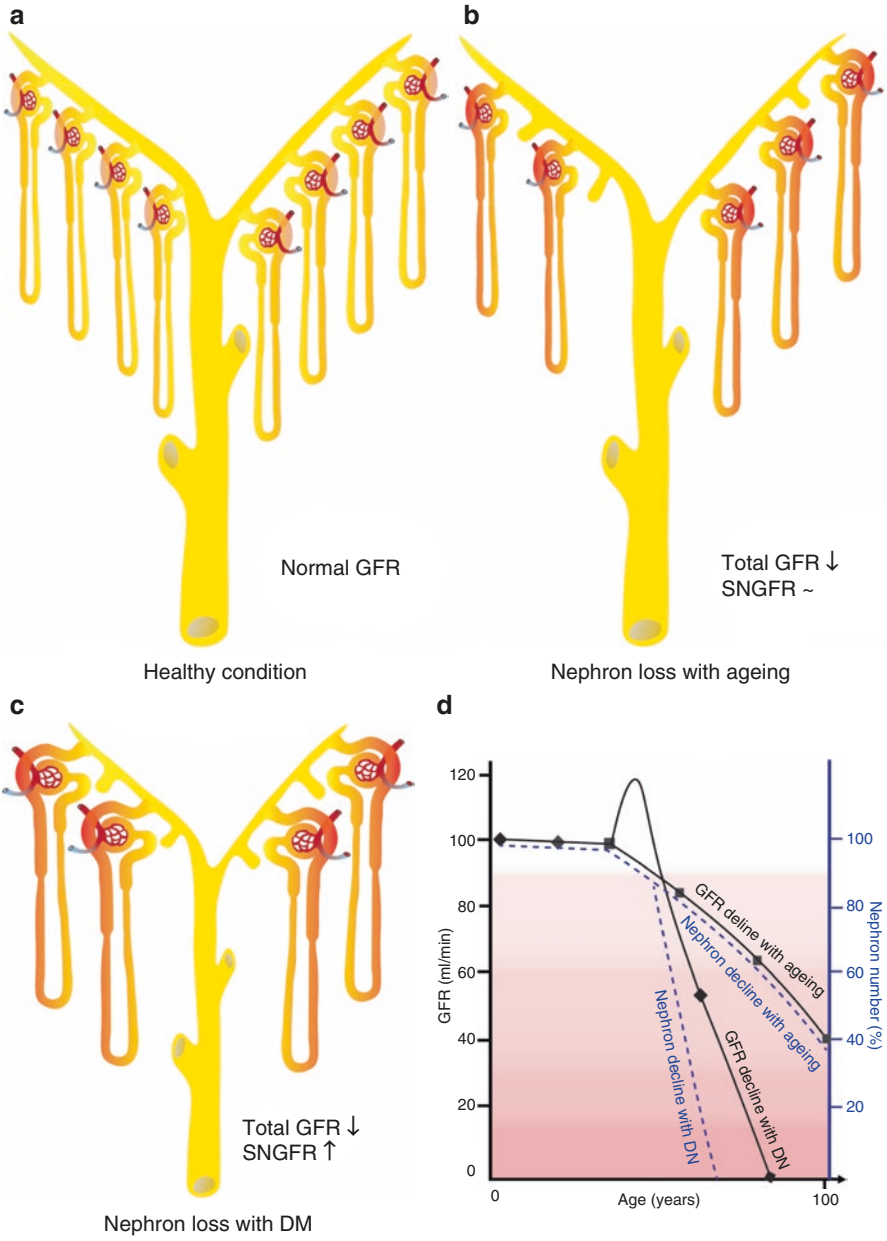

Fig. 5.1 Kidney life span in healthy aging or with a chronic kidney disease. Nephron number is set at birth and declines with age. Because filtration load and metabolic activity also decline with age, this does not require adaption of the remnant nephrons as it becomes obvious by normal dimensions of glomeruli and tubuli and the absence of proteinuria. Single nephron glomerular filtration rate (SNGFR) remains constant. In contrast, any disequilibrium of nephron number and filtration load as it occurs in obesity, pregnancy, or kidney disease-related nephron loss implies an increased SNGFR. Single nephron hyperfiltration and reabsorption induces compensatory adaptations such as increased dimensions of glomeruli and tubuli. In diabetes, hyperglycemia is a central driver of the same mechanisms; thus single nephron hyperfiltration is a central disease pathomechanism of CKD progression in diabetic nephropathy, i.e., shortening of kidney life span

large number of nephrons can handle diabetes-related hyperfiltration, conditions of absolute (CKD, aging, or both) or relative low nephron numbers (low nephron endowment, obesity, pregnancy, previous acute kidney injury) may pass the threshold and promote progressive loss of nephrons [16]. Therefore, reducing single nephron hyperfiltration and hyperreabsorbtion are the main treatment targets in diabetic nephropathy and require a deeper understanding of the factors that determine glomerular filtration in health and diabetes.

Renin-Angiotensin-Aldosterone System

The role of the RAAS in the pathophysiology of diabetic nephropathy has been extensively studied. In the last decade, several studies have demonstrated that the local intrarenal RAAS acts independently of the systemic RAAS and has been shown to be activated in both experimental and human diabetes [21, 22]. The early understanding of the RAAS was limited to angiotensin II (Ang II) and angiotensin II type 1 receptor (AT-1R), but the discovery of angiotensin-converting enzyme 2 (ACE2) with its derived Ang II metabolites angiotensin 1–7 (Ang (1–7)) and angiotensin 1–9 (Ang (1–9)) revealed other important roles in the development and progression of diabetic nephropathy [23, 24].

The renal RAAS is special among the local RAAS because all of the necessary components for intrarenal Ang II production are present along the nephron [25]. Ang II formation depends on the availability of the substrates angiotensinogen (AGT) and angiotensin I (Ang I) and the enzymatic activities of renin, angiotensin-converting enzyme (ACE), ACE2, and ACE-independent enzymatic pathways including the serine proteases, such as chymase. Ang (1–7), a metabolite of Ang II, can be formed directly from Ang II via hydrolysis from ACE2 or indirectly from Ang I via ACE [26] (Fig. 5.2). The study of the evolving and complex interactions between these hormones and their receptors has led to increase the knowledge of the pathophysiology and progression of diabetic nephropathy. However, after years of research in this topic, discrepancies and controversies between the circulating and the intrarenal RAAS remain and need more research to understand this complex system.

Angiotensinogen

Angiotensinogen (AGT) is a 485aa plasma glycoprotein constitutively and mainly synthetized by the liver [27]. It is expressed in the kidney, adipose tissue, brain, heart, adrenal glands, and testes [28]. In situ hybridization experiments localized renal AGT mRNA to the proximal convoluted tubule and the intrarenal vasculature, providing evidence for a local renin-angiotensin system within the kidney [29]. Urinary AGT has been proposed as a new marker for hypertension and tubular damage in diabetes, and urinary AGT levels have been shown to be consistently elevated

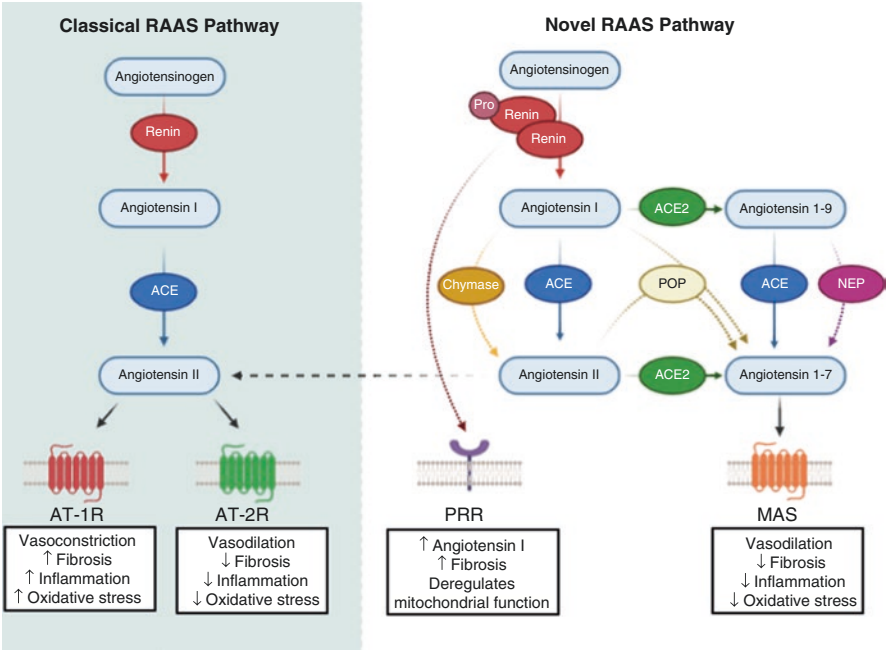

Fig. 5.2 Classical and novel pathways of the renin-angiotensin-aldosterone system modulated in diabetic nephropathy. RAAS, renin-angiotensin-aldosterone system; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; POP, prolyl oligopeptidase; AT-1R, angiotensin II type 1 receptor; AT-2R, angiotensin II type 2 receptor; PRR, (pro)renin receptor; MAS, Mas receptor

in both experimental models and human forms of diabetic nephropathy [30, 31]. In line with this, intrarenal AGT mRNA and protein levels are also increased in patients and rats with diabetes as compared to their controls [32]. In type 1 diabetes, increased urinary AGT precedes higher blood pressure and is associated with intrarenal RAAS activation. In addition, it also antedates the development of stage 3 CKD (eGFR <60 mL/min per 1.73 m^2) in patients with type 1 diabetes [33]. In type 2 diabetes, urinary AGT also showed correlation with albuminuria and urinary α1-microglobulin [34]. These studies suggest that the enhanced AGT expression in the kidney may in part play an important role in the pathogenesis and progression of DN.

ACE-Ang II-AT-1R Axis

The ACE-Ang II-AT-1R axis is the pressor arm of the RAAS. The octapeptide hormone Ang II is generally considered the main effector of RAAS and has diverse actions in the different renal cell types. As mentioned above, it has been established that the intrarenal RAAS is upregulated in diabetic nephropathy, contributing to its

pathophysiology and progression [21, 22]. Ang II causes oxidative stress, inflammation, cell proliferation, and, as a consequence, interstitial matrix accumulation and target organ damage. In the kidney, Ang II has been shown to promote most of its effects in the renal vasculature, the glomeruli, and the tubules, as they all express Ang II receptors in their cells [35]. In the blood vessels, Ang II basically induces vasoconstriction but also endothelial dysfunction and oxidative stress, among other actions [36]. In the glomeruli, Ang II promotes generation of ROS, mesangial matrix accumulation, alterations in GFR, glomerulosclerosis, albuminuria, and podocyte loss [37, 38]. Finally, in the tubulointerstitial compartment, Ang II has shown to stimulate sodium reabsorption, apoptosis, fibrosis, and inflammation by stimulation of superoxide formation and chemokine release [38]. These deleterious actions of Ang II have been mainly ascribed to the stimulation of profibrotic cytokines such as TGF-β, VEGF, and PDGF and also to the downstream activation of signalling pathways involving PKC and NF-κB [39]. The result of the accumulation of intrarenal Ang II in diabetes condition is the development of tubulointerstitial fibrosis and glomerulosclerosis.

Different studies in type 2 diabetes mellitus have shown that there is a major role for ACE-independent formation of Ang II. There have been several reports indicating that chymase is markedly unregulated in mesangial cells, mast cells, and vascular smooth muscle cells in experimental models of diabetic nephropathy and that chymase inhibitors, such as chymostatin, significantly block Ang II formation [40]. Park et al. demonstrated that afferent arteriole vasoconstriction in control kidneys that is produced by Ang I was significantly blunted by ACE inhibition, but not by serine protease inhibition. Interestingly, in diabetic kidneys, serine protease inhibition but not ACE inhibition significantly blunts vasoconstriction of the afferent arteriole produced by intrarenal conversion of Ang I to Ang II [41]. These data suggest a switch from ACE-dependent to serine protease-dependent Ang II formation in the diabetic kidney.

In the kidney, Ang II acts via signalling through two of its receptor subtypes, the AT-1 and AT-2 receptors. The AT-1 receptor is thought to be widely distributed throughout the kidney, while the AT-2 receptor is only found in glomerular endothelial cells and tubular epithelial cells in the cortex, interstitial, and tubular cells in the outer medulla, and inner medullary collecting duct cells [42]. These receptors mediate the opposing effects of Ang II, whereas activation of AT-1 receptors leads to vasoconstriction, sodium retention, and cell proliferation, while activation of the AT-2 receptors leads to vasodilation, natriuresis, and inhibition of cell proliferation [43]. The expression of kidney AT-1 receptors is decreased in diabetic nephropathy; AT-1-A or AT-1-B receptors of Ang II are downregulated heterogeneously in different cells and arterioles (less downregulation in the endothelial cells than in the smooth muscle cells (SMCs)). The enhanced downregulation of AT-1-B in the renin-negative SMCs of the efferent arterioles suggests that the regulation of the glomerular filtration rate by the pre- and post-glomerular arterioles is changed in diabetes [44].

The role of the AT-2 receptor in the pathobiology of the diabetic kidney is poorly understood and there is much conflicting data regarding these receptors. Indeed,

experimental models of diabetic nephropathy have reported both increased and decreased expression of the AT-2 receptor [43]. These divergent findings may in part be related to the different experimental animal models of diabetic nephropathy used in the various studies, discrepancies between the circulating and intrarenal RAAS, duration of diabetes, as well as the techniques used to measure the levels of expression of the RAAS. Two studies have been focused on the effect of stimulating AT-2 receptor in obese diabetic Zucker rats [45, 46]. Sabuhi et al. demonstrated that CGP-42112A (AT-2 receptor agonist) treatment in obese rats reduced the plasma and kidney cortex inflammatory (TNF-α, IL-6) and oxidative stress (gp-91phox) markers and increased plasma antioxidant activity to the levels seen in lean control rats. However, CGP-42112A treatment in lean rats increased inflammatory (TNF-α, IL-6) and oxidative stress (gp-91phox) markers in the plasma and kidney cortex [45]. In line with this, Castoldi et al. demonstrated that C21 treatment (AT-2 receptor agonist) promotes nephroprotection in diabetes by reducing kidney fibrosis, in the absence of a decrease in blood pressure or blood glucose level. Furthermore, C21 treatment blunts the increase in albuminuria in the early stage of the disease and improves the antiproteinuric effects of losartan during the progression of diabetic nephropathy [47]. Taking both studies together, the results indicated a positive effect of AT-2 receptor stimulation in the obese and diabetic kidney. In the last 4–5 years after the blast of the SGLT2 inhibitors, the research of the AT-2 receptor has clearly diminished, and few studies have focused in this receptor.

ACE2-Ang (1–7)-Mas Axis

The complexity of the intrarenal RAAS was clearly demonstrated in 2000 with the discovery of the ACE2 by two simultaneous groups that focused their studies in the heart [23, 48] (Fig. 5.2). Initially ACE2 was thought to be restricted to the heart, kidney, and testes, but later studies demonstrated that it is widely expressed in different organs and cells including the placenta and liver and in circulation among others [46]. ACE2 is the first known metalloprotease ACE homologue of ACE that shares 42% of amino acids, one HEXXH consensus sequence, resulting in monocarboxypeptidase activity [26]. ACE2 is capable of cleaving the terminal leucine from Ang I to generate Ang (1–9); however it has a higher affinity (400-fold) for Ang II, cleaving the terminal phenylalanine residue from Ang II to generate Ang (1–7) [49]. Whereas Ang II has well-known vasoconstrictor, proinflammatory, and prooxidant effects, mediated through the AT-1 receptor, Ang (1–7) produces vasodilation, anti-inflammatory, and antioxidant effects, mediated through the Mas receptor [49].

The kidney is the organ with higher expression and activity of ACE2 followed by the pancreas and heart [21, 50]. Within the kidney ACE2 has been identified in multiple compartments of the kidney including the renal cortical tubules, renal vasculature, and podocyte [51]. Dr. Batlle's laboratory demonstrated that ACE2 is mainly expressed in the bush border of the proximal tubules where it co-localizes with

ACE; in the podocyte it is expressed in podocytes and mesangial cells where it co-localizes with nephrin, synaptopodin, and smooth muscle actin (podocyte and mesangial cells markers, respectively); and in the renal vasculature, it is mainly expressed in the tunica media where it co-localizes with smooth muscle actin marker [51, 52].

ACE2 expression in the kidney has been studied in acute kidney injury, hypertension, and diabetes mellitus type 1 and type 2 models among others. Ye et al. in a type 2 diabetes model, 8-week-old db/db mice, a model of early type 2 diabetes, demonstrated that ACE2 protein expression is increased while ACE is decreased in kidney cortex from diabetic mice. In contrast, in the glomeruli ACE2 expression is decreased, while ACE is increased in diabetic db/db mice [50, 51]. In line with this, later studies by Riera et al. demonstrated that ACE2 is also increased in renal cortex in early NOD diabetic mice (21 days of diabetes). In addition, circulating ACE2 activity is also increased in NOD diabetic mice. This increase was maintained as the kidney disease progresses from 21 days to 40 days of diabetes [21, 53]. Taken together, these studies suggest that in diabetic kidney disease, ACE2 is upregulated, probably as a protective mechanism against the ACE-dependent Ang II formation and subsequent accumulation within the kidney. The study of ACE2 expression and localization within the kidney has been in part controversial, because studies in other animal models such as rats somehow follow different pattern of its expression and it has been mainly associated with different species and gender differences regarding RAAS [54, 55]. Seminal studies showed the deleterious effect of the ACE2 downregulation either by genetic ablation or pharmacological inhibition in diabetic kidney disease [51, 56, 57]. In two diabetic kidney models, streptozotocin and db/db diabetic model, the inhibition of ACE2 by MLN-4760 increased urinary albumin, mesangial matrix expansion, and vascular thickness, accompanied by focal loss of podocytes, indicating that ACE2 may be necessary for podocyte maintenance [51, 56, 57]. Interestingly, ACE2 genetic ablation also impaired the glucose homeostasis in the NOD diabetic mice by promoting oxidative stress and necroptosis in the pancreas [57] (Fig. 5.3). These findings suggest that ACE2 likely participates in a compensatory mechanism in the diabetic kidney prior to the onset of diabetic nephropathy while protecting against podocyte loss and the progression of the renal disease.

Different studies have focused on the assessment of circulating ACE2 activity in the context of kidney disease. Soro-Paavonen et al. were the first to demonstrate that patients with type 1 diabetes and micro- or macrovascular disease displayed a significant increase in serum ACE2 activity as compared with controls or with a diabetic cohort without albuminuria [58]. In addition, circulating ACE2 activity was found to be increased in those male and female patients with diabetes, vascular complications, and decreased estimated glomerular filtration rate, suggesting that counter-regulatory mechanisms are activated in kidney disease [58]. Among type 1 diabetic males, serum ACE2 activity positively correlated with systolic blood pressure and diabetes duration [58]. In line with this, Anguiano et al. demonstrated that ACE2 activity also increases in diabetic CKD patients and it correlates with glycosylated hemoglobin [59]. As previously mentioned, in mice with experimental

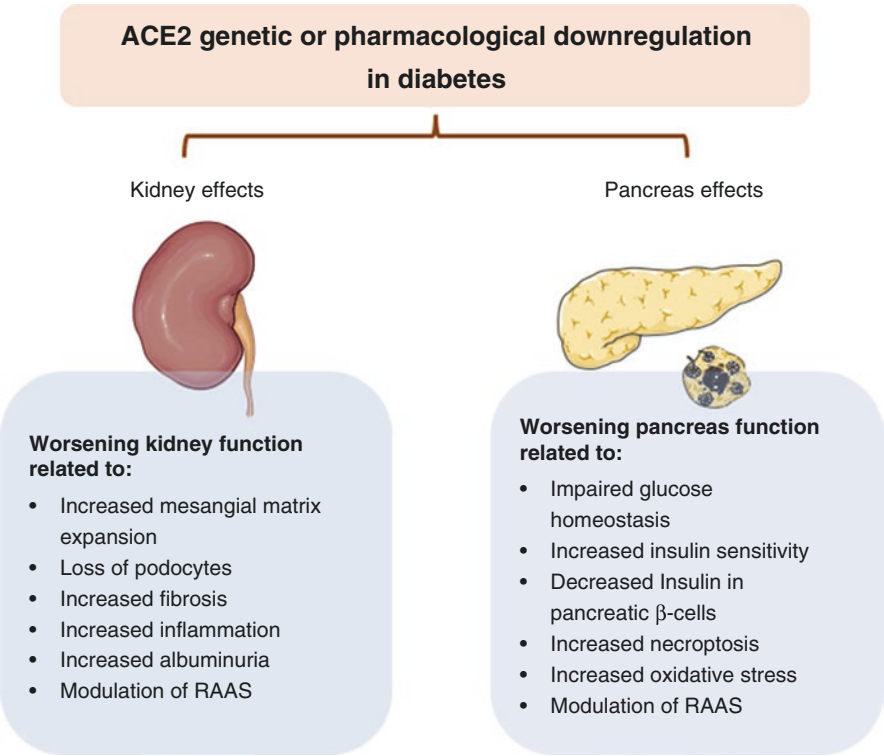

Fig. 5.3 Kidney and pancreas effect of ACE2 genetic or pharmacologic downregulation. ACE2, the discovered enzyme in 2000, is one of the clue important enzymes for maintaining the integrity of the RAAS. In experimental models of diabetes, ACE2 downregulation either by genetic deletion or by pharmacologic inhibition leads to worsening kidney and pancreas function. RAAS, renin-angiotensin-aldosterone system

diabetes, ACE2 activity increased in the renal cortex and in the circulation, suggesting a potential mechanism to adapt to diabetes-associated Ang II overactivity [53]. As circulating ACE2 activity increase starts at an early stage of diabetes and correlates with kidney function, some authors postulated that the measurement of circulating ACE2 may become a biomarker of CV disease in patients with DN [59].

Since its discovery in 2000, the interesting and exciting ACE2 has been in the shadow for years. This year, celebrating the 20th anniversary of the discovery of ACE2, it comes out a pandemic disease named COVID-19 where ACE2 demonstrated to be the receptor for the viral entry into the cell [60]. For this reason, the number of groups currently studying ACE2 has been exponentially growing, and several papers have been published, and currently ongoing studies focused on the effect of RAAS blockade in patients at risk or with COVID-19 disease [61].

Angiotensin (1–7) is a heptapeptide member of the RAAS discovered by Ferrario et al. that can be formed as a result of the metabolism of Ang (1–9) by ACE and metabolism of Ang II by ACE2 (see Fig. 5.2) [62]. In the kidney, whereas some

authors postulate that Ang (1–7) appears to be generated from its precursor Ang I by neprilysin, thimeto ligopeptidase, or prolyl oligopeptidase [63], other studies in rat kidney cortex have shown that Ang (1–7) is primarily generated via ACE2-dependent degradation of Ang II [54], demonstrating again the complexity of the system and their peptides formation and accumulation. Ang (1–7), through Mas receptor, is a potent vasodilator that also exerts antihypertensive, anti-inflammatory, and antiproliferative properties in the kidney [64]. These actions essentially antagonize the actions of Ang II mediated via the AT-1 receptor. To date, there is limited information regarding the direct effects of Ang (1–7) in the diabetic kidney, and few studies have been focused in the assessment of Ang (1–7) levels and expression within the diabetic kidney. Bertoncello et al. demonstrated an increased kidney cortex concentration of Ang (1–7) in diabetic STZ mice bearing one and three copies of Ace gene [65]. In the streptozotocin-induced diabetic spontaneously hypertensive rats, chronic treatment with Ang (1–7) attenuated NADPH oxidase activation, diminished proteinuria, and decreased diabetes-induced increase in kidney vascular responsive to Ang II [66]. Interestingly, in a recent study, acute intrarenal Ang (1–7) infusion resulted in natriuresis in combination with reduced diabetes-induced glomerular hyperfiltration and a paradoxical increased total kidney oxygen consumption in streptozotocin-induced diabetes in the rat [67]. The effect in the oxygen consumption seems to be related to a shift of Na + reabsorption from highly efficient proximal tubule to less efficient distal tubular segments, which increases oxygen consumption to maintain Na + balance. All of these observations support the renoprotective effect of Ang (1–7) in diabetes.

Ang (1–9)

Angiotensin (1–9) is a nonapeptide member of the RAAS that can be formed as a result of the metabolism of Ang I by ACE2 [26]. Several authors postulated that Ang (1–9) is an inactive peptide [68]. However, the role of Ang (1–9) in the kidney remains poorly understood and has not been properly evaluated.

Renin/Prorenin

Renin is released to the blood by juxtaglomerular cells (JC) in response to low blood pressure, decrease of Ang II, or low distal salt concentration and due to sympathetic stimulation. Renin is synthesized as a precursor (prorenin) that remains inactive when its 43-aa long N-terminal propeptide sequence blocks the active site. Once activated this protease cleaves AGN into angiotensin I (Ang I) [69]. To date the only human enzyme described to firmly cleave the propeptide sequence of prorenin is cathepsin B [70–72], an enzyme that is mainly located in acidic compartments such as the lysosomes. This fact supports the idea that prorenin can only be

proteolytically transformed into active renin inside the cells but not in plasma. The JC apparatus secretes prorenin in a constitutive way, and renin is stored in intracellular vesicles that are released to blood under specific stimuli [69] explaining why circulating prorenin levels are five- to tenfold higher than renin levels in healthy individuals [73]. In 2002, Nguyen and collaborators described the (pro)renin receptor (PRR) [74] that is expressed in several tissues, such as the kidney, heart, and liver, among others [75], and can also be found soluble in plasma [76]. The PRR binds both renin and prorenin but the last with higher affinity [77] producing a conformational change that activates prorenin in a non-proteolytic and reversible way [78]. Renin activity is increased in urine of patients with DN [79, 80] suggesting that intrarenal renin system is activated. In this line, streptozotocin (STZ)-induced diabetic mice show increased levels of renin not only in the JC but also in the collecting duct cells [79]; however this is not observed in the nonobese diabetic (NOD) mice [81]. In type 2 diabetic mice db/db, renin is also increased in the kidney mainly due to increased expression in the JC [82] and in the glomeruli [83]. The PRR is also upregulated in human diabetic kidney [84] and in several experimental models [85, 86]. The activation of the PRR is a local source of Ang I production in the renal tissue and, in addition, triggers several signalling pathways that can lead to kidney damage. In mesangial cells, the PRR when activated promotes the synthesis of profibrotic factors and matrix metalloproteases via the mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK-ERK) pathway [87, 88]. Furthermore, the PRR activation by (pro)renin deregulates the mitochondrial function via the PGC-1α/AMPK/SIRT-1 signalling pathway [86]. The PRR also binds Wnt that in fact promotes kidney injury and fibrosis via enhanced Wnt/β-catenin signalling [84]. The contribution of the PRR to DN is further evidenced by the reversion of kidney damage when a PRR blocker (decoy peptide) is administered to STZ-induced diabetic rodent models [89, 90].

The activation of the renin system seems to happen locally in the kidney as most of the patients with overt diabetic nephropathy show low plasma renin activity (PRA) thus not mirroring the renin modulation in the kidney [91]. This paradox, the low-renin state in diabetic nephropathy, has been a puzzle for many years, and still now, there is not a straightforward explanation for it. Half of the diabetic patients with less than 7 years of disease evolution show normal or increased PRA [92–94], while after 15 years, virtually all of the patients have low PRA [92, 93]. Curiously, the PRA states in DN patients are parallel to the hemodynamic changes (Fig. 5.4).

As widely described, diabetic nephropathy appears gradually and characteristic hemodynamic changes happen over time. Although the exact time of onset depends on each individual, the stages of DN can be roughly classified into (1) preclinical, (2) incipient, and (3) overt DN. Preclinical DN happens during about the first 5 years of DM onset, at this early stage, the GFR increases up to 140 mL/min/1.73 m^2 (hyperfiltration) in 70% of the patients with T1DM and in 50% of the patients in T2DM, but microalbuminuria is not detected [95]. Hyperfiltration is a mechanism secondary to increased glucose and Na + reabsorption by the Na+/glucose cotransporter SGLT2 that is located in the luminal membrane of the proximal tubular cells. This leads to decreased Na + delivery to the *macula densa* that is interpreted in a

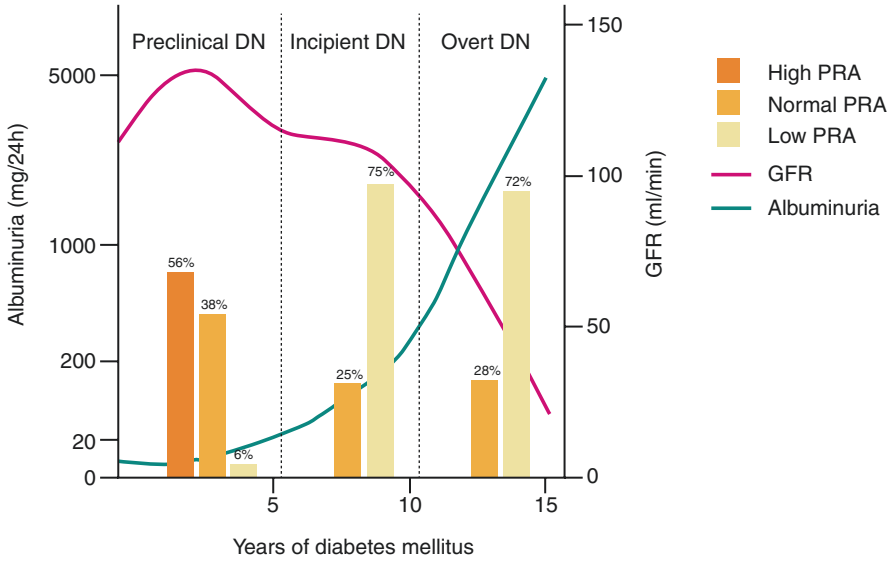

Fig. 5.4 Proportion of patients (%) with high, normal, and low plasma renin activity (PRA) during the evolution of diabetic nephropathy. Most of the patients with diabetic nephropathy have high to normal plasma renin activity (PRA) during first years of evolution of the disease (approximately up to 5 years). Afterward, when albuminuria begins to rise and the GFR tends to decrease, most of the patients have low PRA. The PRA data represented in this scheme belong to "King, J. A., & Fray, J. C. (1994). Hydrogen and potassium regulation of (pro)renin processing and secretion. *The American Journal of Physiology*, *267*(1 Pt 2), F1–F12"

similar way than a drop of blood pressure and thus triggers renin synthesis [96]. The fast hemodynamic regulation of renin synthesis via the *macula densa* is possibly the origin of increased PRA in the first years of DM evolution. After 5 years on average, the GFR normalizes for many years and usually some degree of microalbuminuria is present (incipient DN). Progressively the GFR declines and albuminuria increases (overt DN) due to nephron mass loss [95]. Once the GFR is normal or below normal (>7 years of DM progression), the PRA is decreased in most of the patients [92, 93] (Fig. 5.4). This may be explained by increased intrarenal RAAS activity that leads to Ang II-mediated renin inhibition rather than by a systemic effect as diabetic patients show a relatively normal response to ARB treatment, both hemodynamic (vasodilator) and reactive renin response (increased PRA activity) [91]. In the same line, dietary salt supplementation reverses the increase in PRA induced by ARBs reinforcing the idea that PRA is controlled by hemodynamic effects associated to the systemic RAAS in diabetic patients [97]. The SGLT2 inhibitors (SGLT2i) have nephroprotective effects that are mostly attributed to beneficial hemodynamic effects [96]. Dapagliflozin, an SGLT2i, increased PRA in T2DM patients [98] demonstrating once again that systemic hemodynamic changes correctly modulate PRA. Intriguingly, plasma levels of prorenin are increased in diabetic patients [92, 99], and they correlate with the severity of microvascular complications such as

diabetic nephropathy [100, 101] or diabetic retinopathy [100–102]. In parallel, the soluble PRR (sPRR) blood levels are normal or decreased in a diabetic context [99, 103] suggesting that the total PRA is not only related to decreased renin secretion but also to the interaction of prorenin with sPRR. Finally, a role for baroreceptor and sympathetic-mediated mechanisms cannot be excluded in the modulation of renin synthesis and excretion [104] as well as deregulation of aldosterone function in diabetes [105, 106].

Aldosterone

Aldosterone, a steroidal hormone, is the final effector of the vasoconstrictor arm of the RAAS (ACE-Ang II-ATR1). Its main function is to control the final step of water and electrolyte balance that accounts for a 3% of the total reabsorbed water during the urine production process [107]. This hormone is synthesized by the suprarenal glands under Ang II stimuli and mediates its effects via the mineralocorticoid receptors (MRs) that in the kidney are located in the cytoplasm of the distal tubular cells [108]. The MRs work as all glucocorticoid receptors: aldosterone easily diffuses into the cells due to its liposoluble properties and interacts with the MR. Afterward, the aldosterone-MR complex translocates into the nucleus and promotes the transcription of genes by binding glucocorticoid regulated elements (GRE) of the promoter region of the target genes. The target genes code for the Na^+/K^+ ATPasa, the Na^+/Cl^- cotransporter (NCC), and the epithelial Na^+ channel (ENaC) as well as for regulators of its activity. Aldosterone can also trigger several signalling pathways in a fast non-genomic way such as the ERK1/2, JNK1/2, and PKC and produce ROS via NADPH oxidase. It is under discussion whether these actions are dependent or not of the MR [109]. Aldosterone directly contributes to kidney damage in several experimental CKD scenarios including DN [110–114]. Most probably aldosterone has deleterious effects because the MRs are expressed in other tissues different from epithelia such as the vasculature [109] and also because these receptors can also be activated by glucocorticoids in pathologic conditions [108, 115]. The MR antagonists (MRA) have shown beneficial effects in DN experimental models [116–122], and their efficacy is now being tested in human DKD [123]. Regarding the DN experimental models, in several type 1 or type 2 diabetic mouse and rat models, the treatment with MRA reverted fibrosis and mesangial matrix expansion and decreased the expression of diverse inflammation, fibrosis, and oxidative stress markers in the kidney [116–119]. Spironolactone protected high-fat diet and STZ-induced diabetic rats from diabetic kidney damage by promoting autophagy processes in podocytes [121]. Furthermore, in a STZ-induced diabetic rat model, tight junction proteins (essential proteins for the maintenance of the electrolyte balance) [124] showed altered function in the proximal tubules (claudin 2), distal tubules (claudin 4 and 8), and glomeruli (claudin 5). Spironolactone restored the function of the mentioned tight junction proteins by decreasing oxidative stress and via the serum and glucocorticoid-induced kinase 1 (SGK1), and with-no-lysine

kinase 4 (WNK4) signalling pathways [120]. In a uninephrectomized db/db mice model [125] and in OLETF diabetic rats [126], the MRA treatment had an add-on effect on ACEi treatment although this was not observed in a STZ-induced rat DN model [127]. It is possible that the aldosterone blockade efficacy depends on the degree and the type of kidney damage. For instance, in diabetic eNOS knockout mice, spironolactone (an MRA) reverted kidney damage markers, but the RAAS blockade with enalapril or telmisartan showed a limited effect [122]. In human CKD the MR antagonists (MRA) have shown beneficial effects in terms of proteinuria reduction [128, 129]. Currently, several clinical assays are ongoing to further assess the cardiorenal benefits of the MRA in diabetic patients. The main limitation of these drugs is the hyperkalemia associated to its use; therefore some of the clinical trials (the "Finerenone in Reducing Kidney Failure and Disease Progression (FIDELIO)" and the "Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO)") tested finerenone as this compound is more selective in action as compared to spironolactone and eplerenone [123]. The results of these clinical trials are important because MRA improved the outcome of DN on top of the ACEi or ARB therapy, so that they could be used to prevent the "aldosterone breakthrough" (an increase in blood aldosterone levels) that happens in a proportion of the patients secondary to the use of RAAS blockers [130].

Neprilysin

Neprilysin (or alternatively neutral endopeptidase (NEP), membrane metalloendopeptidase (MME), endopeptidase 24.11, cluster of differentiation 10 (CD10), or common acute lymphoblastic leukemia antigen (CALLA)) is a zinc-dependent transmembrane metallopeptidase that is widely expressed [131], but, according to an immunodetection study performed in pigs, the levels are especially high in the kidney [132]. NEP can also be found soluble in blood as well as in other body fluids [131, 133]. NEP exerts its proteolytic activity upon a variety of substrates including the natriuretic peptides, bradykinin, endothelin, glucagon-like peptide-1 (GLP-1), and angiotensin I (Ang I), all of them are peptides/proteins that are relevant for the cardiovascular system and the kidney [134]. Regarding the RAAS, NEP converts Ang I into Ang (1–7) and competes with ACE and ACE2 for the substrate (ACE converts Ang I into angiotensin II and ACE2 converts Ang I into Ang (1–9)). Studies in an ACE2 knockout mice model have demonstrated that the deletion of ACE2 increases the kidney levels of Ang 1–7 [135, 136] an effect that is partially reversed when the animals are treated with sacubitrilat, a specific inhibitor of NEP [136]. These results suggest that NEP together with other peptidases plays an important role as mediator of the intrarenal RAAS [136]. NEP is thought to act in a renoprotective way as it is a source of Ang (1–7), a peptide that exerts vasodilator effects via the MAS receptor [108]. A study performed in db/db supports that the diabetic milieu induces downregulation of NEP and thereby it would contribute to renal damage [137]. In contrast, in humans increased levels of urinary NEP are associated

to DN progression suggesting an upregulation of NEP in the diabetic kidney [138, 139]. In line with this, increased blood levels of NEP have been associated with improved cardiovascular outcomes in heart failure patients [140, 141]. Furthermore, the dual NEP-AT-1R inhibitor sacubitril-valsartan has demonstrated superiority in cardioprotection over the standard-of-care treatment with enalapril [142] or valsartan [143]. NEP inhibition has also resulted to be beneficial in CKD experimental models including DN [144–146] and possibly also in patients with kidney disease although specific clinical assays to assess renal outcomes have not been performed yet [147–149]. The beneficial effects of NEP inhibition are most probably due to its pleiotropic activity upon a large number of substrates. Although a protective role of NEP locally in the kidney is possible, the systemic inhibition of this enzyme increases the bioavailability of bioactive peptides that have vasodilator, natriuretic, and diuretic properties. In this sense, a putative therapeutic option could be the concurrent inhibition of NEP and activation of ACE2. This has been tested in STZ-induced diabetic rats that when treated with thiorphan/Dize (NEP inhibitor/ACE2 activator) combination showed amelioration of renal function and kidney damage markers as compared to the littermates treated with monotherapy [150].

Prolyl Oligopeptidase

Currently, there are three known proteases responsible of the production of Ang 1–7 from Ang I or Ang II: angiotensin-converting enzyme 2 (ACE2), prolylcarboxypeptidase (PRCP), and prolyl oligopeptidase (POP). ACE2 is the best characterized and its role in diabetic kidney disease is discussed above. PRCP and POP are less studied. PRCP exerts its optimal enzymatic activity upon Ang II and other peptides in acidic conditions [151, 152]; therefore its contribution in physiological conditions may be limited. The POP is a serine protease involved in the hydrolysis of Ang I and Ang II as well as other low molecular weight active peptides (peptide hormones and neuropeptides). In the case of the angiotensin peptides, POP converts both Ang I and Ang II into Ang (1–7) [153–155]. The enzymatic activity of POP is mainly intracellular although it has been found bound to membranes isolated from the bovine brain [156]. This enzyme has been detected in several tissues that include the brain, immunologic tissues, testis, renal cortex, and blood [157, 158]. POP seems to have a role in neurodegenerative diseases and also in inflammation, but in the kidney and in circulation, its exact role is not fully established [155]. A study performed in 2013 demonstrated a role for POP in kidney protection but independent from Ang II. In this study, kidney damage was induced in mice by unilateral ureteral obstruction, and afterward thymosin β4 and a derived peptide (Ac-SDKP) were given to assess their possible anti-fibrotic effect. Thymosin β4 is a substrate for POP that metabolizes this peptide to the anti-fibrotic tetrapeptide (Ac-SDKP). The treatment with Ac-SDKP reduced fibronectin deposition, interstitial fibrosis and inflammation when compared to untreated littermates. Contrarily, the treatment with thymosin β4 plus a POP inhibitor increased kidney fibrosis and inflammation

suggesting that POP is relevant to metabolize thymosin β4 to the anti-fibrotic Ac-SDKP [159]. In a recent study [155], Ang (1–7) levels were measured in blood of ACE2 and PRCP knockout (ACE2$^{-/-}$/PRCP$^{-/-}$) mouse model after Ang II infusion. The ACE2$^{-/-}$/PRCP$^{-/-}$ animals had similar Ang (1–7) levels as their wild-type (WT) littermates after Ang II infusion. Furthermore, when a specific POP inhibitor (Z-pro-prolinal) was used, the levels of Ang (1–7) decreased in both ACE2$^{-/-}$/PRCP$^{-/-}$ and WT, but the decrease was milder in the WT. In addition, Ang II infusion in a POP knockout (POP$^{-/-}$) model produced a blunt in Ang (1–7) rise when compared to WT, and the rate of recovery from acute Ang II-induced hypertension was delayed. These results suggest that the main source of Ang (1–7) in blood is POP activity. These findings were further reinforced by the measurement of Ang (1–7) from added Ang II in serum, lung, and kidney extracts of WT animals with and without Z-pro-prolinal. In serum and in the lung, the administration of Z-pro-prolinal almost abolished the production of Ang (1–7) confirming that POP is responsible for the synthesis of this peptide in blood. In contrast, in the kidney Z-pro-prolinal only decreased partially the production of Ang (1–7) suggesting a major contribution of ACE2. In the same study, the POP $^{-/-}$ mice showed a slower recovery of the hypertension induced by Ang II. This fact arises the possibility that circulating POP has a major role in the systemic RAAS regulation [155, 157].

How Hyperglycemia Affects Single Nephron GFR

The glomerular filtrate of a healthy human adult contains ~180 g glucose per day, accounting for about one-third of the body's caloric expenditure. To maintain homeostasis the proximal convoluted tubule (PCT) recovers almost all of glucose in the glomerular ultrafiltrate; hence normal urine is free of glucose. Studies from the 1980s already identified the two different types of glucose transporters expressed on the apical surface of the PCT [160, 161], which later were cloned and named SGLT-1 and SGLT-2 [162]. The capacity of SGLT2 accounts for 97% of total glucose reabsorption in the PCT (along with sodium), whereas SGLT1 reabsorbs the remaining ~2–3% [163–165]. Both SGLTs first take up glucose into the PCT cells from the luminal brush border membrane followed by a passive exit from the cell via glucose transporter-2 from the basolateral membrane. As sodium is reabsorbed along with glucose transient, any persistent hyperglycemia will also increase sodium chloride recovery in the PCT and decrease sodium chloride delivery to the *macular densa* [166, 167], the contact point of the ascending limb of the loop of Henle with the vascular pole of the glomerulus of the same nephron (Fig. 5.5a). This hyperglycemia-induced low sodium chloride concentration at the *macula densa* has fundamental consequences on the kidney vasculature, glomerular filtration, and nephron structure and, in concert with other risk factors, can lead to diabetic nephropathy progressing to end-stage kidney disease [16, 167, 168]. How is that possible?

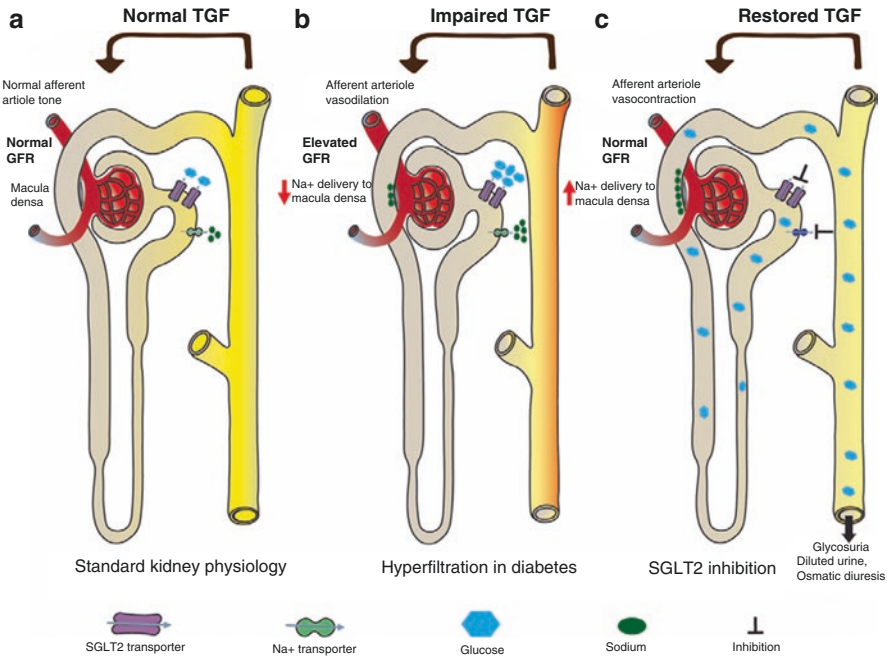

Fig. 5.5 Postulated tubuloglomerular feedback (TGF) mechanisms in normal physiology, early stages of diabetic nephropathy, and after sodium-glucose cotransporter (SGLT2) inhibition. (**a**) Under physiological conditions, TGF signalling maintains stable glomerular filtration rate (GFR) by modulation of pre-glomerular arteriole tone. In cases of conditional increases in GFR, the *macula densa* within the juxtaglomerular apparatus senses an increase in distal tubular sodium delivery and adjusts GFR via TGF accordingly. (**b**) Under chronic hyperglycemic conditions (diabetes mellitus), increased proximal SGLT2-mediated reabsorption of sodium (Na+) and glucose impairs this feedback mechanism. Thus, despite increased GFR, the *macula densa* is exposed to lowered sodium concentrations. This impairment of TGF signalling likely leads to inadequate arteriole tone and increased renal perfusion. (**c**) SGLT2 inhibition with empagliflozin treatment blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium delivery to the *macula densa*. This condition restores TGF via appropriate modulation of arteriolar tone (e.g., afferent vasoconstriction), which in turn reduces renal plasma flow and hyperfiltration

As stable kidney function is key to homeostasis, the numerous mechanisms of renal autoregulation assure a constant GFR across a wide range of blood pressures [169]. Renal autoregulation implies adaptive changes in the diameter of the afferent and efferent arterioles, which maintain constant hydrostatic pressure inside the glomerular capillaries [169]. Neurohumoral activity and the aforementioned intratubular sodium chloride concentration at the *macula densa* represent the set points that regulate the hemodynamics. Under physiological conditions, this works as a so-called tubuloglomerular feedback (TGF) system in each individual nephron, where the components of the distal tubule fluid regulate SNGFR [170, 171]. With normal blood pressure, a moderate concentration of sodium chloride in the distal tubule fluid is delivered to the *macula densa*, causing moderate vasoconstriction of the

afferent arteriole and, via deactivating renin release from the juxtaglomerular apparatus, a moderately open efferent arteriole, i.e., TGF [172]. Declining SNGFR, e.g., due to low blood pressure or otherwise low salt or volume conditions, deactivates the TGF, a compensatory mechanism selected during evolution to normalize GFR in such scenarios. In this setting, little sodium chloride reaches the *macula densa* where the juxtaglomerular apparatus induces vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole, which both increase glomerular perfusion, hydrostatic pressure in the glomerular capillaries, and GFR [169]. Hyperglycemia mimics this scenario and persistently deactivates the TGF for the reasons mentioned before and is illustrated in Fig. 5.5b [166, 167]. Persistent deactivation of the TGF causes vasodilation of the afferent arteriole and renin-angiotensin-driven vasoconstriction of the efferent arteriole leading to persistent glomerular hyperfiltration, i.e., increased SNGFR in each nephron [167, 172]. As long as nephron number is normal, this implies an increased total GFR, but as the number of nephrons declines with aging or progression of CKD, also total GFR declines.

Animal studies suggested that increased glucose reabsorption in the PCT in diabetes is related to an increased expression of the SGLT2 gene [173]. Tubular epithelial cells recovered from the urine of type 2 diabetic patients show enhanced expression and glucose transport capacity via SGLT2 compared to urine cells prepared from nondiabetic controls [174]. Accordingly, SGLT2 null mice that show no spontaneous phenotype do not increase their GFR upon induction of diabetes as observed in wild-type mice [175]. Micropuncture experimentation in rats with streptozotocin-induced diabetes treated with SGLT2 inhibitors demonstrated reductions in PCT sodium reabsorption and single nephron GFR [176]. Finally, video microscopy of mice with hyperglycemia confirmed the aforementioned changes occurring at the afferent and efferent glomerular arterioles upon administration of an SGLT2 inhibitor [177]. Besides the RAAS and SGLT2-driven mechanisms, also endothelin and NFR-2 regulate glomerular perfusion and GFR. Atrasentan leads to restoration of the diminished podocyte number and reduction in proteinuria in diabetic murine model. The benefit of ET_AR antagonism in DN extended to a decrease in mesangial matrix as measured by a reduction in accumulations of collagen type IV in both the atrasentan and atrasentan + losartan-treated groups compared with untreated controls [178]. A diuretic added to the combined RAAS and ET_A blockade has late renoprotective effects in CKD induced by partial nephrectomy in Ren-2 transgenic rats. The diuretic improved kidney function (evaluated as proteinuria and creatinine clearance), kidney morphology (kidney mass, glomerular volume), and histological markers of kidney damage (glomerulosclerosis index, tubulointerstitial injury) [179]. Endothelin plays a role in the hemodynamic events in rat model, and that ET_A receptor antagonists should be investigated as potential therapeutic agents for radiocontrast-induced nephropathy [180].

Thus, hyperglycemia increases single nephron hyperfiltration, which, when nephron number is normal, implies an increased total GFR. This process involves as a first mechanism SGLT2-driven deactivation of the TGF and as a consequence activation of the RAAS. RAAS inhibition alone does not fully recover kidney

autoregulation, but dual RAAS/SGLT2 inhibition can correct most of the hemodynamic alterations induced by persistent hyperglycemia. As another mediator the endothelin system is involved in the alterations of kidney hemodynamics in diabetes; hence also endothelin receptors and NRF2 have been considered as molecular targets for therapeutic intervention in diabetic nephropathy.

Hemodynamics as an Upstream Pathomechanism in Diabetic Nephropathy

Among the numerous pathomechanisms discussed in the pathogenesis of diabetic nephropathy only targeting the hyperglycemia, RAAS, SGLT2, and endothelin receptors demonstrated an effect size of 30% or more on clinically relevant outcomes. Other interventions targeting intrarenal inflammation, fibrosis, or other targets unrelated to kidney hemodynamics failed to show a meaningful efficacy on GFR decline when the final GFR assessment was off-drug. Therefore, after decades of confusion about the hierarchy of the numerous pathomechanisms discussed in the basic science domain, powerful clinical trials now provide the ultimate evidence, which are the upstream and which are the downstream mechanisms in diabetic nephropathy (Fig. 5.6).

Based on the promising findings in animal models, a compelling study explored the effects of empagliflozin on kidney hemodynamics in 40 patients with type 1 diabetes [181] without chronic complications, with normal blood pressure, not on antihypertensive therapy, and with a GFR >60 mL/min/1.73 m^2. At baseline, 27 patients had hyperfiltration (GFR >135 mL/min/1.73 m^2) and 13 had normal GFR. In patients with empagliflozin treatment after 8 weeks, there was a reduction in GFR from 172 ± 23 to 139 ± 25 mL/min/1.73 m^2, while there were no changes in patients with normal baseline GFR. In association with this, there was a 20% reduction in GFR and a parallel reduction in renal plasma flow and an increase in kidney vascular resistance, likely a consequence of afferent arteriolar vasoconstriction. Furthermore, there are several other similar drugs that are in the ongoing clinical trial that may be approved soon. In all the three FDA-approved drugs, empagliflozin has more selectivity for SGLT2 compared to SGLT1, while canagliflozin is the least selective [182]. More recently, several SGLT2 inhibitors have been developed with high selectivity for use in clinical trials in patients with type 2 diabetes mellitus (T2DM) like canagliflozin (Invokana®) and dapagliflozin (Farxiga®) [182, 183]. These drugs consistently helped T2DM patient's glucose levels, along with weight loss and antihypertensive effects [168]. However, there are limited SGLT2 inhibitors that are available in the case of type 1 diabetes (T1D) patients and are mainly derived from experimental animal models.

The efficacy, tolerability, and economic analysis results of the RENAAL study strongly supported the use of losartan as part of the standard of care in patients with type 2 diabetes and nephropathy in order to reduce the risk of progression to ESRD [184]. Furthermore, if dialysis is not readily available, patients may die due to complications of uremia (e.g., hyperkalemia, cardiovascular disease). Thus, death and

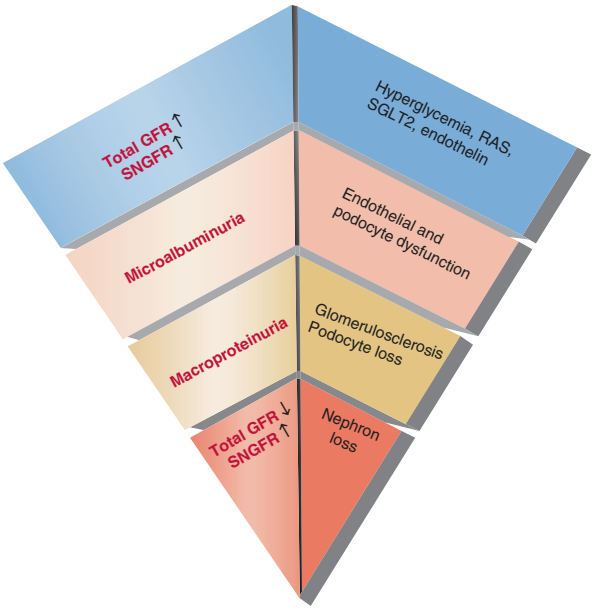

Fig. 5.6 Hierarchy of disease pathomechanisms in diabetic nephropathy. Hyperglycemia immediately disrupts the autoregulation of kidney perfusion and glomerular filtration rate via interference with the renin-angiotensin-aldosterone system (RAAS) and sodium-glucose cotransporters (SGLT). In addition, the endothelin system is involved in this process. The biomarker of this phase in increased total GFR. Long-term consequences of single nephron hyperfiltration and glucotoxicity include endothelial and podocyte dysfunction as well as mesangial sclerosis, all endorsing microalbuminuria. Once the mechanical forces and glucotoxicity exceed the capacity of podocytes for compensation, podocytes detach and get lost followed by more glomerulosclerosis and nephron loss. Macroproteinuria, the related hyperreabsorption in the proximal tubule, and decline of total GFR indicate this phase and imply a further increase in single nephron GFR, which aggravates filtration load on less and fewer remnant nephrons. As the process progresses, GFR declines into the range of what defines CKD III–V. The latter phase is associated with a mesenchymal healing response involving immune cells and interstitial fibrosis to stabilize the remnant nephrons. As inflammation and fibrosis are at the terminal end of the cascade of pathophysiological events, they should be insignificant therapeutic targets for the attenuation of CKD progression in diabetic nephropathy. In contrast, only targeting the upstream mechanism of disease, i.e., hyperglycemia and RAAS-, SGLT-, and endothelin-driven single nephron hyperfiltration, achieved significant effect size in clinical trials (SNGFR, single nephron glomerular filtration rate)

ESRD are competing events and future trials of mortality in this population should include this composite endpoint [185]. Trials of telmisartan in patients with diabetes and varying degrees of nephropathy also suggest that this drug can slow the progression of renal disease, an effect that appears to be at least partly independent of reduction in blood pressure. Telmisartan is therefore an important therapeutic option for optimizing cardiovascular and renal protection in the type 2 diabetic population [186].

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years [187]. In patients with type 2 diabetes at high

cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant kidney events than was placebo when added to standard care [188]. Patients randomized in DAPA-HF were similar to those in other contemporary HF with reduced ejection fraction (HFrEF) registries and trials. These patients were receiving recommended HFrEF therapy and those with diabetes were treated with conventional glucose-lowering therapy. Consequently, DAPA-HF will test the incremental efficacy and safety of dapagliflozin in HFrEF patients with and without diabetes [189].

These data together identify the hemodynamic changes induced by hyperglycemia and their consequences on the workload of the proximal tubule to be the central pathomechanism of diabetic nephropathy. Obviously, genetic factors, comorbidities, metabolic factors, neurohumoral activity, inflammation, and tissue remodeling all contribute to the individual risk constellation and overall disease progression. However, hyperglycemia and the related hemodynamic alterations represent the universal abnormality applying to all patients and therefore represent the prime targets for therapeutic intervention.

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Chapter 6
Pathogenesis: Structural Changes in the Kidneys in Type 1 and Type 2 Diabetes

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Introduction

The last three decades have seen a steeply increase in the incidence of and mortality from chronic kidney disease (CKD), both in high- and low-income countries [1–5]. In 2016, the global incidence of CKD was estimated at 21.3 million cases, an increase of 87.8% compared to 1990 [5]. In 2017, an estimated 697.5 million of people were living with CKD worldwide and 1.2 million people died due to it [2, 3]. This ranked CKD as the 12th leading cause of death worldwide, a significant advance considering that it was 17th in 1990 [2, 3]. It was estimated that, in 2017, CKD resulted in 35.8 million disability-adjusted life years (DALYs) globally, a shocking figure that highlights the devastating impact of this disease on people's health [2, 3]. In the United States (USA), CKD is recognized as an important public health issue. In 2016, 82,539 people died due to CKD in the country and the disease caused an estimate of 1,269,049 DALYs [6]. The economic burden of CKD in the United States is also onerous. Medicare spending for all beneficiaries who had CKD exceeded $84 billion in 2017, an amount that rises to over $120 billion if the costs of health care for patients with end-stage renal disease (ESRD) are added. Such amount represented 33.8% of the total Medicare fee-for-service (FFS) spending in 2017 [7]. Several studies have documented the key contribution of diabetes mellitus (DM) to the increase of the global burden of CKD seen in the last decades [6, 8–11]. Globally, the incidence of DM increased by 102.9% from 1990 to 2017 [12]. In

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2017, an estimate of 22.9 million of new cases of DM were diagnosed worldwide, 98.3% of which were type 2 DM (T2DM) [12]. In that year, 462 million people, that is, 6.3% of the world's population, were living with T2DM, determining a world prevalence rate of 6059 cases per 100,000 [12, 13]. However, if the current trend in T2DM incidence rate continues, the prevalence of the disease is expected to rise to about 7079 cases per 100,000 inhabitants by 2030 [13]. DM has been the leading drivers of the global increase of CKD DALYs in the last three decades, contributing 50.62% of the overall increase [5]. Diabetic nephropathy accounted for nearly a third of 35.8 million DALYs attributed to CKD in 2017 globally [2, 3]. It was also the main contributor to the increase of probability of death due to CKD in US adults aged 20 or older in the period from 2002 to 2016 [6]. Data of 2017 indicate that diabetes was the leading cause of ESRD in the United States, having being listed as the primary cause is 38.6% of the cases [14]. Therefore, the early detection and treatment of diabetic nephropathy must, therefore, be a priority in any healthcare strategy that seeks to ensure a good quality of life for diabetic patients.

A Bit of History

In 1936 Kimmelstiel and Wilson [15] reported a series of eight autopsies from patients in which they observed thickening of the intercapillary regions of the glomerular capillaries with the formation of nodules and suggested that a combination of DM and arteriosclerosis was responsible for the findings. Seven of the patients he described had DM for years preceding their death, and one patient had no information available as he died 3 h after admission with no previous history. The authors concluded that the lesion identified represented the typical changes in the glomerulus that occurred in patients with long-standing DM and termed this lesion diffuse intercapillary glomerulosclerosis. Because of their seminal contribution pointing out the structural changes in glomeruli of diabetic patients, the most salient finding in this lesion, the mesangial nodules are still referred to as Kimmelstiel-Wilson nodules. At about the same time, another diabetic patient was reported by Murakami in Japan [16] with similar histological picture. Since the life span of patients with DM was quite compromised until insulin became available, the renal lesions did not fully develop in many patients. Gellman et al. in 1959 for the first time reported an overview and clinical correlation of findings in renal biopsies from patients with DM [17]. The only material available prior to this manuscript was descriptions based on kidneys examined at autopsy. There have been attempts to separate typical from atypical diabetic nephropathy using various parameters including concomitant superimposed glomerular conditions and other tubulointerstitial and vascular alterations, either directly related to diabetes or superimposed conditions.

The morphological findings in diabetic nephropathy occurring in patients with type 1 and 2 diabetes (T1- and T2DM) overlap significantly to a point that it is virtually of no value to separate them. In general patients with type 2 diabetic

nephropathy reveal more significant vascular alterations and more heterogeneity in their glomerular lesions which can be morphologically altered by the effects of a number of comorbid disorders such as hypertension [18]. The alterations that take place in the kidneys of patients with diabetic nephropathy can be generically conceptualized as expansion of the extracellular matrices which include glomerular basement membrane and mesangial matrix, and segmental glomerular collapse, generally a more advanced change, characterized by focal and segmental glomerulosclerosis/hyalinosis.

Morphologic Findings in Diabetic Nephropathy and Related Physiopathology

The clinically latent period between the onset of clinical detection of diabetes and specific morphological findings that can be related to it generally lasts for more than 10 years. This period is usually manifested in the kidney by hyperperfusion, increased kidney size, enlarged glomeruli, and hyperfiltration [19]. The glomerular hemodynamic changes take place as consequence of increased plasma flow and elevated glomerular transcapillary hydrostatic pressure resulting from a decrease in both afferent and efferent arteriolar resistances with the efferent arterioles being more dilated than the afferent ones. Many factors have been implicated in this phenomenon including prostanoids, nitric oxide (NO), atrial natriuretic factor, growth hormone, glucagon, insulin, and angiotensin II, making this situation a difficult one to sort out. Elevated intraglomerular pressure has been linked to mesangial matrix overproduction and podocyte injury [20]. Other factors of importance in the diabetic milieu which also alter hemodynamics include vascular endothelial growth factor (VEGF) likely mediated through production of NO and the effect of transforming growth factor-β (TGFβ) leading also to hyperfiltration by producing dilatation of the afferent arterioles via inhibiting calcium transients. Shear stress and mechanical stretch caused by hemodynamic alterations represent yet additional factors inducing release of pertinent cytokine and growth factors. The local activation of local cytokines and growth factors mechanistically associates hemodynamic stress to structural changes in the diabetic glomerulus [21–27]. Other researchers have attempted to link glomerular hyperfiltration to a primary defect in tubular sodium reabsorption such that diabetic-induced hypertrophy of tubules mediates stimulation of sodium chloride reabsorption, again linking renal structural changes with the hemodynamic adaptations that take place in diabetic renal disease [17, 24, 28].

In the 30% or so of diabetic patients that will develop overt nephropathy, microalbuminuria is the earliest clinical manifestation which may progress over several years to nephrotic range proteinuria and decreased renal function. However, there are significant numbers of patients with diabetic nephropathy that progress into renal failure without ever developing nephrotic range proteinuria.

There are morphological correlates associated with this progression. The great majority of patients that are biopsied are, as expected, those that have developed clinical manifestations beyond microalbuminuria. The development of nephrotic range proteinuria, in some cases massive proteinuria, is an indication for renal biopsy to attempt to identify if any concomitant glomerulopathies may be responsible for these changes, as therapeutic interventions are needed if that is the case. However, more often than not, that is not the case.

Glomerular basement membrane thickening represents the earliest specific change in the diabetic glomerulus in type 1 and 2 diabetic patients and increases with duration of disease [20, 21, 29]. The overlap that is seen in glomerular diabetic lesions in type 1 and 2 patients has been recognized. The initial finding detectable ultrastructurally is subepithelial lamellation of the lamina densa as a manifestation of early deposition of additional basement membrane material which is responsible for the increase in thickness.

Upper limits for normal glomerular basement membrane thickness vary according to the methods used and, in some instances, fixation and processing of tissues for electron microscopy. If the orthogonal intercept method is employed to measure the glomerular basement membranes, the upper limit of thickness is 520 nm (0.52 μm) for adult men and 471 nm for women [30]. Using cutoff levels based on variations in thickness from normal glomerular basement membrane thickness of more than two standard deviations, Haas et al. published data that indicates that in males over 9 years of age, glomerular basement membranes thicker than 430 nm (0.43 μm) are abnormal and this number reflects the upper limit of acceptable thickness and in females 399 nm (0.399 μm) is the corresponding cutoff [31]. For children younger than 9 years of age, a table provides guidance. The thickness of the glomerular basement membranes may change with fixation and processing protocols used in the various laboratories. It is also markedly altered if material is taken from paraffin for ultrastructural assessment [32]. Each renal pathology laboratory should establish its own reference values to determine normal range of thickness for the glomerular basement membranes using an approach that has been accepted such as the ones mentioned. This will avoid incorrect assessments of the glomerular basement membranes.

Concomitantly with the increased thickness in the glomerular basement membranes, there is deposition of mesangial matrix leading to mesangial expansion [18, 20, 28, 33]. However, this finding by itself is rather nonspecific and can be seen in virtually any primary glomerular disease in its early stages and even as a reactive change in glomeruli in patients with primary tubulointerstitial or vascular diseases. Therefore, the diagnostic value of this finding is rather limited. Once the expanded mesangium becomes nodular, then nodular glomerulosclerosis is recognized, and this finding is far more specific for diabetic nephropathy (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, and 6.9). It is not exclusively seen in diabetic nephropathy, but it is a good marker in the proper clinical setting.

The molecular mechanism responsible for the mesangial matrix expansion is secretion and activation of TGF-β by mesangial cells [18, 34]. Mesangial nodules vary in number and size from glomerulus to glomerulus, and they vary from slightly

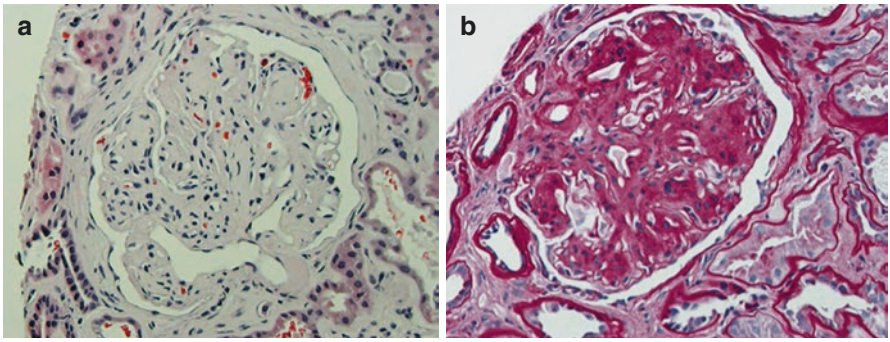

Fig. 6.1 (**a**) Hematoxylin and eosin (H&E) stain, X500; (**b**) periodic acid-Schiff (PAS) stain, X500. Nodular glomerulosclerosis. Diabetic nephropathy. The hallmark of diabetic nephropathy, nodular glomerulosclerosis. Well-defined mesangial nodules of variable size and thickening of peripheral capillary walls. Note that the mesangial cells that remain are at the periphery of the mesangial nodules

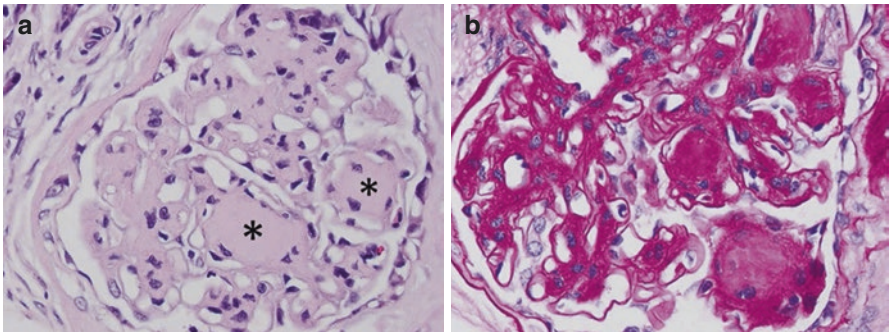

Fig. 6.2 (**a**) H&E stain, X750; (**b**) PAS, X750. Nodular glomerulosclerosis. Diabetic nephropathy. Details of mesangial nodules (asterisks) which are PAS positive

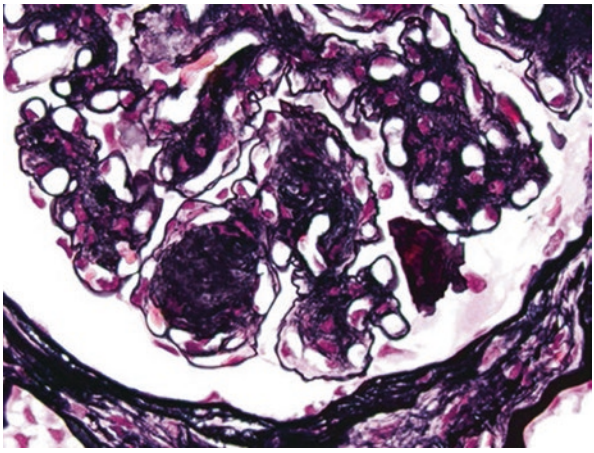

Fig. 6.3 Silver methenamine, X750. Nodular glomerulosclerosis. Diabetic nephropathy. Mesangial nodules are silver positive indicating increased mesangial matrix as their main component. Lamellation of mesangial nodule (*circle*). Few mesangial cells at the periphery

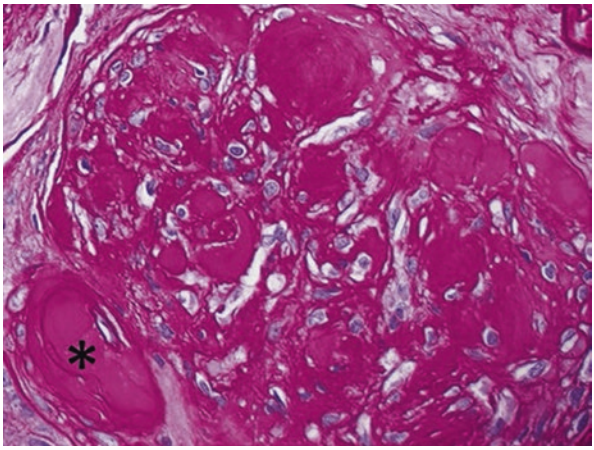

Fig. 6.4 PAS, X750. Hyaline arteriolosclerosis. Diabetic nephropathy. Hyaline material in the wall of arteriole is PAS positive, somewhat glassier than the staining of mesangial nodules

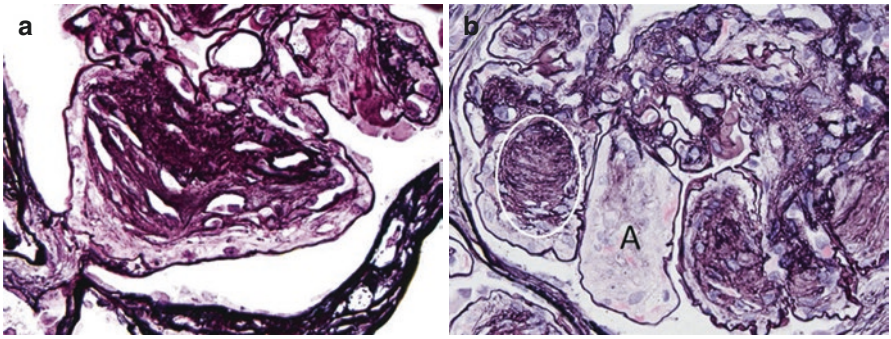

Fig. 6.5 (**a**, **b**) Silver methenamine stain, X750. Microaneurysm formation. Diabetic nephropathy. Process of microaneurysm formation (early events) with mesangiolysis in (**a**) and aneurysm (A) already formed in (**b**). Note that peripheral capillary walls are thinner than normal outlining the aneurysm. Also note mesangiolysis in adjacent mesangial nodules

hypercellular at the beginning to eventually paucicellular or even almost acellular with remaining mesangial cells generally located at the periphery surrounding the acellular center with increased matrix [33]. Mesangial nodules are positive with the PAS (periodic acid-Schiff) and silver methenamine stains (Figs. 6.1b, 6.2b, 6.3, and 6.4) and stain blue with the trichrome stain. In some nodules lamellation is appreciable, most noticeable in the silver methenamine stained sections.

Mesangiolysis is a key injury in the development and progression of nodular glomerulosclerosis, the most characteristic advanced lesion in diabetic nephropathy [33, 35–37]. Experimental studies by Matsusaka et al. [38] have shown that podocyte death is inducible and that if the degree of such injury is sufficient, mesangiolysis ensues. The loss of podocytes early in the process of diabetic nephropathy represents a significant contributory factor to mesangiolysis and resultant mesangial matrix accumulation. Mesangiolysis is associated with formation of microaneurysms. In aneurysmal areas, the surrounding glomerular basement membrane

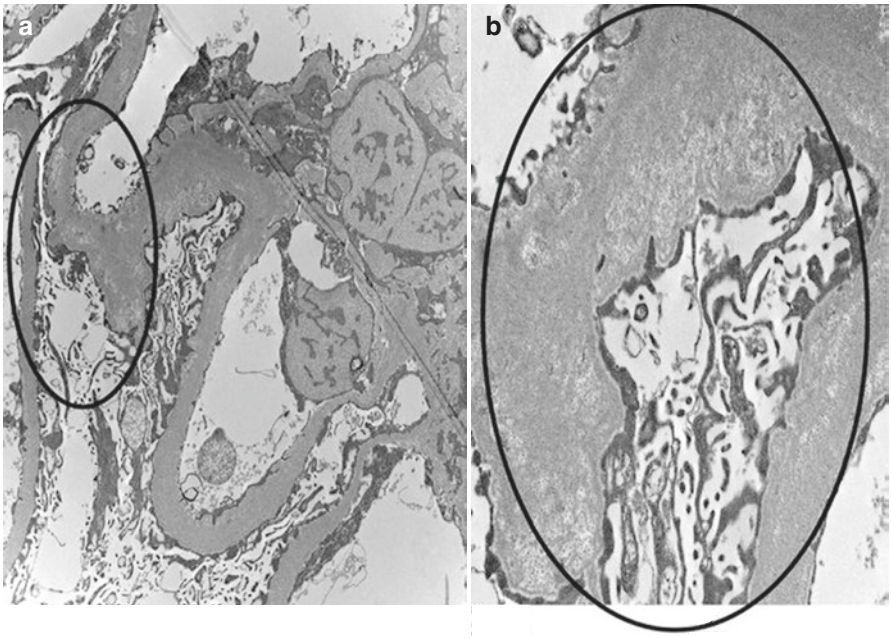

Fig. 6.6 (A, B) Transmission electron microscopy, uranyl acetate and lead citrate, AX15500, BX13500. Diabetic nephropathy. Thickening of glomerular basement membranes accompanied by subepithelial lamellation (a), the latter best seen on (b) (*circled areas*)

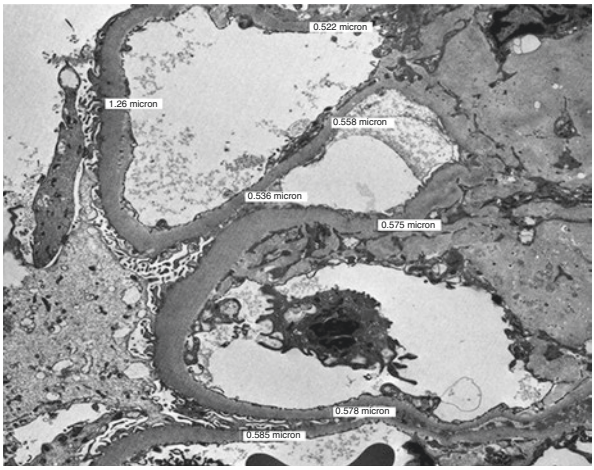

Fig. 6.7 Transmission electron microscopy, uranyl acetate and lead citrate, X8500. Diabetic nephropathy. Uniform thickening of the glomerular basement membranes (all measuring more than 520 nm to 0.52 μm) in thickness

becomes thin. So the process has been delineated by some authors as occurring as follows: repetitive mesangiolysis (destruction/dissolution of mesangial matrix) resulting in formation of microaneurysms, capillary collapse, and matrix deposition leading to the formation of mesangial nodules (Fig. 6.5) [35].

Other glomerular findings include insudative and exudative deposits. In 1994, L.C. Stout and associates defined "insudative lesions" as consisting of intramural accumulations of presumably imbibed plasma proteins and lipids within renal arterioles, glomerular capillaries, Bowman's capsule, or proximal convoluted tubules [39]. These deposits are eosinophilic and acellular, thus described as "hyaline." If they are seen "hanging" from or within Bowman's capsule, they are referred to capsular drops (Fig. 6.10). They are typically found between parietal epithelial cells and Bowman's capsule. L.C. Stout and associates pointed out that these lesions can be identified in 5.3% of biopsies from patients with glomerular pathology other than diabetic nephropathy [33, 39]. These lesions are rather suggestive of diabetic nephropathy but not entirely specific for it, although some believe that the capsular

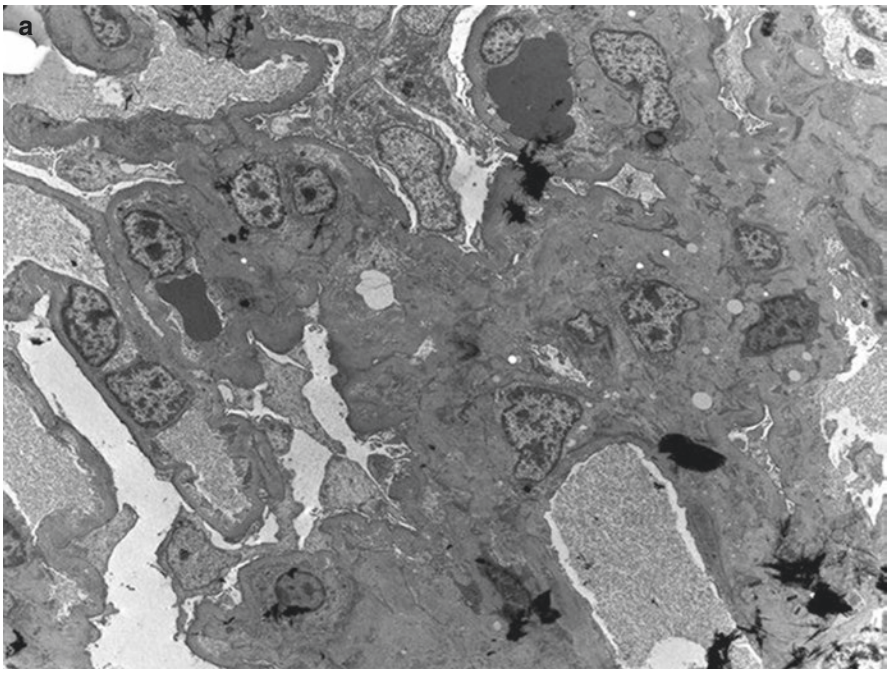

Fig. 6.8 (**a**, **b**) Transmission electron microscopy, uranyl acetate and lead citrate, AX7500, BX12500. Diabetic nephropathy. Mesangial expansion in (**a**) with increased matrix clearly seen in (**b**) associated with formation of obvious mesangial nodule

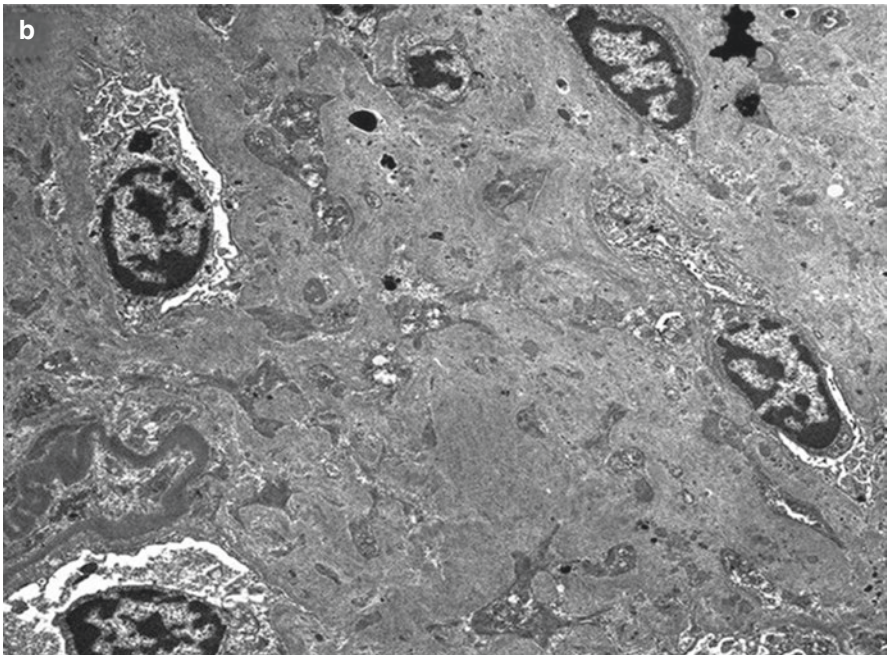

Fig. 6.8 (continued)

drops are specific, but not entirely pathognomonic of diabetic nephropathy [40]. If, in turn, they protrude from or are intimately related to the peripheral capillary walls, they are called hyaline of "fibrin" caps. However, the term fibrin cap is considered obsolete as they contain no fibrin. Hyalinosis is a much better term [41, 42].

Associated lesions are observed in the vasculature (Figs. 6.4 and 6.11). Hyaline arteriolosclerosis of both afferent and efferent arterioles is a characteristic diabetic finding. In fact, according to Stout et al., hyalinosis of the efferent arteriole is rather specific for diabetic nephropathy [39]. In contrast, hyalinosis of the afferent arteriole occurs in a number of other conditions, most notably vascular nephrosclerosis and cyclosporine nephrotoxicity [40]. Identifying efferent arterioles in renal samples cannot be done reliably which makes this finding a difficult one to confirm, and the dogma has been to determine the presence of hyalinosis in both arterioles at the vascular pole in glomeruli as the finding to be trusted is a typical finding in diabetic nephropathy.

In regard to atherosclerosis, lesions found in the arterioles and arteries are relatively nonspecific (Figs. 6.12 and 6.13) [39]. However, accelerated atherosclerosis represents a rather common alteration appreciated in renal biopsies from patients

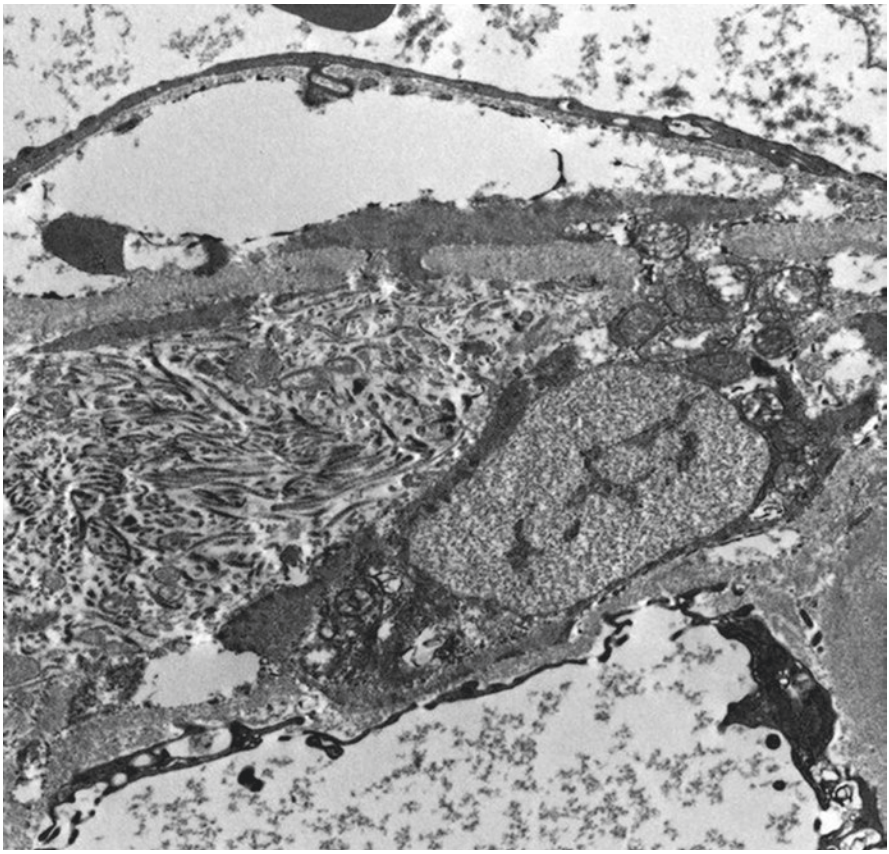

Fig. 6.9 Transmission electron microscopy, uranyl acetate and lead citrate, X12500. Diabetic nephropathy. Fibrillary collagen in mesangial nodule. Note parallel disposition of collagen fibers and periodicity in fibers

with diabetes, predominantly in those with advanced renal disease (Fig. 6.13). Bohle and associates found that the accelerated atherosclerosis was most common in those patients with advanced diabetic nephropathy [43]. Intimal fibrous thickening is the most characteristic finding; however, thickening of the media can also be seen.

Tubulointerstitial manifestations characterized by interstitial fibrosis, tubular atrophy, and dropout (Fig. 6.14) typically occur associated with and as a direct result of the glomerular and vascular changes, and, as expected, these changes parallel in degree the findings seen in the other two renal compartments [33, 37]. Tubular basement membranes thicken in parallel to similar alterations in the

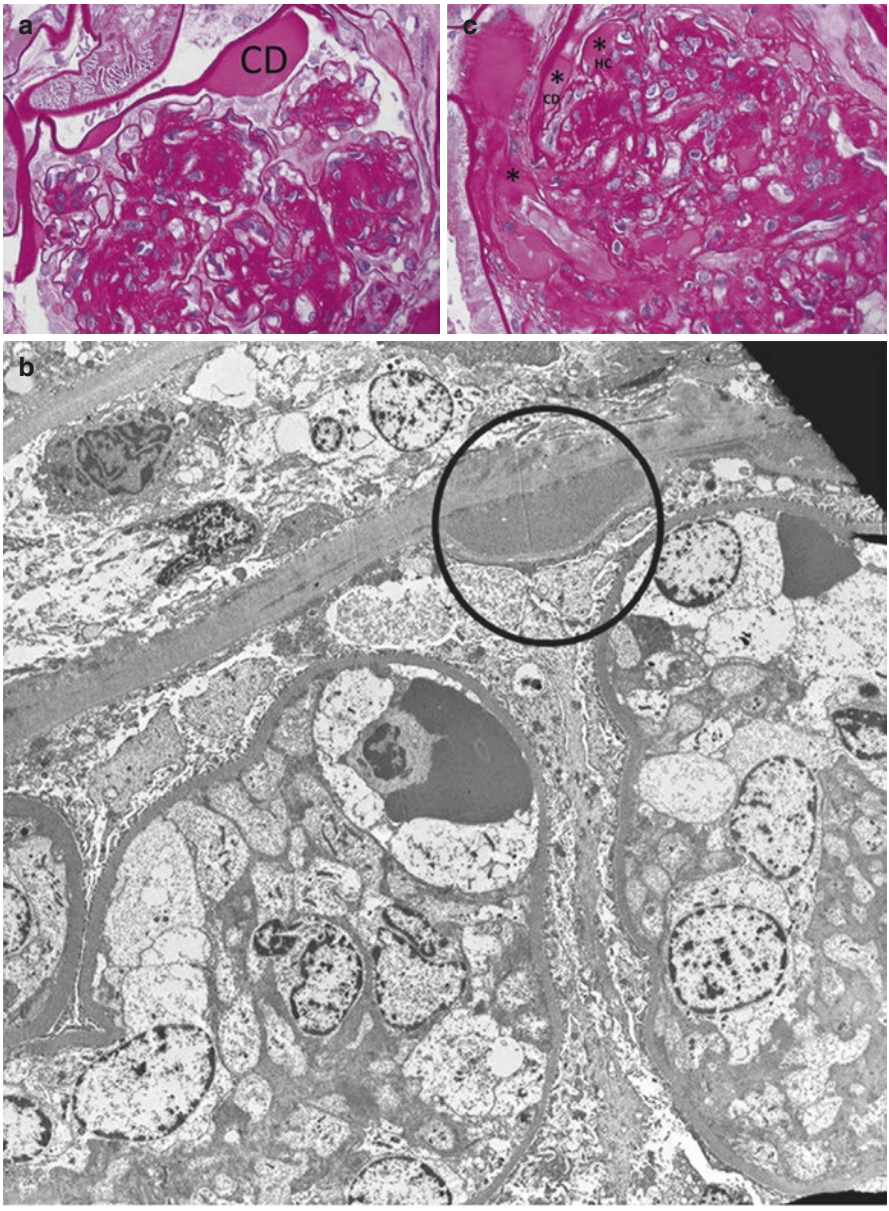

Fig. 6.10 (**a**, **c**) PAS stain; (**b**) transmission electron microscopy, uranyl acetate and lead citrate, AX750, BX5800, CX750. Diabetic nephropathy. In (**a**) capsular drop (PAS positive) (CD) hanging from Bowman's capsule with corresponding ultrastructural appearance in (**b**) (*circled*). In (**c**) capsular drop (*CD) and hyaline cap (*HC)

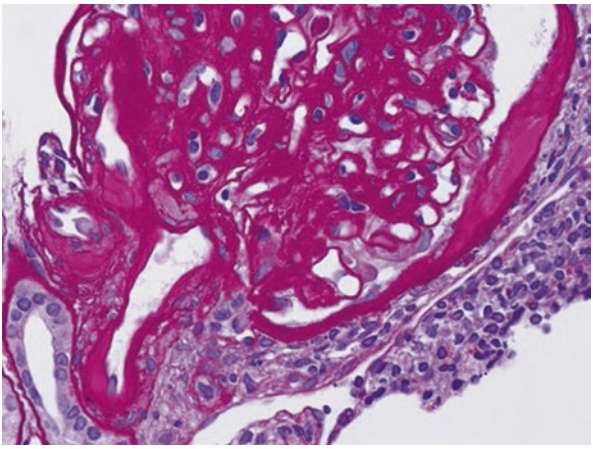

Fig. 6.11 PAS stain, X750. Diabetic nephropathy. Hyaline arteriolosclerosis in afferent and efferent arterioles

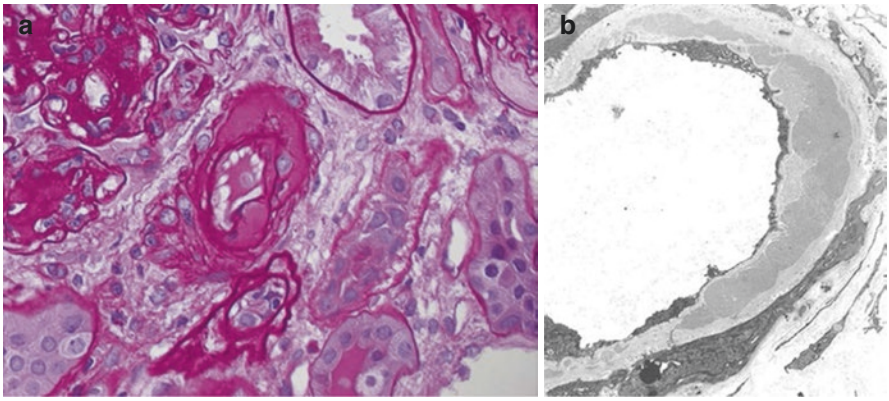

Fig. 6.12 (**a**) PAS stain; (**b**) transmission electron microscopy, uranyl acetate and lead citrate, AX7500, B-X350. Diabetic nephropathy. Hyalinosis in the wall of small-size artery in (**a**). Electron-dense material in vessel wall in (**b**) corresponds to the area with hyalinosis

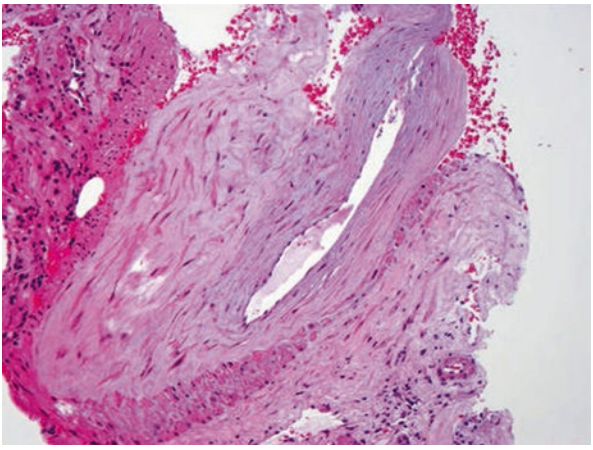

Fig. 6.13 H&E, X350. Diabetic nephropathy. Atherosclerosis in medium- to large-size arteries

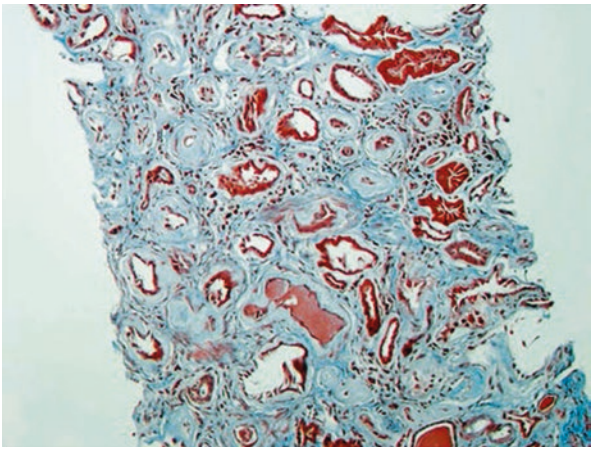

Fig. 6.14 Trichrome stain, X350. Diabetic kidney disease. Interstitial fibrosis (blue staining) associated with tubular atrophy/dropout and thickening of tubular basement membranes

glomerular basement membranes. Interstitial inflammation generally with mononuclear cells occurs and also leads to interstitial fibrosis, tubular atrophy, and dropout. Many studies show that the severity of chronic glomerular and tubulointerstitial pathology is closely related [43].

Focal, segmental glomerulosclerosis has been shown to be also an important component of the glomerular lesions in some diabetic patients, usually occurring in the more advanced stages of the disease. The implications for this finding are significant in the prognosis and management of these patients and will be discussed later.

Comparison of Diabetic Nephropathy in Type 1 and 2 Diabetic Patients

Most of our knowledge of diabetic nephropathy has come from studying the disease in type 2 diabetic patients since they are much more common than type 1 only (about 20 % of all diabetic patients), but there has been a significant number of studies focusing on the renal pathology in type 1 diabetic patients. As previously stated, much overlap exists in the renal structural changes that occur in both conditions.

About 40 % of patients with long-standing T1DM develop overt renal disease progressing to significant renal insufficiency [33]. The decline in glomerular filtration rate, hypertension, and proteinuria in general seem to correlate with a number of renal structural abnormalities, including increased mesangial fractional volume [Vv(mes/glom)], decreased glomerular filtration surface, interstitial expansion, increased numbers of globally sclerosed glomeruli, and arteriolar hyalinosis. However, since all these appear to correlate, it has been impossible to determine if one of these findings is more closely related to progressive renal functional impairment in diabetic nephropathy in cross-sectional studies [44–48].

However, the correlation of structural changes with renal functional findings is difficult in some instances, especially in type 1 diabetic patients, in some specific aspects. It has been shown that severe glomerular lesions may be seen in normoalbuminuric patients with T1DM and also that normoalbuminuric patients with decreased glomerular filtration rate have more advanced lesions than expected. Glomerular basement membrane width after long T1DM duration is a strong independent predictor of diabetic nephropathy risk in normoalbuminuric patients [49].

A study by Fioretto et al. attempted to relate structural renal changes to functional alterations in insulin-dependent diabetic patients [46]. It was found in a 5-year follow-up study that increasing mesangial fractional volume was closely linked to the development of albuminuria and early overt nephropathy, while interstitial expansion and glomerular glomerulosclerosis did not progress this time period as anticipated would happen. In addition, the structural changes of diabetic nephropathy were progressive, even in patients with stable renal function [48].

Perrin et al. also evaluated the course of diabetic nephropathy in normoalbuminuric patients with T1DM for 6 years with sequential renal biopsies. The study consisted of a cohort of six patients who had hypertension and were treated with antihypertensive medications for 2 years or more, and this group was compared with an untreated group composed of four similar additional patients. The study demonstrated that no progression occurred in the treated patients who also improved their metabolic control, but morphologic parameters deteriorated in the untreated patients. Glomerular and mesangial volume, mesangial matrix volume fraction, and foot process width of visceral epithelial cells increased significantly [48].

The role of hypertension in the progression of diabetic nephropathy has been a subject of debate. Initially it was felt that the development of serious diabetic nephropathy was independent of hypertension. More recently, studies have indicated that the presence of hypertension in patients with overt diabetic nephropathy is associated with a more rapid decline of glomerular filtration rate and that effective treatment of the hypertension has resulted in slowing the rate of decline of the glomerular filtration rate in these patients, who are far more commonly patients with type 2 diabetes [48]. Furthermore, the interaction between high blood pressure and diabetic nephropathy appears to be bidirectional. A study performed in Japan found that hypertension resistant to antihypertensive agents was common in patients with type 2 DM and increased with the progression of chronic kidney disease (CKD). The strict control of blood pressure became difficult in type 2 DM individuals who were in advanced stages of CKD as graded based on the estimated glomerular filtration rate (eGFR) and the urinary albumin excretion levels [50].

Podocytes are reduced in nephropathy associated with both T1- and T2DM [34]. Podocyte reduction has also been demonstrated in animal models of diabetic nephropathy [49, 51]. This reduction in podocytes may precede, and in some studies predict, the appearance of clinically detectable proteinuria. It does not appear that podocytopathy is more common in patients with either type 1 or 2 diabetic nephropathy.

The information available in the literature supports that glomerular, predominantly mesangial, structural changes are important in the clinical transition to microalbuminuria or overt nephropathy (rather than glomerular basement

membrane thickening), at least in insulin-dependent diabetic patients, while interstitial pathology does not seem to have a pathogenetic role at this stage of the disease [37, 52]. Interstitial fibrosis is more likely directly implicated in the progression of the diabetic nephropathy to ESRD.

More heterogeneity is seen in biopsies from patients with nephropathy and T2DM when compared with those with T1DM [33]. This is probably a result of aging, hypertension, and atherosclerosis, conditions that are usually present in these cases in a more florid manner, but the possibility that this may be at least partly inherent to the disease process in this subset of diabetic patients cannot be completely excluded at this time.

If type 2 diabetic patients with similar renal function are compared with type 1 patients, structural changes related to diabetic nephropathy are less severe, and the correlations between renal function and glomerular structural alterations are less precise, probably because there are a number of factors playing a role related to vascular pathology and other conditions that are not integral parts of the nephropathy in type 1 diabetic patients [33].

Finally, some researchers have noted that by the time renal function abnormalities become manifest, renal structural lesions are quite advanced [27].

Pathologic Classification of Diabetic Nephropathy

In order to better understand diabetic nephropathy, a unifying pathologic classification has been proposed to encompass renal lesions seen in T1- and T2DM to be able to relate them to structural kidney alterations and, consequently, clinical manifestations [37]. The glomerular alterations that may occur in diabetic patients with glomerular alterations are divided into four classes:

Class I is characterized by glomerular basement membrane thickening proven by electron microscopy and only, mild nonspecific changes by light microscopy that do not meet criteria for any of the other classes. Class II encompasses mesangial expansion which is divided into mild (IIa) or severe (IIb) but without identifiable mesangial nodularity. This category is analogous to what has been referred to as "diffuse diabetic glomerulosclerosis." If the mesangial matrix is more than 25% of the total mesangium, it should be classified as Class IIb but without mesangial nodularity in more than 50% of the glomeruli. Class III is referred to as nodular glomerulosclerosis.

At least one convincing mesangial nodule should be present in a glomerulus to be included in this category. No more than 50% globally sclerosed glomeruli should be present in the specimen examined. Class IV represents a more advanced form of nodular glomerulosclerosis with more than 50% globally sclerosed glomeruli in the sample. This classification has been tested with good interobserver reproducibility (intraclass correlation coefficient = 0.84).

This classification serves several purposes including the following: it (1) improves communication between renal pathologists among themselves and with

clinicians, (2) provides structural criteria to be used for prognostic and interventional studies, and (3) improves ability to manage patients clinically using morphologic parameters to evaluate efficacy of various interventions in delaying progression or renal disease and aids in determining the need for other therapeutic maneuvers. According to the authors, this classification is based on glomerular pathology only because these are relatively easy to recognize with good interobserver agreement and also because glomerular lesions best reflect the natural course of progressive diabetic nephropathy [33].

Tubulointerstitial and vascular pathology are not incorporated into this categorization of renal lesions in samples from diabetic nephropathy but are encouraged to be tabulated in a scoring format for a more comprehensive evaluation of the findings.

This classification ignores focal, segmental glomerulosclerosis, an important lesion that may carry with it clinical and prognostic significance, especially as it directly relates to podocyte injury and related issues addressed later in the chapter.

Structural Abnormalities of the Thickened Glomerular Basement Membranes and Expanded Mesangium in Diabetic Nephropathy: Light, Ultrastructural, and Immunofluorescence Microscopy Data.

Although there is a tendency to consider diabetic nephropathy a progressive disease as patients live longer with the disease, there is evidence that functional abnormalities are not always progressive and regression from one state to a better one occurs [18, 53, 54]. Renal biopsies have shown that glomerular changes reflect and correlated with renal dysfunction but interstitial fibrosis is the best indicator of prognosis/progression to ESRD [33].

Seminal studies carried out by several ways led to the concept that the structural and functional architecture and composition of the glomerular basement membranes consist of a backbone of collagen IV that forms a compacted meshwork and plays a crucial role in the size and charge-selective sieving properties of the ultrafiltration unit in the kidney. The proteoglycan-containing layer provides a negatively charged screen which is placed in front of the lamina densa with a major role in filtration of macromolecules. Glomerular basement membranes undergo fundamental alterations in diabetes that impair the filtration barrier. Biochemical alterations of the glomerular basement membranes occur along with the thickening of the lamina densa that typically occurs in diabetic nephropathy. It has been proposed that there is increased synthesis of basement membrane components and decreased incorporation of heparan sulfates into glycosaminoglycans resulting in decreased amounts of heparan sulfate proteoglycans (HSPG) in the diabetic glomerular basement membranes in relation to total protein [55]. However, the contribution of HSPG to early albuminuria has been challenged. In vivo rat studies removing HSPG from the glomerular basement membranes did not result in proteinuria [56], suggesting that heparan sulfate is not a major

determinant for the charge-selective characteristics of the capillary wall. Also, recent studies using antibodies for heparan sulfate in renal biopsies with type I diabetic nephropathy have demonstrated that the staining is not different in intensity to that detected in controls [57]. This last study convincingly demonstrated a lack of scientific evidence to support those changes in heparin sulfate expression, structure, or sulfation played a role in the early proteinuria in patients with diabetic nephropathy.

In the normal glomerulus, the mesangium predominantly contains collagen IV, though many other extracellular matrix proteins and glycoproteins are also typically observed. In diabetic nephropathy there is increased mesangial staining for collagen IV, laminin, and fibronectin, while staining for HSPG in the glomerular basement membranes has recently been found to be similar than in control glomeruli. As mesangial nodules became bigger, it has been shown that the staining for interstitial collagens such as V and III (but not collagen I) increased, while the corresponding staining for collagen IV decreased [58, 59]. However, it has been shown that the amount of collagen IV in mesangial nodules actually is increased and its decreased staining is due to decreased density of collagen IV in relation to other extracellular matrix proteins. This also correlates with the focal deposition of fi collagen in some mesangial nodules, typically observed in advanced diabetic nephropathy [52]. Another protein that accumulates in the mesangial nodules is tenascin which makes the restructuring of the mesangium a challenge as destruction of tenascin by metalloproteinases is difficult [60].

Mesangial expansion represents the first noticeable finding by light microscopy in patients with diabetic nephropathy but is often considered nonspecific and of questionable value in making a definitive diagnosis of diabetic nephropathy. Mesangial matrix expansion has been documented in renal biopsies within 5 years of the diagnosis of diabetes mellitus.

Immunofluorescence features of diabetic nephropathy are rather constant. Linear staining for IgG and albumin (Fig. 5.15a) along peripheral capillary walls in glomeruli and along tubular basement membranes represents the most characteristic findings. In some cases, there is also linearity with similar pattern for both light chains. This pattern of linear staining in diabetic glomeruli has been thought to be due to stickiness of the glomerular basement membranes to antibodies used for immunofluorescence and is not related to immune complex-mediated processes or circulating cytotoxic antibodies. Granular deposition of C3 and IgM (Fig. 5.15b) is also seen with some frequency, especially in the more advanced cases. If segmental glomerulosclerosis/hyalinosis is present in addition to trapping of C3 and IgM, there is also variable granular C1q staining, also attributed to trapping.

Ultrastructurally the light microscopic findings are confirmed. Thickening of the glomerular basement membranes and expansion of mesangial areas eventually leading to the formation of well-defined nodules with increased extracellular matrix are

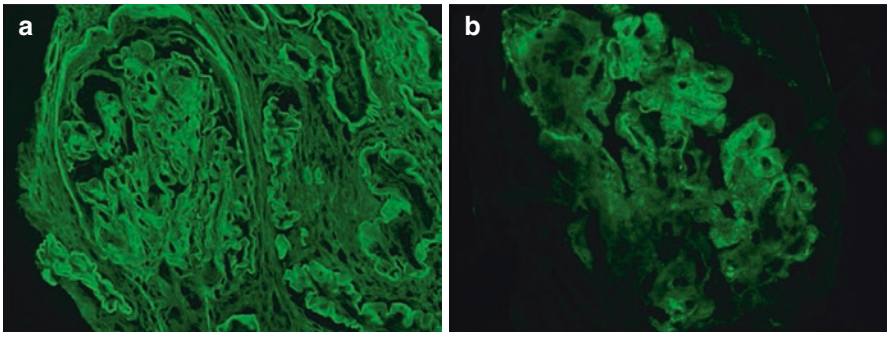

Fig. 6.15 Direct immunofluorescence for IgG and IgM, respectively, AX350, BX500. Diabetic kidney disease. Linear staining along peripheral capillary walls in glomeruli and along tubular basement membranes for IgG in (**a**). Granular, predominantly mesangial staining for IgM in (**b**)

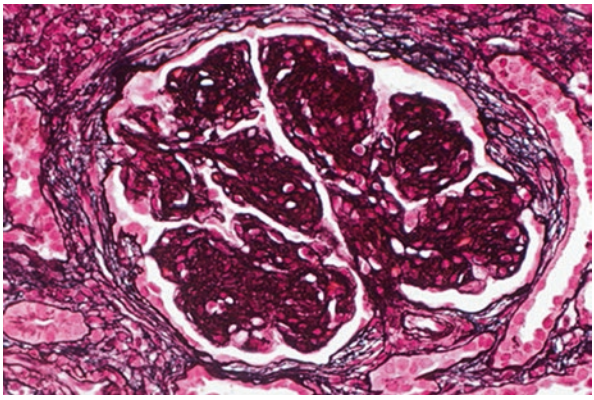

Fig. 6.16 Silver methenamine stain, X500. Diabetic fibrillosis. Note increased staining in mesangial nodules alternating with empty appearing (nonstaining) areas where the fibrillary material (which does not take the silver) accumulates

observed (Fig. 6.8). These changes are diffuse and generalized but can vary considerably from one glomerulus to the next. In the early stages of diabetic nephropathy when glomerular basement membrane thickening represents an early development, light microscopy is limited in terms of assessing this finding unequivocally making it a must to rely on ultrastructural evaluation to determine that the glomerular basement membranes are indeed thickened. Glomerular basement membrane thickening detected ultrastructurally may be seen as early as 2 years after the diagnosis of DM in some patients, and increased thickness of the glomerular basement membranes occurs with time [29, 33, 61].

In addition, there is effacement of the foot processes of the visceral epithelial cells, and sometimes these are detached from the glomerular basement membranes, most commonly in advanced lesions. The glomerular basement membranes sometimes exhibit subepithelial lamellation, predominantly in early cases (Fig. 6.6).

Mesangial expansion with increased matrix and focal hyalinotic foci is seen in mesangial nodules [33]. There is also cellular debris and, in some cases, mostly those with advanced alterations, fibrillary collagen is seen (Fig. 6.9). Hyaline deposits, represented by electron-dense areas, containing plasma proteins can be seen in various glomerular locations corresponding the already described "capsular drops and/or hyaline caps." Similar hyaline deposits are confirmed predominantly in arterioles and small arteries (Fig. 6.12).

In a small number of patients with diabetic nodular glomerulosclerosis, there is deposition of randomly disposed fibrillary material composed of 10–25 nm in diameter non-branching fibrils (Figs. 6.16 and 6.17) [62]. This could be a confusing finding for pathologists who will need to exclude a number of conditions, but diabetic patients with diabetic fibrillosis behave clinically identical to those patients with similar degree of structural renal abnormalities. Microaneurysms can be detected. There are no immune complexes, monoclonal protein deposits, or fibrils with characteristics of amyloid, all of these finding of importance when a differential diagnosis with some other entities that may have similar morphological glomerular findings is being considered.

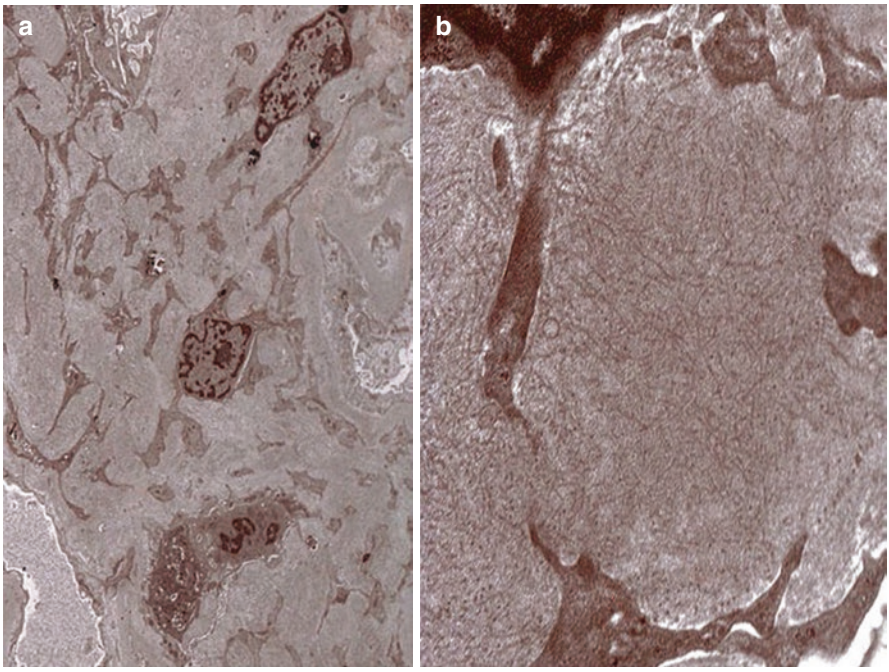

Fig. 6.17 (**a**–**c**) Transmission electron microscopy, uranyl acetate and lead citrate, AX9500, BX12500, CX17500. Diabetic fibrillosis. Fibrils measuring 15–25 nm in diameter in mesangial nodules

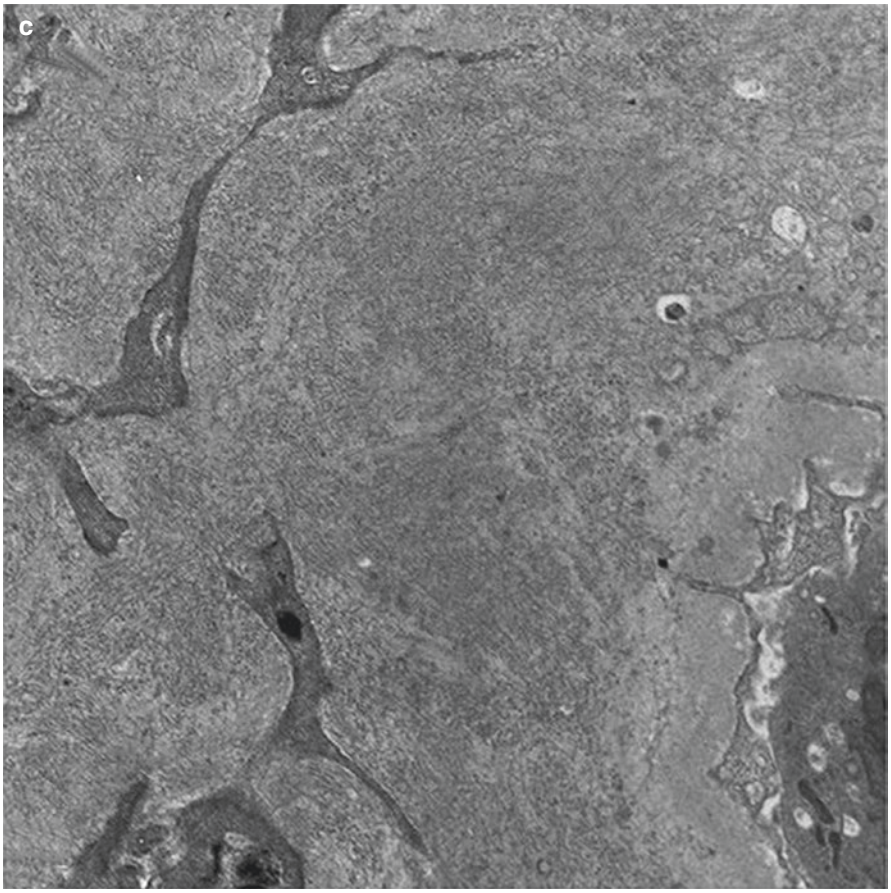

Fig. 6.17 (continued)

Understanding the Pathology in Diabetic Kidney Disease: From the Research Laboratory to the Evaluation of Kidney Samples

In the last 30–35 years, extensive research has been conducted dealing with the pathogenesis of diabetic nephropathy and addressing issues such as progression to ESRD. Emphasis has been placed on understanding the pathogenesis of diabetic nephropathy in an effort to decipher new therapeutic protocols aimed at ameliorating and/or stopping the development and/or progression of diabetic nephropathy.

Diabetic renal lesions develop for at least one decade before they result in detectable renal functional alterations, so there is plenty of time to work on reversing initial changes that may take place heralding the more deleterious structural effects more difficult to control and ameliorate/stop.

While many different pathobiological pathways have been considered to play a role in the genesis of the renal lesions in diabetes mellitus, some have gained more acceptability over the years. In particular, there are three pathways that appear to be the most important in diabetic nephropathy, for all of which hyperglycemia appears to be the main driving force: (1) the myoinositol/polyol pathway, (2) the pathways associated with formation of advanced glycation end products (AGEs) and generation of reactive oxygen species (ROS), and (3) hyperfiltration. The cyclohexanehexol myoinositol (also called polyol) pathway remains at the center of most hypotheses [34, 63].

Chronic hyperglycemia is postulated to be associated with impaired myoinositol metabolism and end-organ damage. DM has been shown to cause increased polyol pathway activity generating decreased tissue myoinositol by depleting tissue stores of myoinositol, paving the way to the genesis of pathological changes. Reduced intracellular myoinositol is thought to result in abnormal phospholipid metabolism and decreased Na^+-K^+-ATPase activity leading to abnormal cellular function. Investigators have substantiated that myoinositol is decreased in the diabetic kidney. Another important event in this pathway is activation of protein kinase C-β (PCK-β). The sequence of events that occur in this pathway has been described in an animal model of STZ-induced diabetic rats (model of T1DM) and db/db mice (model of T2DM—leptin deficiency) [64, 65]. When these animals are treated with inhibitors of PCK-β or inhibitors of the polyol pathway (i.e., aldose reductase), amelioration of the disease was noted. This suggests that therapeutic interventions aiming at this pathway may be attractive as treatments to ameliorate the progression of diabetic nephropathy.

The second pathway is characterized by the interaction of AGEs with their receptor, RAGE, to lead to a complex series of events that culminate in cellular dysfunction, thus generating an inflammatory response and ROS leading to oxidative stress. Both in vitro and in vivo animal studies have shown the relevance of this pathway in diabetic nephropathy. It remains to demonstrate that the same is true in humans.

The ROS generated also results in cellular dysfunction affecting both the glomerular and tubular cells, compounding the negative effects on renal function. ROS is generated predominantly via the NADPH oxidase system or at the level of the mitochondria. NADPH oxidase inhibitors work well in ameliorating the effects of this pathway in animal studies, representing additional possible therapeutic avenues to address diabetic nephropathy and its progression [44].

The third pathway relates to the hyperfiltration that is present in patients with diabetic nephropathy and has proven to have an adverse effect on the course of diabetic nephropathy promoting progression to renal failure. Reduction of glomerular hyperfiltration using angiotensin system inhibitors has had remarkable beneficial effects in the decrease of proteinuria and progression of diabetic nephropathy in animal studies and in human trials of patients with diabetic nephropathy.

The three pathways converge and produce simultaneous damage to glomerular, tubular, interstitial, and endothelial cells acting as the axis of renal structural damage in diabetic nephropathy (Fig. 6.18) [44].

Expansion of the glomerular mesangium at the expense of glomerular capillary filtration surface area represents a crucial and well-established mechanism leading to progressive loss of renal function in diabetic nephropathy.

Pathogenetic events involved in the creation of the characteristic glomerular lesion have been delineated. Though much work remains to be done, the evidence available points toward initial glomerular basement membrane and peripheral capillary wall alterations, namely, thickening and biochemical changes of the glomerular basement membranes followed by mesangial changes leading to the formation of mesangial nodules. The role that TGF-β plays in the generation of mesangial nodules has been well established.

In vitro studies have allowed detailed examination of the mechanisms involved when mesangial cells are cultured in high ambient glucose concentrations with emphasis on cell function [44]. Extension of these studies to in vivo situations has confirmed that most of the in vitro findings reflect reality as it occurs in humans. Studies of diabetic mice indicate that like in humans there is variable susceptibility to developing diabetic nephropathy [62, 64, 65]. In contrast, unlike in humans, each inbred mouse strain represents a genetically homogeneous and easily replenishable resource that is amenable to be used in repeated experimental studies providing an excellent platform to gain insights into the pathogenesis of diabetic nephropathy. Mice provide unparalleled flexibility for studying diabetic nephropathy. There are many mice models modified by strain and genetic mutations that have been used, and these are reviewed in a recent publication, highlighting their value and pitfalls

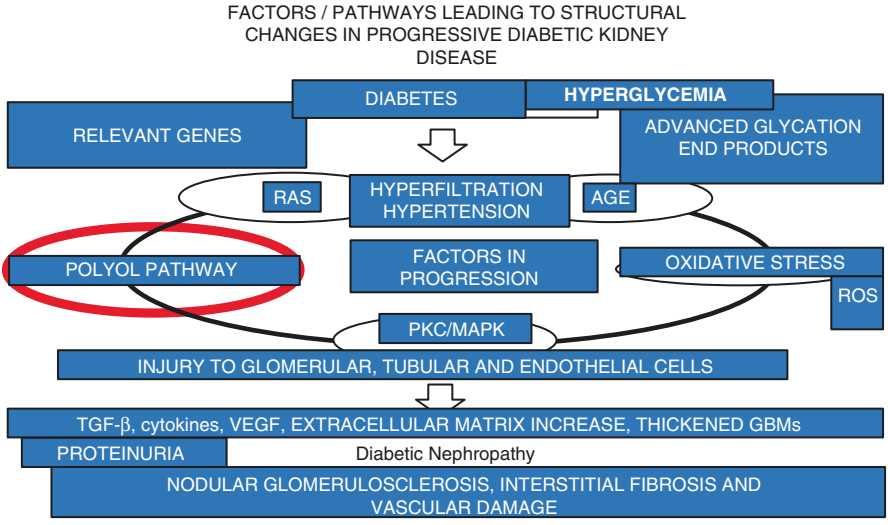

Fig. 6.18 Schematic representation of factors/pathways leading to structural changes in progressive diabetic nephropathy

for various applications [64]. Obviously the most useful ones recapitulate morphological changes in humans, including glomerular basement membrane thickening and mesangial expansion. These are the db/db and Akita mice models. Some of these mice recapitulate early and late morphologic manifestations of diabetic nephropathy (mice with eNOS deficiency, OVE26 FVB mice, and BTBR ob/ob mice). Unfortunately, all animal models of diabetic nephropathy also have important limitations.

The in vitro studies have shown increased mesangial cell proliferation driven by PDFG-beta followed by TGF-β secretion and/or activation leading to mesangial matrix deposition; however, the rats do not progress to renal failure. In contrast, prolonged mild type 2 DM results in morphological changes typical of preclinical diabetic nephropathy in GK (Goto-Kakizaki) rats but does not lead to albuminuria or progressive renal disease. Finally, the association of type 2 diabetes with hyperlipidemia in obese Zucker rats results in early podocyte damage and subsequent progression to sequential glomerulosclerosis suggesting that in at least a subset of patients with diabetic nephropathy, a concomitant podocytopathy occurs [66]. In clinical practice, there are diabetic patients that develop massive proteinuria and show in their biopsies segmental glomerulosclerosis; this subset of patients with diabetic nephropathy may be the ones with the concomitant podocytopathy [34, 62]. It remains to be deciphered whether the podocyte dysfunction is directly related to the diabetic nephropathy or a secondary pathological process.

Experimental studies have shown that the damage to the podocytes results from modification of the podocytes themselves [51]. Podocyte loss but not necessarily injury likely occurs late in the course of diabetic nephropathy and appears to correlate best with progression of the diabetic nephropathy [67]. Morphological alterations have been noted that appear to be of importance in characterizing and understanding this lesion in diabetes. Podocytes detach from the glomerular basement membranes and bulge exposing endocytotic vesicles rich in albumin. The detachment of the podocytes from the glomerular basement membranes appears to be a key initial finding that initiates the cascade of events that follow. This detachment has been suggested to be linked to the disappearance of the α3β1 integrin, a key molecule which is likely bound to the laminin in the glomerular basement membranes and anchors the visceral epithelial cells to the glomerular basement membranes [68]. Collapse of the glomerular capillary walls follows with progressive disappearance of capillary walls and accumulation of hyaline and lipidic material together with synthesis of extracellular matrix components, including some that are not part of the normal glomerular composition. As a result of the above, the glomerular basement membranes and the basement membranes of the Bowman's capsule form attachments, and this interaction further fosters generation and eventual deposition of additional extracellular matrix.

Interestingly, pathophysiological alterations in mesangial cells have been traditionally considered to be the essence of diabetic kidney disease, in terms of initiation, development, and progression of this disorder. Recent evidence implicates the podocyte as a likely player in early disease initiation. Furthermore, insulin resistance appears to contribute to endothelial dysfunction suggesting some role also for

glomerular endothelial cell damage in the pathogenesis of diabetic nephropathy [34]. Insulin resistance likely contributes to endothelial dysfunction [34].

The additional understanding of how podocyte damage can participate in the initiation and/or progression of diabetic nephropathy represents an important contribution to the understanding of how diabetic patients progress into renal failure and why some of these patients do so rapidly after years of stable renal function. Regoli and Bendayan have suggested that a decrease of α3β1 at the podocyte basal membrane facing the glomerular basement membrane may be an important biochemical alteration leading to dysfunction of the capillary walls [68]. This change occurs before morphological alterations are detectable in the glomerular basement membranes and appears to be, therefore, an early (and perhaps key initiating) event preceding overt diabetic nephropathy.

Progression of diabetic nephropathy has been addressed in the research laboratory using cell culture and animal models [69]. For example, exposure of glomerular mesangial cells and proximal tubular cells to hyperglycemic conditions may alter cell proliferation and/or extracellular matrix turnover by means of modulating cytokine production. Mechanisms involved in these processes have been elucidated. Extension of these studies to experimental in vivo situations has confirmed a significant number of these findings but has also shown some unexpected results. Increased glomerular cellular proliferation and mesangial matrix accumulation driven by the combined effects of PDGF-β and TGF-β occur in streptozotocin-induced diabetes, but this is not accompanied by the development of the nephropathy to renal failure. Furthermore, although prolonged mild type 2 diabetes induces morphological changes characteristic of preclinical diabetic nephropathy in GK rats, it does not result in albuminuria or in progressive renal disease [69].

Endothelial cell injury is extremely important in diabetic nephropathy. Injury to the renal vasculature via damage to endothelial cells leads to increased expression of adhesion molecules and chemokines, resulting in macrophage influx into the renal parenchyma, and establishes a microenvironment of constant “low-grade inflammation” [34].

Finally, the association of type 2 diabetes with hyperlipidemia in obese Zucker rats results in early podocyte damage and subsequent progression to glomerulosclerosis, tubulointerstitial damage, and renal insufficiency emphasis after the role of podocyte injury [55, 70]. There is much work left to be done to identify specific mediators involved in the genesis and development of the abovementioned processes, including defining conditions/mechanisms that will determine progression of subclinical morphological changes to overt nephropathy. This area remains as one of the most important to focus on in future novel developments of therapeutic interventions in diabetes.

Another approach that has been taken to further enhance our understanding of events that participate in the progression of diabetic nephropathy is to study genes that can be involved in this progression. High-throughput and genome-wide approaches in animal models have been used to detect relevant genes. Several genes such as Tim44 (translocase of inner mitochondrial membrane 44), RSOR/MIOX (renal-specific oxidoreductase/myoinositol oxygenase), UbA52 (ubiquitin A), Rap1b (Ras-related

GTPase), gremlin, osteopontin, hydroxysteroid dehydrogenase-3β isotype 4, and those in the Wnt signaling pathway have been identified as differentially expressed in kidneys of diabetic rodents. Functional analysis of those genes and translational research efforts to determine the impact of these genes in humans will be of potential value in the prevention and treatment of diabetic nephropathy. Identification of other pertinent biomarkers and therapeutic target genes will soon follow [71].

Papillary necrosis occurs with some frequency in patients with diabetic nephropathy and deserves a few comments. It is more common in females. A common risk for developing papillary necrosis is recurrent urinary tract infections, which tend to occur with some frequency in patients with diabetes mellitus. Clinical presentation is typically pyuria and microscopic hematuria, though there are cases, which present with acute renal failure, if there is bilateral ureteral obstruction due to sloughing of papillae. The presence of papillary necrosis is usually a poor prognostic sign for patients with DM and most times accompanies other manifestations of diabetic nephropathy.

Reversibility of Structural and Functional Damage in Advanced Diabetic Kidney Disease

Reversibility of the structural changes that occur in diabetic nephropathy remains controversial [18, 54, 67, 71]. The mainstay of current therapy for diabetic nephropathy includes control of hyperglycemia and blood pressure, and inhibition of the renin-angiotensin-aldosterone system (RAAS). While these therapies can be effective in slowing progression, they have had no proven effect on reversing structural or functional damage, and their efficacy is indeed limited. The paradigm to be deciphered poses the question whether restoration of a normal metabolic milieu or direct effects of given molecules such as leptin represent the best avenue toward attempting to reverse the changes attributed to the diabetic nephropathy.

To evaluate possible therapeutic interventions that can be aimed at reversing lesions, there is a need to use effective in vitro and in vivo platforms in the research laboratory. No relevant animal models exist in which reversibility can be tested. One of the issues that have become important is the role of podocytes in the advancement and irreversibility of diabetic nephropathy. As diabetic nephropathy advances, podocytes are lost in at least a subset of these patients, mostly those with advanced nephropathy. Podocytes are nonreplicating cells which make reversibility by means of regeneration of visceral epithelial cells not possible. Some investigators defend the opinion that the restoration of functional podocytes abrogates the injury process in diabetic nephropathy and allows reversal of the structural changes during the reparative phase. Therefore, conceptually speaking, while reconstitution of a normal glomerulus after podocyte loss may be a significant challenge, it has been shown that this problem can be overcome, at least experimentally. Some believe that podocytes in diabetic nephropathy can regenerate so that reversal of diabetic nephropathy is attainable.

In a murine model of type 2 diabetic nephropathy, BTBR ob/ob leptin-deficient mice with diabetic nephropathy were administered leptin. The identification of leptin receptors within isolated glomeruli from BTBR mice established the possibility that leptin can exert a direct effect in reversing alterations. In fact, leptin replacement, but not inhibition of the renin-angiotensin-aldosterone system (RAAS), resulted in near complete reversal of structural and functional alterations. Mesangial matrix expansion, mesangiolysis, basement membrane thickening, and podocyte loss were all reversed along with proteinuria and accumulation of ROS. This model closely resembles diabetic nephropathy (much better than other animal models available) which emphasizes the importance of these studies and their relevance to humans [72].

Some studies have shown to a limited but yet important degree that reversal of nephropathy is governed by leptin signaling rather than by restoration of a normal metabolic milieu in the mesangium [54]. The demonstration showed pStat3, a key downstream molecule in the leptin signaling pathway, provides strong evidence that leptin signaling in the kidney contributes, though to an unknown degree, to reversal of nephropathy, although it is recognized that the pStat3 could be the result of other signaling pathways. Studies to address these two possibilities will provide the final answer to this question [54].

Biomarkers for the Early Diagnosis of Diabetic Kidney Disease.

Microalbuminuria: The Gold Standard for Diagnosis of Diabetic Kidney Disease

Biomarkers are defined characteristics that are measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Those that allow to detect or confirm the presence of a disease or condition of interest or identify an individual with a subtype of the disease are defined as *diagnostic biomarkers* [73, 74]. An important criterion for the diagnosis of diabetic nephropathy is the development of sustained albuminuria in a patient with DM of several years of evolution that cannot be explained by a different renal disorder [75]. The urinary albumin excretion rate (UAER) considered normal is <30 mg in a 24-hour urine specimen. When UAER is in the range of 30–300 mg/24 h (or 20–200 μg/min), it is said that the patient has microalbuminuria. This concentration, while above the level of normal albuminuria, is below of the limit of detection of ordinary dipstick tests [76]. Macroalbuminuria is then defined as the urinary excretion of albumin that exceeds 300 mg/24h. It is worth noting that R. Rachmani et al. assessed the validity of the threshold value for microalbuminuria of 30 mg/24 h, by analyzing an 8-year follow-up data of 599 patients with T2DM, normal blood pressure, and baseline UAER ≤30 mg/24 h. They found that renal and cardiovascular risks increased progressively in this group with increasing albumin excretion even within the range considered as normoalbuminuria [77]. They suggested that the

arbitrary threshold value for screening and for preventive strategies should be set at 20 rather than at 30 mg/24 h [77].

On the other hand, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines use different categories to classify and grade albuminuria in CKD patients, taking as reference the value the urinary albumin-creatinine ratio (ACR) [78, 79] (https://kdigo.org/guidelines/diabetes-ckd/). KDIGO classifies albuminuria as A1, or normal to mildly increased (ACR <30 mg/g or <3 mg/mmol); A2, or moderately increased (ACR 30–300 mg/g or 3–30 mg/mmol); and A3, or severely increased (ACR >300 mg/g or >30 mg/mmol). These categories correspond to normo-, micro-, and macroalbuminuria, respectively [79]. Since these terms are still used in many research and clinic literature on CKD, we will use them in this chapter.

Microalbuminuria is currently considered the best available marker for early diagnosis of diabetic nephropathy. Its history as an abnormal event associated to DM dates to the article entitled *The concomitants of raised blood sugar: studies in newly-detected hyperglycaemics: II. Urinary albumin excretion, blood pressure and their relation to blood sugar levels*, published in 1969 by H. Keen, C. Chlouverakis, J. Fuller, and R.J. Jarrett in the journal *Guy's Hospital Reports*. However, it is from several studies published at the first half of the 1980s showing the utility of microalbuminuria as predictor of renal disease in DM patients that it begins to be widely accepted as biomarker of diabetic nephropathy [80–84]. Its subsequent implementation in the clinical evaluation of patients with DM has been pivotal for the development of strategies of prevention and treatment of diabetic nephropathy and cardiovascular disease [85].

A recent study suggests that the within-person variability of the measurements of albuminuria is high. It was found that the within-person coefficients of variation for albuminuria were 33.2% for first-morning urinary albumin concentration (UAC), 50.6% for random spot UAC, 32.5% for first-morning ACR, and 29.7% for random spot ACR [86]. Therefore, while a spot measurement of microalbuminuria may provide relevant information about the magnitude of the renal damage, such practice may be misleading and is less reliable than the serial measurements. Serial measurement allows to determine the rate of change of albuminuria and differentiate acute transitory events from chronic renal disease. A sustained rise in albumin excretion rate is usually expression of a progressive renal disease [79, 87].

The prevalence of microalbuminuria in diabetic patients varies from one population to another, depending on the contribution of different sociocultural, economic, environmental, and genetic factors, as well as the concurrence of comorbidities, some of which, as the hypertensive disease, share risk factors with diabetes. Several studies performed in the 1980s in European patients with T1DM reported prevalence that ranged from 16 to 23% [88–92]. A significant correlation between albumin excretion rate in microalbuminuric patients and mean arterial blood pressure was then observed [88–92]. In another contemporary study, C. Schnack et al. reported significantly higher prevalence of microalbuminuria in Austrian patients with T2DM (59%) and T1DM (43%) [93].

A study conducted in the United Kingdom in the 1990s in patients with T1DM with more than 5 years of disease evolution reported a prevalence of 30.7% and

2.7% of micro- and macroalbuminuria, respectively [94]. H. M. Mather et al. reported similar prevalence of microalbuminuria in England men with T2DM (33%) but significantly lower prevalence (19%) in T2DM female patients [95]. A. N. Dixon et al. found an overall 20% prevalence of microalbuminuria, which falls to 10.1% in patients with normal, untreated blood pressure [96]. Given that the health system in the United Kingdom is funded by the government, which ensures access to medical care for the entire population, the differences in the prevalence of microalbuminuria reported in diabetics from that country probably reflect ethnocultural, genetic, and gender differences of the studied populations.

Significantly higher prevalence of microalbuminuria has been reported in other European populations. O. Vasovic et al. found microalbuminuria in 42% and 47% of a relatively small cohort of Servian patients with T1DM and T2DM, respectively. Such finding was likely related with the concurrence of high blood pressure in the studied cohorts, since 34% of T1DM patients and 78% of T2DM patients were hypertensive [97]. Others have also studied the contribution of high blood pressure to the risk of microalbuminuria in diabetic Europeans. N. Pasko et al. found 40.8% and 2.8% prevalence of micro- and macroalbuminuria, respectively, in Albanians with T2DM patients aged 40–70 years. They found that systolic and diastolic blood pressure, HbA1c, and fasting plasma glucose were significantly higher in microalbuminuric than in normoalbuminuric subjects [98]. High prevalence of microalbuminuria was also reported by P. Marques da Silva et al. in a large cohort of 9198 Portuguese patients with high blood pressure and/or T2DM. Overall, the prevalence of microalbuminuria was 58% in patients with T2DM and high blood pressure (3100 individuals), 51% in patients with T2DM but not high blood pressure (423 individuals), 43% in patients with high blood pressure but not DM (3769 individuals), and 12% in normotensive, nondiabetic patients (controls). They found that the presence of T2DM or high blood pressure, HbA1c, male gender, age, systolic blood pressure, and total cholesterol were predictors for microalbuminuria [99].

Prevalence of microalbuminuria has also been assessed in European adolescents and young adults with T1- or T2DM. Bruno et al. studied 211 young Italians with T1DM with short duration of disease (3–9 years) and found a prevalence of microalbuminuria of 7% in subjects with disease duration of 3–9 years and 4% in subjects with disease duration of 3–5 years. Interestingly, they observed that in almost 50% of the cohort, HbA1c levels were over 9%, whereas only in 10.9% HbA1c levels were lower than 6.6%. These findings highlight the relevance of the time of disease evolution, in addition to factors as the glycemic control obtained, in the development of microalbuminuria [100]. C. J. Schultz et al. also found correlation between the level of HbA1c and the probability to develop microalbuminuria in a cohort of 514 children who developed T1DM before the age of 16 years [101]. On the other hand, M. L. Marcovecchio et al. studied the prevalence of abnormal lipid profiles and their relationship with the development of microalbuminuria in 895 European adolescents with T1DM. They found that total cholesterol and non-HDL cholesterol were independently related to longitudinal changes in albuminuria, measured as ACR. The increase of blood total cholesterol and non-HDL cholesterol after the age of 15–16 years was particularly marked in patients with persistent

microalbuminuria when compared with individuals with transient microalbuminuria and normoalbuminuria. They suggested that disorders of cholesterol metabolism may play a role in the pathogenesis of diabetic nephropathy [102].

European adolescent and young adults with T2DM appear to be more at risk of developing complications associated to diabetes than those with T1DM. In a very recent study, A. E. Ek et al. compared the incidence of microalbuminuria and retinopathy in 1413 early-onset T2DM and 3748 T1DM patients, 10–25 years of age, registered in the Swedish Pediatric Quality Diabetes Register and the Swedish National Diabetes Register [103]. They found that 7.7% of the adolescents with T2DM had microalbuminuria and 24.6% had signs of retinopathy 5 years after diagnosis, whereas in the adolescent with T1DM of similar time of disease evolution, the prevalence of microalbuminuria and retinopathy was significantly lower, 3.8% and 19.2%, respectively. Moreover, in young adults with T2DM with 10 years of disease progression, they found prevalence of 15.2% and 39.7% for microalbuminuria and retinopathy, respectively, whereas for their counterparts with T1DM, the respective figures were 4.8% and 43.8%. The author concluded that, overall, adolescents and young adults with T2DM had significantly higher risk of microalbuminuria and retinopathy than those with T1DM [103]. J. A. Damm et al. reported a prevalence of diabetic nephropathy of 2.3% and 2.5% in pregnant women with T2DM and T1DM, respectively. In the same population, the prevalence of microalbuminuria was 4.5% and 3.4% for T2DM and T1DM patients, respectively. These findings suggest that, unlike what was observed in adolescents and young adults, there does not appear to be a great difference in the prevalence of diabetic nephropathy and microalbuminuria in pregnant women with T2- or T1DM [104].

Several studies have also evaluated the prevalence of microalbuminuria in diabetic patients in the United States (USA), and, as in Europe, differences attributable to sociocultural, economic, ethnic, and environmental factors have been observed. In an early study, L. Ramirez et al. found a low prevalence of microalbuminuria (12.2%) in a cohort of 156 normotensive subjects with T1DM. Compared to the normoalbuminuric subjects, the microalbuminuric patients had a significantly longer duration of diabetes, higher diastolic blood pressure, and serum cholesterol concentration [105]. In another study, R. Klein et al. reported a prevalence of microalbuminuria of 29.2% in 435 T1DM and 22.0% in 363 T2DM patients aged ≥ 30 years. In that population, microalbuminuria was significantly associated with the male sex, older age, higher systolic blood pressure, higher HbA1c, use of insulin, higher recent alcohol consumption, and a history of cardiovascular disease [106].

Significant ethnic differences in prevalence of microalbuminuria have also been observed in US population-based studies. B. A. M. G. Goldschmid et al. assessed the prevalence of microalbuminuria in 466 consecutive African American patients with T2DM presenting for the first time to the Grady Memorial Hospital Diabetes Unit in Atlanta, GA. Although the median from disease diagnosis was only 1 year, the estimated prevalence of microalbuminuria and nephropathy was 24% and 12%, respectively. Of note is that, among 219 patients with < 1 year from disease diagnosis, the prevalence remained high: 25% and 5% for microalbuminuria and nephropathy, respectively. Interestingly, the authors did not find association between

microalbuminuria or diabetic nephropathy and metabolic control, suggesting that other risk factors, as high blood pressure, or particularities of the genetic background of this population, could be more important [107].

Microalbuminuria has also been found to be highly prevalent in African American women with history of gestational DM (GDM). R. C. Go et al. reported an overall prevalence of microalbuminuria of 20% in a cohort of 289 African American women with a history of GDM, figure that increased to 36% in those with diabetes. The presence of microalbuminuria was not associated with insulin resistance but was significantly associated with HbA1c levels and hypertension. Based on such associations, the author suggested that hypertension and glucose intolerance may influence microalbuminuria through different mechanisms [108].

More recently, Young et al. assessed the prevalence of micro- and macroalbuminuria in an US ethnically diverse cohort of 2969 primary care diabetic patients with comparable access to health care. The unadjusted prevalence of micro- and macroalbuminuria was 30.9%, similar among the various racial/ethnic groups. However, Asians had twofold and threefold greater micro- and macroalbuminuria, respectively, than white Americans (WA) when patients without high blood pressure were compared. Hispanic and AA had a higher probability to have micro- and macroalbuminuria than WA, when patients with high blood pressure were compared [109]. High prevalence of microalbuminuria (27.3%) was also reported by S. E. Farah et al. in a cohort of 40 pediatric patients, predominantly AA and Caribbean Hispanic adolescents, with early-onset T2DM [110]. Overall, these findings suggest differences between individuals of distinct ethnic origin with respect to genetic, sociocultural, and environmental factors contribute to the risk of developing microalbuminuria. This agrees with a study performed by H. M. Mather et al., who found higher prevalence of microalbuminuria in a cohort of South Asian patients with T2DM that were living in England, compared to their white European counterparts [95]. The South Asians also had a worse glycemic control, and higher prevalence of hypertension, retinopathy, and heart disease. While risk factors for microalbuminuria in both ethnic groups were similar (glycemic control, diabetes duration, blood pressure, triglyceride, and retinopathy), none accounted for the higher prevalence of microalbuminuria observed in South Asians [95]. In a later study, A. N. Dixon et al. also found significantly higher prevalence of microalbuminuria in South Asian patients with T2DM compared to white European patients. Among patients with normal, untreated blood pressure, the proportion who had microalbuminuria was three times higher among South Asian patients than in the white European group [96].

Studies carried out in the 1990s and the first decade of the 2000s evaluated the prevalence of microalbuminuria in diabetics from South Asian countries (India and Pakistan). The prevalence of microalbuminuria ranged between 24% and 40% for patients with T2DM [111–115]. Of note, it was found that in patients with duration of diabetes less than 1 year, the prevalence of microalbuminuria was 24.7% and that of macroproteinuria was 6.2% [115]. A very recent study carried out in 1048 DM adult patients aged 18–65 years from a rural population of Bangladesh reported a prevalence of microalbuminuria of 29.72 [116].

Overall, the risk factors associated with microalbuminuria and macroproteinuria in population from South Asia are poor glycemic control, as measured as HbA1c level, retinopathy, longer duration of diabetes (more than 5 years), and higher systolic blood pressure.

The evolution of microalbuminuria in diabetic patients can be variable, as it can regress toward normal values [117, 118], progress toward macroalbuminuria, or remain unchanged for long time. Their relationship with the severity of histopathological changes in the nephron, though significant, is weak. Factors found to be associated with remission/regression of microalbuminuria are sex (female), higher HDL cholesterol, lower HbA1c, and lower systolic blood pressure [119]. The ease of obtaining the sample for analysis and the relative low cost and complexity of the measurement procedure have promoted the use of microalbuminuria as a screening method for the diagnosis of diabetic nephropathy [120, 121]. However, microalbuminuria is not specific of diabetes nephropathy [122, 123]. Some studies suggest that it is not a sufficiently accurate predictor of diabetic nephropathy risk [124–129]. Therefore, recent years has seen a great interest in identifying new biomarkers with better characteristics of sensitivity and predictive power for the detection of early stages of diabetic nephropathy and progressive kidney function decline in diabetic patients. Biomarkers that can be measured in urine represent an attractive option due to the easy accessibility and low invasiveness involved in obtaining the sample, which makes them suitable for population screening [130]. Moreover, due to that some of them are natural constituents of the nephron, their detection in a normal amount in urine provides valuable information about kidney injury at specific sites along the nephron (e.g., glomerular/podocyte damage and tubular damage) as well as regarding the potential mechanism of damage (e.g., oxidative stress, inflammation, and activation of the intrarenal renin-angiotensin system) [130].

Other Urinary Biomarkers of Diabetic Kidney Disease

Nephrin is a type 1 transmembrane glycoprotein primarily expressed in the renal tissue. In human, it is encoded by *NPHS1* gene. Nephrin is located at the cell surface of podocytes, specifically in the area between two podocytes called the slit diaphragm, a structure that functions as a filtration barrier, preventing larger molecules like proteins from passing through. Nephrin is essential for the formation of the slit diaphragm and its anchoring to the podocytes, as well as for its function as a filtration barrier for the blood components [131]. Early studies found that the expression of nephrin in kidney biopsies of patients with diabetic nephropathy was downregulated as compared with controls [132]. Moreover, urinary nephrin levels (nephrinuria) were found to be present in 100% of diabetic patients with micro- and macroalbuminuria, as well as 54% of patients with normoalbuminuria. Nephrinuria correlated positively with albuminuria, and systolic blood pressure, but correlated negatively with serum albumin and eGFR [132]. I. Kostovska et al. reported similar findings in a recent study aimed to evaluate nephrinuria as an early marker of

diabetic nephropathy in T2DM patients [133]. They found that nephrin has a total predicted probability of 96% in patients with diabetic nephropathy.

Podocalyxin is an extensively O-glycosylated and sialylated type I transmembrane protein that is normally expressed in kidney podocytes, but also in hematopoietic progenitor cells, vascular endothelia, and a subset of neurons [134]. Podocalyxin is the main component of the sialic acid-rich glycocalyx, termed epithelial polyanion, located in the apical surface of podocytes, which faces the urinary space [134]. M. Hara et al. found that the levels of urinary podocalyxin (u-PDX) were elevated in DM patients but also in others with various glomerular diseases [135]. In patients with diabetes, u-PDX level was abnormally high in 53.8% patients at the normoalbuminuric stage, 64.7% at the microalbuminuric stage, and 66.7% at the macroalbuminuric stage. They observed a positive correlation between u-PDX levels and HbA1c, urinary β_2-microglobulin, α_1-microglobulin, and urinary N-acetyl-beta-D-glycosaminidase. On the other hand, u-PDX levels were not correlated with blood pressure, lipid level, serum creatinine, eGFR, or proteinuria [135]. More recently, I. Kostovska et al. evaluated the sensitivity and specificity of u-PDX as a biomarker for early detection of diabetic nephropathy. They found that at cutoff level of 43.8 ng/ml, u-PDX showed 73.3% sensitivity and 93.3% specificity to detect diabetic nephropathy in early stage [136]. R. Wang et al. investigated the relationship between the level of podocalyxin expression in renal biopsies and its excretion in urine with the renal function in patients with diabetic nephropathy [137]. It was found that patients with diabetic nephropathy had a significantly lower renal expression of podocalyxin and higher u-PDX/creatinine ratio. Among the group of patients with diabetic nephropathy, those that showed lower expression of podocalyxin in renal biopsies had longer diabetes duration; lower plasma albumin and eGFR; higher HbA1c, 24 h urinary protein, serum creatinine, and urinary podocalyxin/creatinine ratio; and more severe glomerular, tubulointerstitial, and renal interstitial inflammation than those with higher expression. Reduced podocalyxin expression in renal biopsy and increased level of u-PDX were associated with poor renal outcome [137].

Proteomic techniques are noted for their high sensitivity and unmatched ability to resolve complex mixtures of biomolecules in body fluids. These attributes make proteomics an ideal approach to identify and validate biomarkers in complex diseases such as diabetic nephropathy. The application of proteomics in biomarker research has the advantage that it not only provides information on variations of individual components of a specific biological sample but also allows the identification of disease-specific patterns that result from the combination of multiple biomarkers [138]. Relying on biomarker patterns more than individual biomarkers has the additional advantage of increasing the robustness of the diagnostic tool, since a panel of biomarkers will better tolerate changes in individual components without significantly compromising diagnostic accuracy. Taking advantage of such capability, D. M. Good et al. used capillary electrophoresis coupled to mass spectrometry to characterize the urinary peptidome of 3600 individuals, including patients with CKD of different etiology. They identified a set of 273 CKD-specific peptide biomarkers, termed urinary peptide-based classifier CKD273, that diagnose CKD with

a sensitivity of 85.5% and a specificity of 100% [138]. The performance of CKD273 classifier in the detection of diabetic nephropathy in patients with T2DM was validated in a multicenter prospective study performed in the context of the "Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria trial" (PRIORITY) [139]. The CKD273 classifier performance was highly consistent across the different centers and showed to be independent of patient gender and age in the range tested (16–89 years). It was also showed that peptide fragments most consistently found in the urine samples were those originated from blood-derived and extracellular matrix proteins [139]. Later studies in relatively large cohorts of normoalbuminuric T2DM patients have shown that the CKD273 classifier is an independent predictor of microalbuminuria in this population [140, 141]. In PRIORITY trial, those T2DM patients with normoalbuminuria but with a high-risk CKD273 classifier score had increased risk of progression to microalbuminuria in over a median of 2.5 years, independent of clinical characteristics [142]. The extensive application of both qualitative and quantitative proteomic methods in studies aimed at identifying new urinary biomarkers for diabetic nephropathy prediction promises that new candidates will soon appear in clinical trials [143–148]. Time will tell if urinary proteomics will become the method of choice for the early diagnosis of diabetic nephropathy, and/or the identification of individuals at high risk of suffering from it.

Other Biomarkers of Diabetic Kidney Disease Under Study

Since inflammation is part of the mechanism that causes diabetic nephropathy, there has been interest in evaluating the potential use of inflammation-associated molecules as diagnostic/prognostic markers of renal damage in DM patients. Minyoung Lee et al. investigated the association between the serum concentration of the extracellular portion of cluster of differentiation 93 (sCD93) and clinical parameters linked to diabetic nephropathy. sCD93 is a glycoprotein expressed in activated endothelial cells that is secreted soluble under inflammatory conditions. They found that the serum sCD93 was an independent determinant of both UACR and the eGFR. They also found that the risk of prevalent diabetic nephropathy was higher in the group of patients with higher serum sCD93 [149].

Karyne Pelletier et al. studied the relationship between the urine levels of sC5b-9 membrane attack complex (MAC) and proteinuria and the rate of renal function decline in T2DM patients. They found that the relationship between proteinuria and the rate of renal function decline was more pronounced in patients with higher levels of urinary MAC than in those with low urinary MAC. They also found that patients with diabetic nephropathy had levels of urinary sC5b-9 comparable to autoimmune glomerulonephritis, when stratified by the level of proteinuria [150].

Fatima Abid Khan et al. determined the serum concentration of kidney injury molecule-1 (KIM-1), a peptide released into circulation in conditions that cause

tubular injury, in diabetic patients with and without kidney disease. They found higher KIM-1 serum levels in diabetic patients with previous kidney disease, as well as the increase of KIM-1 level in those patients in who the disease evolution resulted in the appearance of microalbuminuria, indicative of renal damage [151]. The clinical value of urinary KIM-1 as a biomarker of diabetic nephropathy in T2DM patients has been recently evaluated. It was found that KIM-1-to-creatinine ratio increased significantly with the increase in kidney disease severity and varied according to different albuminuria statuses and estimated glomerular filtration rates [152].

Chitinase-3-like protein 1 (CHI3L1), also known as TYKL-40, is a 40 kDa heparin and chitin-binding glycoprotein that is secreted by a variety of cells such as neutrophils and activated macrophages in different tissues with inflammation. It is elevated in serum/plasma of patients with a variety of inflammatory disorders, being considered a biomarker of inflammation [153]. It has been shown that it is elevated in plasma of T2DM patients and its level correlates with insulin resistance [154]. Since chronic inflammation is believed to play a key role in the early stages of diabetic nephropathy, there has been interest in evaluating the clinical value of YKL-40 as a disease biomarker. In a study that involved a cohort of 75 T2DM patients, it was found that the plasma levels of YKL-40, but not the urine concentration, were significantly higher in the normoalbuminuric patients compared to the healthy controls. Plasma YKL-40 was significantly correlated with albuminuria [155]. More recently, D. Umapathy et al. compared the plasma level of YKL-40 in healthy individuals with that of normo- and microalbuminuric patients with T2DM and found that the median plasma levels of YKL-40 showed a marked stepwise increase from normo- to macroalbuminuric patients and positively correlated with eGFR. Receiver operating curve (ROC) analysis indicated that YKL-40 is a better biomarker for early diagnosis of incipient diabetic nephropathy than other acute phase markers, as C-reactive protein, IL-6, and TNF-α [156]. In a recent meta-analysis that included six different studies, G. V. Kapoula et al. estimated an overall sensitivity and specificity of YKL-40 for the diagnosis of early diabetic nephropathy in T2DM of 0.83 and 0.85, respectively. The DOR was 28 and AUC was 0.91, which suggest that YKL-40 is an accurate diagnostic biomarker for diabetic nephropathy [157]. The same meta-analysis-based study evaluated the diagnostic performance of urinary KIM-1 (uKIM-1) for early diabetic nephropathy in T2DM. It was reported an overall sensitivity and specificity of 0.68 and 0.83, respectively, with a DOR of 11. The AUC of uKIM-1 was 0.87, suggesting a moderate diagnostic accuracy for the diagnosis of early diabetic nephropathy [157].

Another protein that has been recently evaluated as marker of diabetic nephropathy is galectin-3, a ~30 kDa protein encoded by the LGALS3 gene that is member of lectin family. It was found that serum levels of galectin-3 are significantly higher in patients with macroalbuminuria than in those with microalbuminuria and normoalbuminuria. Furthermore, galectin-3 showed to be a significant predictor for progression to microalbuminuria, macroalbuminuria, dialysis, and death among patients with T2DM [158].

Another protein whose association with diabetic nephropathy has been also suggested is the adipocytokine zinc alpha2 glycoprotein (ZAG). ZAG is a 278 amino

acids polypeptide encoded in human by the AZGP1 gene. It stimulates lipolysis in adipocytes and causes the extensive fat losses associated with some advanced cancers. It was found that serum and urine levels of ZAG were higher in patients with T2DM compared to healthy individuals. Urine ZAG levels were positively correlated with UACR, and both urine and serum levels of ZAG were negatively correlated with eGFR [159, 160].

The association of urinary soluble Met tyrosine kinase (cMet), the receptor of hepatocyte growth factor, with diabetic nephropathy was studied by Y. C. Kim et al. in a group of 218 patients. They found that the levels of urinary cMet were higher in patients with decreased renal function than in those with relatively preserved renal function. A urinary cMet cutoff of 2.9 ng/mL was associated with a hazard ratio for ESRD of 2.33. Moreover, they found that the addition of urinary cMet to serum creatinine and proteinuria improved the predictive value for ESRD [161].

In human cells, the number of mitochondria varies according to the cell type, developmental stage, and metabolic status but also as consequence of disease. Each mitochondrion can contain two to ten copies of the ~16.5 kbp circular mitochondrial DNA (mtDNA). Variation of the mtDNA copy number (mtDNA-CN) has been observed in several disorders, and it is proposed to be a potential biomarker of mitochondrial dysfunction. Notably, it was reported that a reduction in the renal mtDNA-CN is implicated in the pathogenesis of diabetic nephropathy. G. Al-Kafaji et al. investigated the potential applicability of the measurement of mtDNA-CN in the peripheral blood as biomarker for diabetic nephropathy in T2DM patients. They found that patients with diabetic nephropathy had lower mtDNA-CN than those with T2DM but without signs of diabetic nephropathy, and healthy individuals. They also found that a decreased mtDNA-CN was associated with the severity of diabetic nephropathy, as patients with this disorder and macroalbuminuria had lower mtDNA-CN than those with microalbuminuria or those with T2DM with normoalbuminuria. Multivariate analysis revealed that the mtDNA-CN was significantly and independently associated with the occurrence and progression of diabetic nephropathy, even after adjustment for age, mean blood pressure, HbA1c, and total cholesterol [162].

Differential Diagnosis of Diabetic Kidney Disease

From a structural point of view, the lesions in diabetic nephropathy are not specific. Therefore, there is a differential diagnosis to be considered depending on which findings are present.

Isolated glomerular basement membrane thickening can be a nonspecific alteration in vascular nephrosclerosis. This is accompanied by alterations in the renal vasculature that can support such diagnosis; however, vascular changes are also common in diabetic nephropathy, sometimes preceding detectable characteristic glomerular changes. The combination of the typical glomerular alterations and the accompanying vascular changes, most notably hyalinosis in afferent and efferent

arterioles with the typical immunofluorescence pattern and ultrastructural features, are sufficient to establish a solid diagnosis of diabetic nephropathy, nodular glomerulosclerosis.

The finding of nodular glomerulosclerosis should instigate a focused differential diagnosis. While diabetic nephropathy is by far the most common pathology responsible for the formation of mesangial nodules, these are not specific at all. The one important lesion to differentiate from nodular diabetic glomerulosclerosis is light/heavy chain deposition disease (Figs. 6.19 and 6.20) [62]. In this case detection of monotypical light or heavy chains in the glomerulus, interstitium, and/or vasculature permits an accurate diagnosis.

However, there are situations where the deposition of the monoclonal proteins may be subtle or early and fluorescence and ultrastructural manifestations may be quite subtle. It is also a challenge to diagnose superimposed light or heavy chain deposition disease in a patient with diabetic nephropathy as the pathological glomerular findings overlap significantly and the glomerular diabetic milieu makes it difficult to detect the abnormal proteins in the glomerulus. It is often easier to look for the monoclonal protein in the tubulointerstitial compartment generally along tubular basement membranes and confirm its presence by immunofluorescence and/or electron microscopy.

There is a subset of patients with so-called idiopathic nodular glomerulosclerosis. This entity was first described by Alpers and Biava in 1989 [56]. Herzenberg et al. coined the term idiopathic nodular glomerulosclerosis to refer to this condition [163]. These patients exhibit in their renal tissue findings identical to those observed in diabetic nephropathy by light, immunofluorescence, and ultrastructural examination. This entity has been epidemiologically linked to hypertension and smoking. The incidence of this condition is low; it was found in 0.45% of 5073 renal biopsies

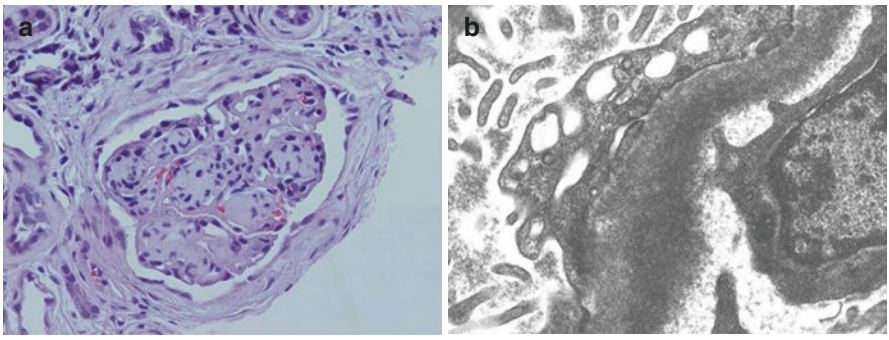

Fig. 6.19 (**a**) H&E, X500; (**b**) transmission electron microscopy, uranyl acetate and lead citrate, X18500. Nodular glomerulosclerosis. Light chain deposition disease. In (**a**) note pattern of nodular glomerulosclerosis similar to what is seen in diabetic nephropathy. Punctate electron-dense material (light chains) in subendothelial zones making possible a diagnosis of light chain deposition disease

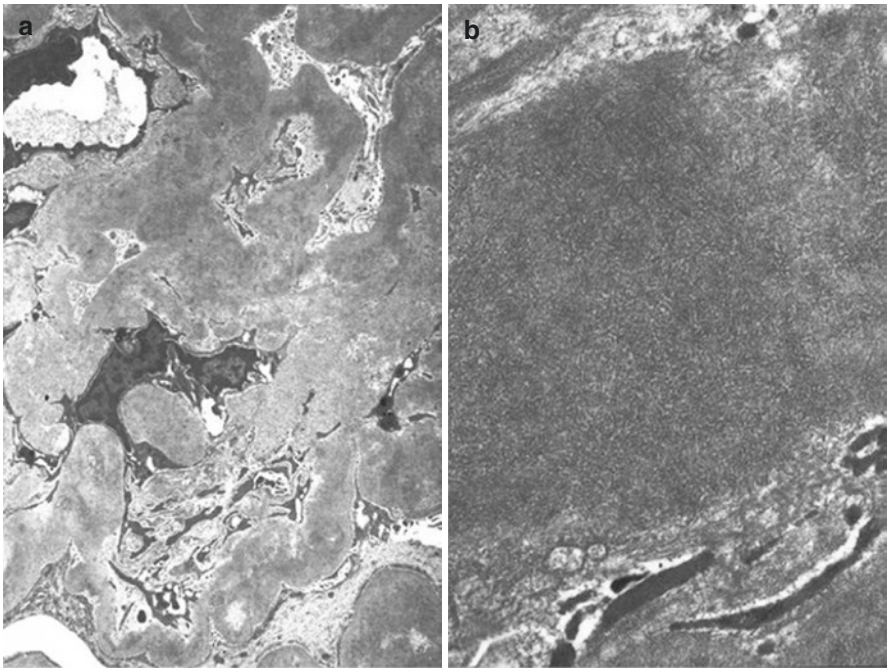

Fig. 6.20 (**a**, **b**) Transmission electron microscopy, uranyl acetate and lead citrate, AX8500, BX15000. Nodular glomerulosclerosis. Light chain deposition disease. Note mesangial nodule with increased matrix (**a**) and deposition of punctate electron-dense material in mesangium best shown in (**b**)

examined at Columbia University in a 5-year period [164]. The authors of all idiopathic glomerulosclerosis publications carefully excluded cases with clinical or preclinical diabetes from their series. Idiopathic nodular glomerulosclerosis involves interplay of hypertension, smoking, increased glomerular extracellular matrix production, and angiogenesis [164]. Neovascularization in the affected glomeruli represents a rather constant finding in these cases. Secretion and activation of TGF-β is responsible in the same manner as it is in diabetic nephropathy, for the increased mesangial matrix and eventual mesangial nodularity.

Other entities in the differential diagnosis, though usually creating less of a dilemma in differentiation from diabetic nephropathy, include chronic thrombotic microangiopathy, membranoproliferative glomerulonephritis with “lobular” glomerular appearance, amyloidosis (Fig. 6.21), and fibrillary and immunotactoid glomerulopathies which in some cases may mimic nodular glomerulosclerosis. The combination of light, special stains, immunofluorescence, and electron microscopy suffices to make the correct diagnosis in the great majority of the cases [164].

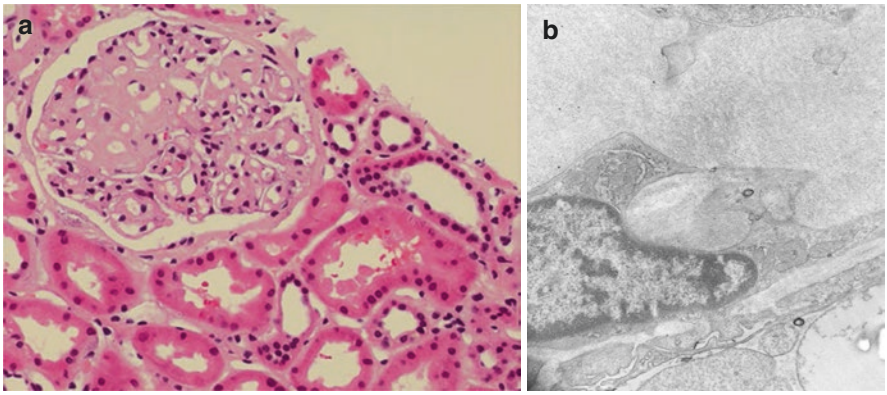

Fig. 6.21 (**a**) H&E; (**b**) transmission electron microscopy, uranyl acetate and lead citrate, AX350; BX13500. AL amyloidosis superimposed on diabetic nephropathy. Note amorphous, eosinophilic material in expanded mesangial area in (**a**). In (**b**) note randomly disposed, non-branching fibrils indicative of amyloid

Superimposed Pathology (Nondiabetic Lesions) That Can Alter Structural Alterations in Diabetic Nephropathy Cases

Diabetic patients with renal disease attributable to their disease are usually not biopsied unless the clinical course is not the usual one. There are a number of clinical situations that lead to a renal biopsy. Among these are progression to renal failure faster than expected, especially if other findings are detected such as the presence of circulating monoclonal proteins, positive serologies for collagen vascular disease, and ANCA (anti-neutrophilic cytoplasmic antibodies) in the serum, or nephrotic range proteinuria. One of the complicating factors in the understanding of structural changes that are part of diabetic nephropathy is that other conditions can coexist with diabetic nephropathy changing the characteristic structural alterations that are present. Virtually any immune complex-mediated process can be seen in a diabetic glomerulus. A renal biopsy is indicated if there is a clinical suspicion that this is the case. Immunofluorescence and electron microscopy will highlight the particular finding associated with these superimposed processes. The most common immune complex-mediated lesion found in diabetic patients superimposed on diabetic nephropathy is membranous nephropathy [33].

There are also tubulointerstitial conditions such as acute tubular necrosis (Fig. 6.22) and acute tubulointerstitial nephritis (Fig. 6.23) that may accelerate the pace of renal failure in patients with diabetic kidney disease. A renal biopsy will make the diagnosis.

The same is true of superimposed vascular diseases that may be uncovered in renal biopsies. Some of these include thrombotic microangiopathy and vasculitis.

The presence of monoclonal proteins in the renal biopsy detected by immunofluorescence, proliferative glomerular changes, glomerular necrosis/crescents, and

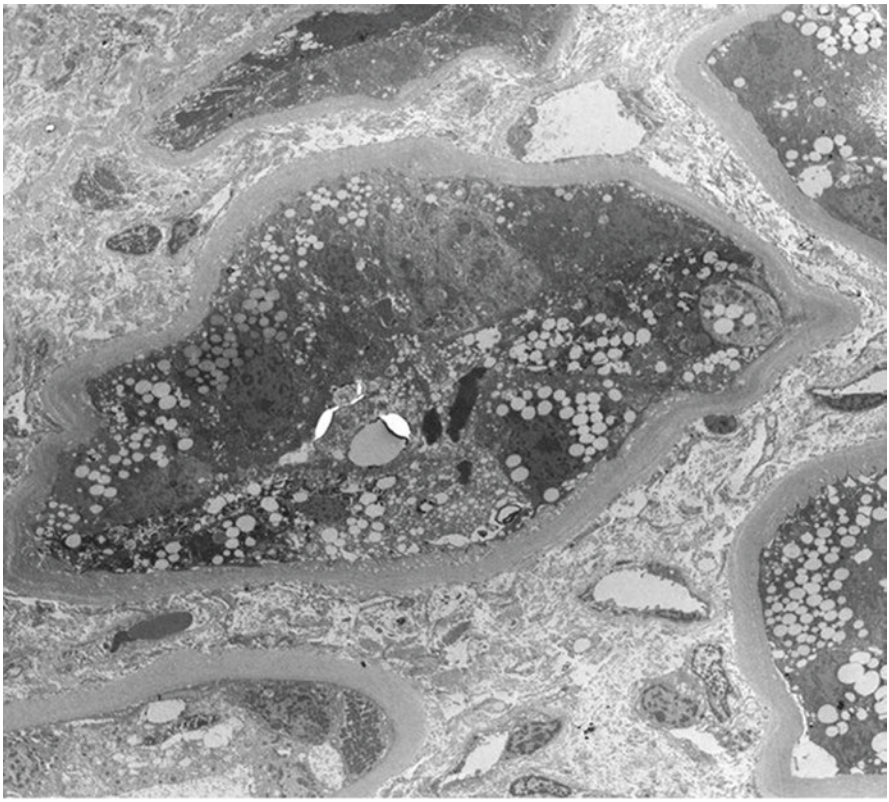

Fig. 6.22 X7500. Transmission electron microscopy, uranyl acetate and lead citrate. Acute tubular necrosis superimposed on diabetic nephropathy. Tubular injury in a background of interstitial edema and no inflammatory activity

immune complexes detectable by immunofluorescence/electron microscopy indicate a superimposed process in a diabetic patient with evidence of nephropathy.

A recent publication highlights nondiabetic conditions that can be seen in patients with diabetic nephropathy with focal segmental glomerulosclerosis being the most common followed by hypertensive nephrosclerosis and acute tubular necrosis [59].

Finding of concomitant diseases alerts the clinician to treat those with the hope to improve renal function. Frequently, the clinical response is slow and sometimes quite sluggish, as the damage in the renal parenchyma caused by the diabetic changes makes recuperation from these superimposed conditions much more difficult.

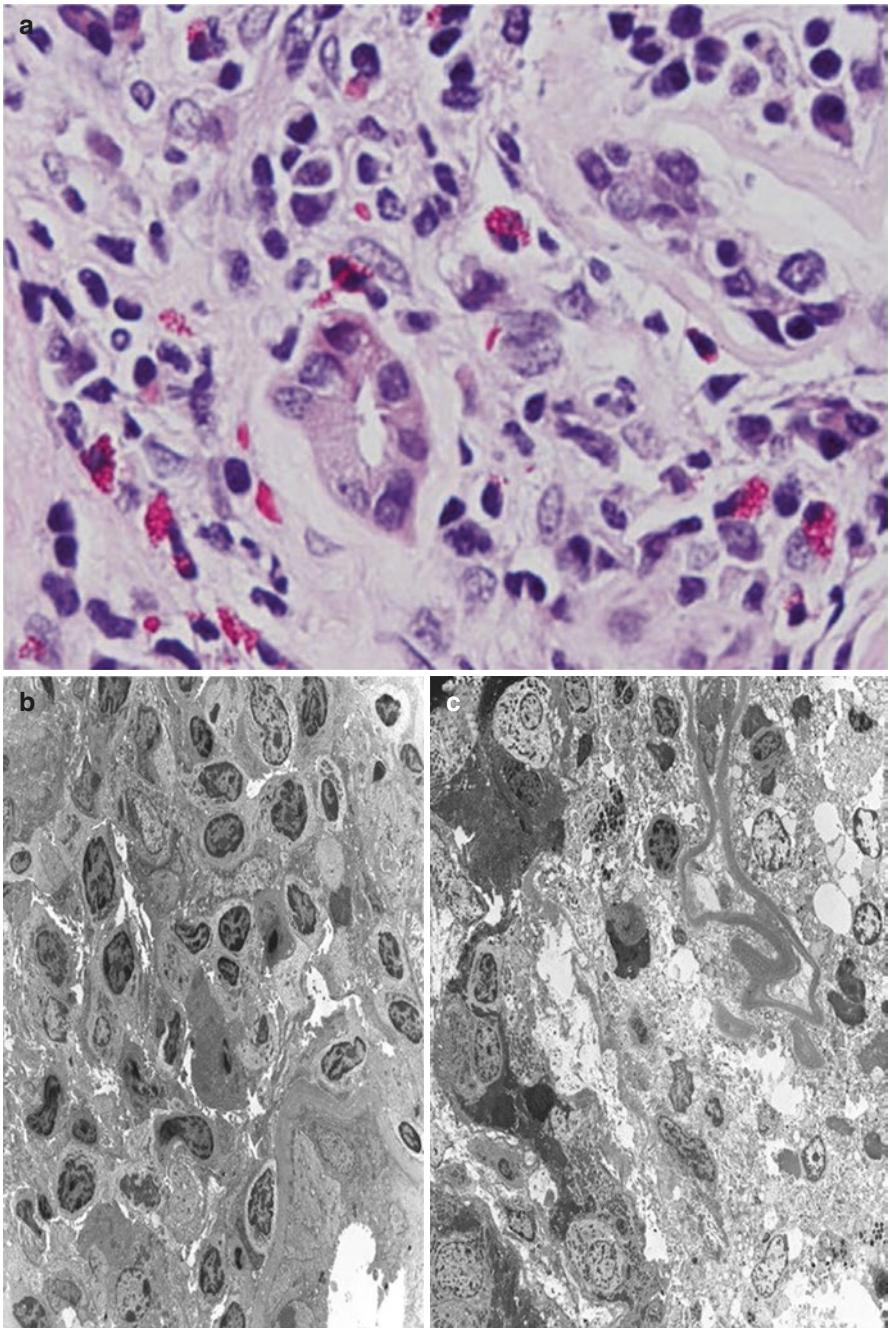

Fig. 6.23 (**a**) H&E stain; (**b**, **c**) transmission electron microscopy, uranyl acetate and lead citrate. AX500, BX7500, CX8500. In (**a**) note interstitial inflammatory process with eosinophils associated with focal tubulitis and tubular damage. (**b**, **c**) Illustrate corresponding ultrastructural findings with a dense interstitial inflammatory infiltrate associated with focal tubular damage and tubulitis

Conclusions

Diabetic kidney disease represents a well-characterized entity with structural abnormalities in the renal parenchyma that can generally be recognized with certainty in specimens submitted for pathological assessment.

The ideal biomarker for diabetic kidney disease does not exist. Despite the large number of biomarkers that have been discovered, with the probable sole exception of urinary proteomics, none has been proven to be superior to albuminuria [165].

There are a number of experimental models that have provided crucial information regarding how lesions in this condition develop and progress. The elucidation of mechanistic phenomena that lead to the morphological/structural changes provides a solid platform to device new therapeutic interventions to ameliorate or reduce the speed of progression to renal failure or to stop its progression altogether. The main problem is that there are many intertwined factors that are involved and teasing these becomes rather complicated. It is likely that a multipronged approach will remain necessary in the treatment of these patients in order to obtain positive results. Controlling blood sugar, blood pressure, and proteinuria are all beneficial and very much indicated for the management of these patients with diabetic nephropathy. These therapeutic interventions may be even considered milestones in the treatment of diabetic nephropathy. However, these maneuvers have not been proven to be enough to stop completely progression of the renal damage and eventual ESRD. The challenge for the future rests in a better understanding of the complex interactions between hyperglycemia and metabolic, hemodynamic, and intracellular factors together with the actions of growth factors and cytokines involved in the pathogenesis of diabetic nephropathy to design new therapeutic interventions with a broader range of action aimed directly at molecular mechanisms that play a role in progression to ESRD. New approaches that have been proposed include those targeting oxygen biology, such as hypoxia, oxidative stress, and dyserythropoiesis, all of which have been implicated in diabetic nephropathy [166].

More recently used approaches such as transcriptome and proteome profiling and molecular genetics using cell lines, animal models, and human samples have increased our understanding of the mechanisms important in the progression of diabetic nephropathy. As a result, new biomarkers have been discovered which could lead to therapeutic maneuvers that can contribute to the amelioration of the diabetic nephropathy and decrease mortality and morbidity in chronic kidney disease patients that progress to ESRD. Target genes can also be modulated using data mining to identify those that are of relevance for the diagnosis and therapy of diabetic nephropathy [71].

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Chapter 7
Diabetes in Children and Adolescents

Mary Alice Rossi and Ihor V. Yosypiv

Introduction

Diabetes mellitus (DM) is a disease of the metabolic homeostasis characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. There are two main types of DM: type 1 and type 2 [1]. Type 1 DM (T1DM) is caused by an absolute insulin deficiency resulting from an autoimmune-mediated loss of the insulin-producing β-cells of the pancreas. Type 2 DM (T2DM) is caused by the relative insulin deficiency where insulin resistance is compensated for initially by an increased insulin secretion followed by insufficient insulin secretion to match the increased requirements imposed by the insulin-resistant state. Despite the different etiologies, there is a great deal of overlap between T1DM and T2DM, making distinguishing between the two disorders difficult.

Epidemiology of DM

Though diabetes is one of the most common chronic diseases of childhood, the incidence varies widely based on geography and ethnicity. Though rates of type 2 diabetes are increasing, type 1 diabetes is still the most common type of diabetes in pediatric patients, accounting for almost 80% of new diagnosis in the United States [2]. Mean annual incidence rates for T1DM in 0–14 years of age group in different countries vary between 0.1 and 57.6 per 100,000. It is lowest in Asia (China, 0.1 per 100.000; Japan, 2.4 per 100.000) and highest in Finland (57.6 per 100,000). In the United States, it is highest in white (27 per 100,000), followed by African American

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(18 per 100,000) and Hispanic (15 per 100,000) children [3]. A rise in the incidence was reported in many countries with most cases presenting in cooler months of the year. T1DM is two to three times more common in the offspring of diabetic men (3.6–8.5%) compared with diabetic women (1.3–3.6%) [3]. When both parents are affected, the risk increases to 30%. The age of clinical presentation of T1DM has a bimodal distribution with one peak at 4–6 years of age and a second at 10–14 years of age [4]. T2DM is becoming increasingly more common and in certain at-risk populations accounts for almost half of new diagnosis [5]. In African-American and Caribbean-Hispanic adolescents in the United States, T2DM accounted for 12% of all new cases of pediatric diabetes in 1990, whereas by 2000, almost 50% of patients diagnosed with diabetes had T2DM [5, 6]. T2DM accounted for 26% of prevalent black case subjects and 10% of non-Hispanic white case subjects 0–19 years of age. Among black female subjects 10–19 years of age, 46% of new cases of diabetes were classified as T2DM [7]. At mean age of 14 years in patients with T2DM, 41.1% were Hispanic, 31.5% black and 27.4% white, 89.4% had a family history of DM and 64.9% were female [8].

Etiology of DM

Etiological classification of DM is presented in Table 7.1 [1]. Major causes of non-monogenic DM include (1) a common polygenic predisposing pattern; (2) epigenetic mechanisms, at least partially linked to nutritional disturbances during gestation

Table 7.1 Etiological classification of DM

Type 1
(a) Immune mediated.
(b) Idiopathic.
Type 2
Genetic defects of β-cell function:
HNF-1α (MODY3)
HNF-4α (MODY1)
HNF-1β (MODY5)
Glucokinase (MODY2)
IPF1 (MODY4)
NeuroD1 (MODY6)
KCNJ11
Mitochondrial DNA mutation
Genetic defects of insulin action:
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes

Table 7.1 (continued)

Diseases of exocrine pancreas:
Pancreatitis
Pancreatic trauma or neoplasia
Cystic fibrosis
Hemochromatosis
Endocrinopathies:
Acromegaly
Cushing's syndrome
Glucagonoma
Pheochromocytoma
Hyperthyroidism
Somatostatinoma
Aldosteronoma
Drug- or chemical-induced:
Glucocorticoids
Thyroid hormone
Diazoxide
β-Adrenergic agonists
Thiazides
Dilantin
A-interferon
Infections:
Congenital rubella
Cytomegalovirus
Uncommon forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes:
Down
Klinefelter
Turner
Wolfram
Friedreich's ataxia
Huntington's chorea
Laurence-Moon-Biedl
Myotonic dystrophy
Porphyria
Prader-Willi

HNF hepatocyte nuclear factor, *MODY* maturity-onset diabetes of the young

influencing fetal programming; and (3) detrimental societal environment promoting the development of obesity by (a) giving free access to excess food rich in calories, sucrose, and lipids, (b) limiting physical activity, and/or (c) exposing to pollutants or infectious agents that could exert a toxic effect on the β-cell. Although the exact

prevalence of monogenic DM in children is unknown, the majority of patients with genetically proven monogenic DM are initially incorrectly diagnosed as T1DM or T2DM [9]. In children, almost all monogenic DM results from mutations in genes that regulate β-cell function with few cases resulting from insulin resistance [10].

Pathophysiology of DM

Most cases of T1DM are due to T-cell-mediated destruction of pancreatic β-cells. T1DM becomes clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed [11]. Both genetic and environmental factors contribute to the development of T1DM. Susceptibility to autoimmune T1DM is determined by multiple genes with HLA genes having the strongest known association [12]. The environmental triggers (chemical or viral), which initiate destruction of pancreatic β-cells, remain largely unknown [13, 14]. In a recent study, 17.8% of children with diabetic ketoacidosis (DKA) had viral and 12.9% had bacterial infection [15]. Once the autoimmune process is triggered, effector mechanisms like antibody-dependent cellular cytotoxicity, delayed hypersensitivity, complement activation, and cytotoxic concentrations of cytokines like interferon-γ and interleukin-1 could result in destruction of β-cells [14].

Development of the Pancreas

The mature pancreas is a glandular organ that carries out two major functions: exocrine and endocrine. The exocrine pancreas, constituting almost 99% of the total mass of the organ, comprises a ramifying tubular tree of ductal branches, which drain the digestive enzymes secreted by acinar cells to the duodenum [16]. The endocrine pancreas comprises the islets of Langerhans, clusters of 100–1000 hormone-secreting cells scattered throughout the exocrine tissue and interconnected via blood vessels. The primary function of islets is to maintain metabolic homeostasis through the production of hormones that regulate blood glucose levels. Five primary endocrine cell types, each responsible for secreting a particular hormone, are found in islets: α-cells (glucagon); β-cells (insulin); δ-cells (somatostatin); ε-cells (ghrelin); and PP (pancreatic polypeptide) cells [16, 17].

Understanding how the pancreas develops is vital to finding new treatments for a range of pancreatic diseases, including DM. In the developing embryo, appropriate patterning of the endoderm destined to become pancreas requires the spatial and temporal coordination of transcription and soluble growth factors secreted by the surrounding tissues. Once pancreatic progenitor cells are specified in the developing epithelial endoderm, epithelial-mesenchymal interactions, as well as a network of transcription factors, delineate three distinct lineages, including endocrine, exocrine, and ductal cells (Fig. 7.1). Both endocrine and exocrine lineages arise from

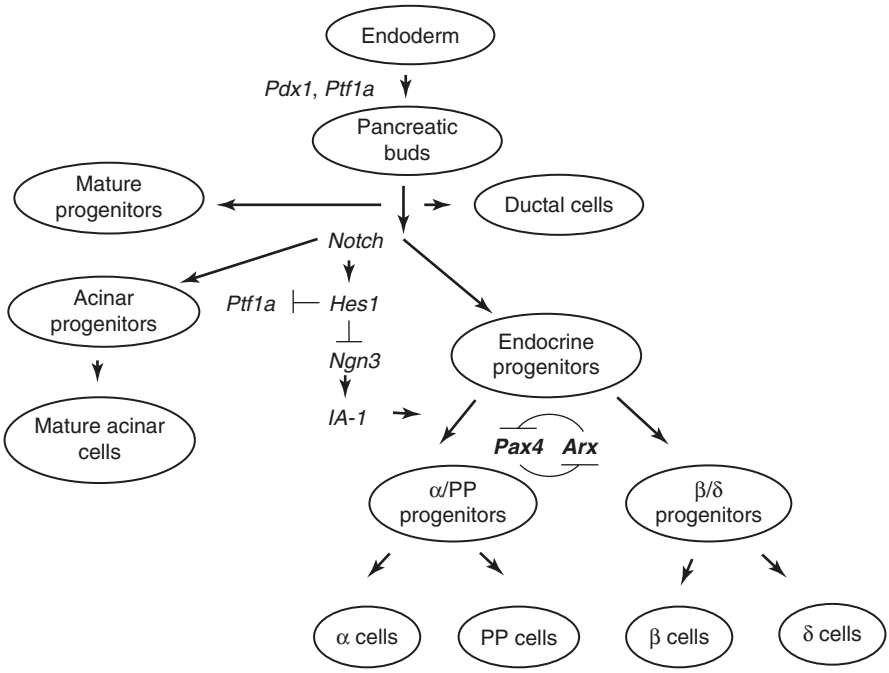

Fig. 7.1 Schematic diagram of key steps of development and differentiation of pancreatic cell types. Please see text for details

embryonic endodermal epithelium (Fig. 7.1), which expresses the proteins pancreatic and duodenal homeobox 1 (Pdx1) and pancreas-specific transcription factor 1 (Ptf1a) [16, 18]. During development of the pancreatic epithelium, endocrine cells emerge in two waves of differentiation as they exit the tubular epithelium, differentiate, migrate, coalesce to form islets, and proliferate. In the mouse, endocrine differentiation begins on embryonic day 9.5 (E9.5) [18]. Following early differentiation, the epithelium undergoes a second wave of expansion and differentiation called the "secondary transition," starting around E12.5 in the mouse and the sixth week of embryonic development in humans [18, 19]. Scattered cells located within the "trunk" domain of the ductal epithelium individually take on an endocrine fate marked by transient expression of neurogenin 3 (Ngn3) and its downstream target gene, zinc-finger transcription factor insulinoma-associated protein 1 (IA-1), delaminate, and form endocrine cell clusters, while acinar cells at branch tips actively proliferate and increase in size as they accumulate digestive enzyme. Lateral interactions between epithelial cells, mediated via Notch/Hes1 signaling, are central to the control of endocrine/exocrine specification [20, 21]. Downstream of the Ngn3-positive pan-endocrine progenitor cell population, α/PP and β/δ lineages are specified by the opposing actions of transcription factors aristaless-related homeobox gene (Arx) and paired box 4 (Pax4), respectively (Fig. 7.1). Secondary wave endocrine cells primarily differentiate into β-cells, along with other endocrine

lineages, delaminate from the epithelium, and coalesce into small islet-like clusters that progressively form larger islet aggregates during postnatal development. In adults, the formation of new β-cells gradually ceases, but can be induced under conditions of increased metabolic demand, such as insulin resistance. Most available evidence suggests that duplication of pre-existing differentiated β-cells, rather than differentiation of stem or progenitor cells, is the predominant mechanism [1]. Unraveling the intrinsic versus extrinsic mechanisms that drive β-cell generation, either during development, homeostasis, or disease, remains a major and immediate challenge of the field [22].

Developmental Programming of DM

A growing body of evidence supports the concept that changes in the intrauterine milieu during "sensitive" periods of embryonic development or in infant diet after birth affect the developing individual, resulting in general health alterations later in life. This phenomenon is referred to as "developmental programming" or "developmental origins of health and disease." The risk of developing T2DM is increased in infants born prematurely at <37 weeks of gestation, in low birth weight (LBW) infants (<2.5 kg) [23, 24], and in high birth weight infants (>4 kg) [25]. In addition, LBW neonates undergoing catch-up growth have impaired glucose tolerance at 7 years of age [26, 27]. Thus, accelerated postnatal growth during early postnatal life is an independent risk factor for adverse metabolic outcomes. In mono- and dizygotic twins discordant for T2DM, LBW twins had higher rates of T2DM compared to their co-twin, indicating that nongenetic intrauterine factors are important in determining the risk of T2DM [28]. Developmental programming due to intrauterine growth retardation (IUGR) resulting from maternal undernutrition or gestational DM increases the risk of insulin resistance and T2DM [29, 30]. In gestational DM, intrauterine exposure to hyperglycemia and hyperinsulinemia may affect development of pancreatic β-cells and adipose tissue resulting in obesity and altered glucose metabolism in later life. Experimental animal studies demonstrate that exposure to intrauterine DM may be associated with impaired renal function and hypertension in an offspring. In this regard, maternal streptozotocin-induced DM in the rat results in glomerular hypertrophy, reduced GFR, and an elevated blood pressure in the offspring without change in total nephron number as early as 1 month after birth [31]. Changes in vascular reactivity could be contributing to the hypertension observed in these offsprings of diabetic mothers [32].

Epigenetic modifications provide one potential mechanism for how environmental influences in early life cause long-term changes in chronic disease susceptibility. The major players in epigenetic mechanisms of gene expression and regulation are DNA or chromatin protein methylation, acetylation, and chromatin remodeling. Posttranslational modifications of histones such as histone acetylation and methylation of cytosine bases adjacent to guanines (CpG dinucleotides) may affect chromatin function and alter gene expression in the absence of changes in DNA sequence

[33, 34]. It has been shown that a maternal low-protein diet or tobacco use is associated with reduced global methylation in the liver of the offspring in the rat and in the human placenta, a metabolic and endocrine organ that may be considered an "imprint" of fetal exposure in utero [35, 36]. In the rat model of IUGR, reduced expression of pancreatic and duodenal homeobox 1 (*Pdx1*), a key transcription factor that directs pancreatic progenitor cell development, was associated with changes in histone acetylation and methylation at this locus in the offspring [37]. Epigenetic modifications of the hepatocyte nuclear factor 4α (*HNF-4α*), a key transcription factor that regulates differentiation of pancreatic *β*-cells, have been reported in the offspring of mothers subjected to dietary protein restriction during gestation [38]. In addition, histone modifications of *GLUT4*, an insulin-responsive glucose transporter gene in skeletal muscle, are observed in the rat IUGR offspring [39]. Together, these findings support a role for both pancreatic and peripheral epigenetic modifications in metabolic disease pathogenesis and represent a plausible mechanism by which early life environment may alter gene expression to influence an individual's susceptibility to metabolic disease in later life.

Environmental influences during an individual's early life are not the sole cause of long-term changes in chronic disease susceptibility. Emerging data suggest that integration of signals from an individual's mother's lifetime nutritional and health experience contributes to intergenerational transfer of environmental information. For example, offsprings of LBW or preterm mothers are more likely to be born LBW or preterm, indicating transgenerational effect for LBW or preterm birth [40]. Epigenetic imprinting, alteration of gene expression based on their methylation status, is likely to play a role in transmitting epigenetic information from previous generations [41].

Clinical Manifestations of DM

The classic symptoms of DM are polydipsia, polyuria, and weight loss. Re-emergence of bed-wetting, nocturia, daytime urine incontinence, and a need to leave classes in school to use the restroom suggest polyuria. In younger children who are not toilet trained, increased frequency of wet diapers and diapers that are more heavy (wet) may be noted by caregivers. In girls, perineal candidiasis may be observed [42]. Initially, appetite is increased, but over time, children may become anorexic, contributing to weight loss. Weight loss results from hypovolemia (from polyuria) and increased catabolism (from impaired glucose utilization in skeletal muscle and increased fat and muscle breakdown). In the absence of the classic symptoms, DM can be suspected in the presence of elevated plasma glucose levels or glucosuria. T2DM is also frequently associated with acanthosis nigricans, polycystic ovary syndrome (PCOS), and metabolic syndrome [43–45]. However, it should be noted that about 40% of pediatric patients diagnosed with T2DM are asymptomatic at the time of diagnosis; therefore, lack of symptoms should not prevent testing for T2DM in high-risk patients [46].

Acute Complications of DM

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS; also known as nonketotic hyperglycemia) are two of the most serious acute complications of DM. DKA results from absolute or relative insulin deficiency and the combined effects of increased levels of the counterregulatory hormones: catecholamines, glucagon, cortisol, and growth hormone [47]. The combination of low serum insulin and high levels of counterregulatory hormones results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis); impaired peripheral glucose utilization, resulting in hyperglycemia and hyperosmolality; increased lipolysis, and ketogenesis, causing ketonemia and metabolic acidosis. DKA occurs in 15–70% of children with DM at the time of diagnosis [48–50]. In the presence of DKA, tachypnea, deep respirations, a fruity breath secondary to exhaled acetone, and neurologic findings ranging from drowsiness, lethargy, and obtundation to coma may be observed. Clinical signs of cerebral edema include fluctuating level of consciousness, sustained heart rate deceleration (decline more than 20 beats per minute) not attributable to improved intravascular volume or sleep state, age-inappropriate incontinence, vomiting, headache, lethargy or difficulty to be aroused from sleep, and diastolic blood pressure > 90 mmHg [51]. The mortality rate from DKA in children is 0.15–0.30% with cerebral edema accounting for 60%–90% of all DKA-related deaths [52, 53].

HHS may occur in children with T1DM, but is more common in T2DM [48]. In the United States, population rates for HHS hospitalization rose 52.4% from 2.1 to 3.2 per one million children from 1997 to 2009 [54]. Symptoms of HHS develop more insidiously, as compared to DKA. The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. As the degree or duration of hyperglycemia progresses, neurologic symptoms, including lethargy, focal signs, and obtundation, can be seen. Neurologic symptoms are most common in HHS, while hyperventilation and abdominal pain are primarily limited to patients with DKA. The criteria for HHS include plasma glucose concentration > 600 mg/dL (>33.3 mmol/L), serum osmolality >320 mOsm/kg, small ketonuria, absent to mild ketonemia, arterial pH > 7.30, serum bicarbonate >15 mmol/L, stupor, and coma.

Diagnosis

It is important to diagnose DM promptly and differentiate T1DM from T2DM or monogenic DM. The diagnostic criteria for DM are based upon the guidelines of the American Diabetes Association (ADA) and are the same as those used in adults: fasting plasma glucose >126 mg/dl (7 mmol/L), symptoms of hyperglycemia and a random venous plasma glucose >200 mg/dl (11.1 mmol/L), abnormal OGTT defined as plasma glucose >200 mg/dL (11.1 mmol/L) measured 2 h after a glucose load of 1.75 g/kg (maximum dose of 75 g), or a hemoglobin A1C (A1C) >6.5%

[55]. Patients who manifest impaired fasting glucose (100–125 mg/dL or 5.6–6.9 mmol/L), glucose tolerance (140–199 mg/dL or 7.8–11.0 mmol/L), or A1C 5.7–6.4 are considered to have prediabetes. The following findings generally suggest the presence of T2DM: BMI > 85th percentile, presentation after the onset of puberty, presence of acanthosis nigricans, hypertension, dyslipidemia, PCOS, ethnicity (Hispanic, African, Native, and Asian American). In T1DM, the presence of pancreatic islet cell autoantibodies, reduced insulin and C-peptide levels, and no evidence of insulin resistance are usually observed. Patients with T1DM and T2DM can have a family history of DM and present with ketoacidosis. The following findings may suggest the presence of monogenic DM: diagnosis of DM before 6 months of age, family history of DM with a parent affected, nonobese patient, absent pancreatic islet autoantibodies, evidence of endogenous insulin production outside the "honeymoon" period (after 3 years of diabetes) with detectable C-peptide (>200 nmol/L) when glucose >8 mmol/L, and presence of specific gene mutations known to be associated with DM (Table 7.1) [12, 56]. Overall, 70% of pediatric patients can clearly be classified as T1DM (55%) or T2DM (16%). An additional 20% exhibit both autoimmunity and insulin resistance, a pattern typical for obese patients with T1DM. The final 10% of patients are insulin sensitive in the absence of β-cell autoimmunity, suggesting that these patients need additional evaluation for the possibility of monogenic DM [57]. In addition, DM may result from other diseases of pancreatic exocrine system, endocrine anomalies in glucose regulation, use of medications, or viruses (Table 7.1).

Monogenic DM

Genetic Defects of β-Cell Function

DM associated with monogenetic defects in β-cell function is characterized by onset of hyperglycemia at an early age (generally before age 25 years). This spectrum of DM is referred to as maturity-onset diabetes of the young (MODY) and is characterized by impaired insulin secretion with minimal or no defects in insulin action. MODY is the most common form of monogenic DM, accounting for 2–5% of diabetes [58]. It is inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date (Table 7.1). The most common form is associated with mutations in a hepatic transcription factor (HNF)-1α [59]. A second form is associated with mutations in the glucokinase gene resulting in a defective glucokinase, an enzyme that converts glucose to glucose-6-phosphate. Because of defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion [60]. The less common forms of MODY result from mutations in other transcription factors, including HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and neurogenic differentiation factor-1 (NeuroD1). *IPF1* gene mutations can lead to MODY4 by

reduced binding of the protein to the insulin gene promoter [61]. Mutations in the *HNF-1β* gene cause MODY5. In addition to early-onset DM, affected patients can develop pancreatic atrophy, congenital anomalies of the kidney and urinary tract (CAKUT) (renal dysplasia, renal cysts, glomerulocystic disease, oligomeganephronia), chronic kidney disease (CKD), and genital abnormalities (epididymal cysts, atresia of vas deferens, and bicornuate uterus) [62]. Some patients may have a phenotype consistent with familial juvenile hyperuricemic nephropathy or autosomal recessive form of polycystic kidney disease [63, 64]. NeuroD1 normally functions as a regulatory switch for endocrine pancreatic development. *NeuroD1* mutations cause MODY6 [65].

Other Causes of Familial DM

Transient neonatal DM (TNDM) or permanent neonatal DM (PNDM) is usually diagnosed in the first 3 months of life. TNDM will resolve at a median age of 3 months, but can relapse in up to 50% of cases [66]. Most patients with TNDM have abnormal imprinting of the *ZAC* and *HYMAI* genes on chromosome 6q. The most common known cause of PNDM is mutation in the KCNJ11 gene which encodes the Kir6.2 subunit of the β-cell K_{ATP} channel [67]. Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome can also lead to neonatal DM. IPEX syndrome is a rare monogenic primary immunodeficiency due to mutations of *FOXP3*, a key transcription factor for regulatory T-cells [68]. The initial presenting symptoms are severe enteritis and type 1 diabetes mellitus, alone or in combination with eczema and elevated serum IgE. Most patients with this disorder die within the first year of life regardless of the type and site of the mutation. Point mutations in mitochondrial DNA have been found to be associated with diabetes and deafness. The most common mutation occurs at position 3243 in the tRNA gene [69]. Patients have a defect in insulin secretion and sensorineural hearing loss. The mean age of onset of diabetes and hearing loss is between the ages of 30 and 40.

Other types of monogenic DM result from a dominantly inherited missense mutation in the sulfonylurea 1 receptor subunit (Sur1) characterized by hyperinsulinemia in childhood and diabetes in adulthood, inability to convert proinsulin to insulin, production of mutant insulin molecules, or insulin resistance [70–73]. For example, leprechaunism and the Rabson-Mendenhall syndrome are due to mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance [10]. Leprechaunism is usually fatal in infancy and is characterized by small body size, elfin facies, and enlarged clitoris and breasts. Rabson-Mendenhall syndrome is a rare, autosomal recessive disorder characterized by growth retardation, coarse and senile-looking faces, mental precocity, early dentition, and pineal hyperplasia. Particular forms of PCO syndrome with severe hyperandrogenism, acanthosis nigricans, and marked insulin resistance define the type A insulin resistance syndrome. Familial partial lipodystrophy

(FPLD) is a monogenic form of dominantly inherited DM caused by a mutation in the *LMNA* gene and associated with the loss of subcutaneous fat from the limbs and trunk, with excess fat deposited around the face and neck [74]. Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) is a rare autosomal recessive disorder with incomplete penetrance [75, 76]. Patients with Wolfram syndrome develop insulin-requiring DM and optic atrophy in early childhood. Later in adolescence, they develop diabetes insipidus, hydronephrosis, progressive sensorineural deafness, and neurologic dysfunction [77]. Wolcott-Rallison syndrome is another rare autosomal recessive disorder associated with mutations in *EIF2AK3* and characterized by onset of DM in the first 3 years of life, epiphyseal dysplasia, CKD, acute hepatic failure, and developmental restriction [78].

It is important to distinguish MODY from T1DM or T2DM because the optimal treatment and risk for diabetes complications vary with the underlying genetic defect. For example, patients with MODY due to HNF-1α or HNF-4α mutations are frequently misdiagnosed as having insulin requiring T1DM because they present at an early age and are not obese. However, many of these patients can be successfully managed with sulfonylurea monotherapy. In addition, diagnosing monogenic DM allows earlier identification of family members at risk. In a patient with presumed T1DM, measurement of serum autoantibodies (islet cell antibodies (ICA), glutamic acid decarboxylase (GAD65), insulin, tyrosine phosphatases, IA-2 and IA-2β) should be performed prior to consideration of genetic testing for MODY. The presence of autoantibodies makes MODY very unlikely. Unfortunately, there are currently no biochemical tests that reliably differentiate between the MODY and T2DM diseases. The diagnosis of MODY is made by performing diagnostic genetic testing by direct sequencing of the gene. A list of laboratories is available at www.ncbi.nlm.nih.gov/sites/GeneTests *or* www.athenadiagnostics.com. Genetic testing should only be performed after informed consent and genetic counseling.

Treatment of DM

Therapy of DM by a multidisciplinary team involves training the caregivers and the patient to provide appropriate care; education and lifestyle modifications, specifically diet, exercise, and weight loss; and progressive increase in independence and self-care by the growing child. Strict glycemic control, avoidance of severe hypoglycemia, and control of comorbidities are essential for the maintenance of normal growth and development. Specific guidelines are given on administering insulin and other medications, checking blood sugars, appropriate nutrition and carbohydrate intake, testing urine for ketones at times of illness or significant hyperglycemia, and intervening with dietary measures and/or glucagon for hypoglycemia [55]. Adolescent drivers with DM should test blood glucose levels before driving and carry carbohydrate snacks with them at all times. Adolescents should be counseled on risky behaviors such as alcohol or drug use, eating disorders, cigarette smoking,

and unprotected sexual intercourse. A system to ensure gradual transition into adult care should be in place.

Treatment of T1DM

Insulin

All insulin is now manufactured by recombinant DNA technology and is based on the amino acid sequence of human insulin. Three rapid-acting insulin analogues are available: lispro (Humalog/Admelog), aspart (NovoLog/Fiasp), and glulisine (Apidra). These insulins start to act in 15–20 min and last for 3–5 h. Rapid-acting analogues are used as prandial or snack boluses and in insulin pumps. Regular insulin is short-acting and is used in intravenous infusion to treat DKA. Neutral protamine Hagedorn (NPH) is intermediate in peak and duration of action (onset, 2–4; peak, 4–12; duration, 12–24 h). Basal long-acting analogues include detemir (Levemir) and glargine (Lantus/Basaglar) (onset, 1–4; peak, 6–12; duration, 20–24 h).

Insulin Regimens

During the honeymoon period, single daily injection of long-acting basal insulin may be sufficient. Ultimately, however, most patients will require at least two injections of insulin per day (at breakfast and dinner) with mixing short−/rapid-acting (1/3 of a dose) and NPH (2/3 of a dose) insulin. Children on this regimen often require more (~2/3) of the total insulin dose in the morning and less (~1/3) in the evening. Basal-bolus regimen aims to achieve more physiologic insulin concentrations and is generally the preferred insulin regimen, as it provides more optimal glycemic control [79]. The basal insulin provides fasting insulin needs, and the bolus insulin provides insulin to cover food requirements and to correct hyperglycemia. Of the total daily insulin requirements, 40–60% should be basal insulin and the rest – preprandial rapid-acting or regular insulin. Insulin pumps continuously deliver rapid-acting insulin via a subcutaneous catheter in an attempt to mimic physiologic insulin delivery by the B-cells. Low doses of insulin are delivered in basal rates (small amounts of insulin delivered every few minutes), and insulin boluses are administered at mealtimes and to correct hyperglycemia. There are several advantages to insulin pumps, including eliminating the need for frequent injections (often 6–7 per day), the ability to have multiple basal rates, and the ability to precisely deliver small amounts of insulin [80]. Insulin dosage depends of such factors as age, weight, stage of puberty, duration and phase of DM, nutritional intake, exercise, results of blood glucose monitoring, and intercurrent illness. During the honeymoon

period, the total daily insulin dose is <0.5 IU/kg/day. Outside the honeymoon period, prepubertal children usually require 0.7–1.0 IU/kg/day, while pubertal children require 1–2 IU/kg/day of insulin [81].

Monitoring

Optimal glycemic control depends on frequent blood sugar monitoring. Monitoring can be done through multiple finger sticks or via a continuous glucose monitor (CGM). When using finger sticks, blood glucose should be monitored a minimum of four times per day: fasting, before meals, and at bedtime [82]. CGMs use subcutaneous glucose sensors that continuously measure the interstitial glucose level. Most CGMs give real-time feedback and have alarms that alert the patient and their family when blood sugars reach predefined thresholds. There are now CGMs that pair with insulin pumps in a hybrid closed-loop system to adjust insulin doses automatically to prevent hypoglycemia and manage hyperglycemia. Patients are still required to administer premeal insulin bolus. Reasonable goals for preprandial and overnight blood glucose levels are 90–130 and 90–150, respectively [83]. The goal for A1C (representing blood sugar average over the previous 2–3 months) is <7%; however, a less rigid goal of 7.5% might be more appropriate for younger children and other patients who are limited in their ability to communicate hypoglycemia symptoms [84]. Urine or blood ketones should be monitored when blood glucose values are >250 mg/dL (13.9 mmol/L) or when children are not feeling well to abort episodes of DKA.

Treatment of T2DM

Nonpharmacologic therapy aimed at reduction of BMI, improved dietary quality, and balancing food intake and physical activity should be initiated in all patients with T2DM and prediabetes [84].

Currently only metformin, insulin, and liraglutide are FDA approved for the treatment of T2DM in children. Metformin is the first-line therapy for most patients and works by improving insulin sensitivity, increasing glucose uptake in the peripheral tissues, and decreasing hepatic glucose production [85]. Liraglutide is a glucagon-like peptide-1 analogue and works by increasing glucose-dependent insulin secretion. It also has the advantage of being associated with weight loss due to delayed gastric emptying and possibly central appetite suppression [86]. Insulin therapy is used for patients with ketosis and severe hyperglycemia or if adequate control cannot be achieved with lifestyle and/or the previously mentioned medications. Insulin should be considered when random plasma glucose is >250 or A1C is >9. A large number of patients with type 2 diabetes will eventually require insulin therapy [83]. Lifestyle changes in diet and exercise should be continued in addition

to pharmacologic therapy. Patients at risk for pregnancy should be counseled on the effects of DM and oral agents on conception and fetal development. Bariatric surgery may be recommended in adolescents with T2DM with BMI > 35 [87]. Studies demonstrate resolution of T2DM in more than 95% of adolescent patients who underwent gastric bypass surgery [88].

Treatment of DKA and HHS

The biochemical criteria for the diagnosis of DKA are hyperglycemia (>200 mg/dL (>11 mmol/L), venous pH < 7.3 or bicarbonate <15 mmol/L, ketonemia, and ketonuria. The severity of DKA is categorized by the degree of acidosis: mild, venous pH < 7.3 or bicarbonate <15 mmol/L; moderate, pH < 7.2, bicarbonate <10 mmol/L; and severe, pH < 7.1, bicarbonate <5 mmol/L. Goals of therapy are to correct dehydration, acidosis, and reverse ketosis, restore blood glucose to near normal, and avoid complications of therapy. In severe volume depletion or shock, isotonic saline (or Ringer's lactate) in 20 ml/kg boluses should be given to restore circulatory volume. Insulin therapy is essential to normalize blood glucose and suppress lipolysis and ketogenesis. Insulin at 0.1 unit/kg/hour should be administered after initial fluid replacement and continued until resolution of DKA (pH > 7.30, bicarbonate >15 mmol/L). 5% glucose should be added to IV fluid when plasma glucose falls to 250–300 mg/dL (14–17 mmol/L) to prevent hypoglycemia. If the patient is hypokalemic, potassium replacement (40 mmol/L) should be initiated at the time of initial volume expansion. Otherwise, potassium should be given after initial volume expansion and concurrent with starting insulin therapy. If patient is hyperkalemic, potassium administration should be deferred until urine output is documented. Bicarbonate or phosphorus administration is not recommended unless the acidosis is profound. Transition from IV to subcutaneous insulin should be initiated when oral intake is tolerated before a mealtime 15–30 min (rapid insulin) or 1–2 h (regular insulin) before stopping insulin infusion [48]. Treatment of cerebral edema involves elevation of the head of the bed, reduction of fluid administration by one-third, and giving mannitol (0.5–1.0 g/kg IV over 20 min) or 3% saline [89]. After treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracranial causes of neurologic deterioration (e.g., thrombosis or hemorrhage). Intubation may be necessary for impending respiratory failure.

Treatment of Monogenic DM

TNDM and PNDM usually require treatment with insulin [56]. These patients may be also treated with sulfonylureas which are used in higher doses compared to doses used in adults [90]. Patients with MODY3 (*HNF-1α* mutations) or MODY1 (*HNF-4α* mutations) can be treated with diet, insulin, and low doses of

Table 7.2 Useful resources on DM for patients, parents, and caregivers

Children with Diabetes:
www.childrenwithdiabetes.com
National Institute of Diabetes and Digestive and Kidney Diseases:
www.niddk.nih.gov
American Diabetes Association:
www.diabetes.org
Children's Diabetes Foundation:
www.childrensdiabetesfoundation.org
The Endocrine Society:
www.endo-society.org

sulfonylureas (gliclazide) [91]. Patients with MODY5 (*HNF-1β* mutations), mitochondrial DM, and Wolfram or Roger's syndrome are treated with insulin [92]. Treatment of insulin resistance syndromes (type A insulin resistance, lipodystrophy, leprechaunism, and Rabson-Mendenhall syndrome) includes the use of insulin sensitizers (metformin and glitazones) and insulin [10]. In patients with pancreatic aplasia, exocrine pancreatic supplements are required. The only known effective cure for IPEX syndrome is hematopoietic stem cell transplantation [68]. Table 7.2 lists the useful resources on DM for patients, parents, and caregivers.

Chronic Complications and Comorbidities of DM

Children and adolescents with DM are at risk for a number of comorbid conditions. Associated autoimmune diseases (e.g., thyroid dysfunction, celiac disease) occur more frequently in children with T1DM [93]. Linear growth is affected negatively by DM. Patients with DM are at increased risk for dyslipidemia, a major risk factor for cardiovascular disease. Dyslipidemia is observed in 33% of children with T2DM [94]. Obesity and T2DM are also associated with nonalcoholic fatty liver disease (NAFLD) [95]. Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy [95]. Screening for retinopathy is recommended when the child has had DM for 3–5 years. DM-associated nephropathy is a progressive disorder of the microvasculature of the kidney, occurring in 14–22% of children with T2DM at presentation [95]. The prevalence and risk of progression of neuropathy has not been systematically studied among children with DM. Macrovascular complications (coronary artery, peripheral, and cerebral vascular disease) are frequent in adolescents with T2DM. Observational studies of children report essential hypertension in 5.9% and in 17–32% of patients at presentation in T1DM and T2DM, respectively [96]. Left ventricular hypertrophy is observed in 22–47% of children with T2DM [95]. Increased arterial stiffness is reported in adolescents with T2DM compared to obese and healthy-weight controls, indicating premature aging of the cardiovascular system [97, 98]. Blunted nocturnal dipping of blood pressure

is associated with nephropathy in children with T1DM and T2DM, and may be an early marker for impaired renal function [99, 100]. Studies show that children and adolescents diagnosed with T2DM have increased risk of diabetic kidney disease, retinopathy, and peripheral neuropathy when compared with those diagnosed with T1DM. Both had similar risk for hypertension and increased arterial stiffness [101]. Psychological complications in adolescents with T2DM include an increased risk for depression and binge eating, observed in 15–26% of patients [102, 103]. Notably, both men and women with T1DM have a smaller number of live births than matched controls, indicating that T1DM has an effect on fertility and family size in humans [104].

Diabetic Kidney Disease

Diabetic kidney disease (DKD) is one of the most severe complications in patients with diabetes, often leading to ESRD and the need for renal replacement therapy. Diabetes is the number one cause of chronic kidney disease and ESRD. The risk is particularly high for pediatric patients with T2DM, who develop ESRD at a higher rate than both pediatric patients with T1DM and adult patients with T2DM [105]. Initially, DKD was classified solely as diabetic nephropathy defined as progressive albuminuria eventually leading to decreased GFR; however, it has become clear that DKD is a heterogenous disease whose etiologies include changes in glomerular hemodynamics, inflammation (including oxidative stress), interstitial fibrosis, and tubular atrophy [106].

Diabetic Kidney Disease

The earliest sign of diabetic nephropathy is microalbuminuria (persistent albumin excretion between 30 and 300 mg/day or 20–200 microgram/min). Recent studies suggest that novel biomarkers for diabetic nephropathy in children may include profibrotic growth factors such as TGF-β1. In this regard, children with T1DM have increased levels of TGF-β1 in the urine at disease onset with reduction after metabolic control with insulin [107]. Microalbuminuria, if not treated successfully, may progress to overt proteinuria, defined as persistent albumin excretion >300 mg/day (>200 microgram/min) [108]. In a large population-based study, the cumulative prevalence of microalbuminuria was 26% after 10 years of diabetes and 51% after 19 years of diabetes [109].

Hyperfiltration

Diabetes activates the renin-angiotensin-aldosterone system, which triggers renal hypertrophy and increased renal plasma flow leading to an elevated glomerular filtration rate (a state referred to as glomerular hyperfiltration). This process appears to be at least partially driven by insulin resistance, which would explain why hyperfiltration is common in pediatric patients with T2DM [105]. This hyperfiltration along with increased glucose filtration leads to increased energy and oxygen needs; however, data suggests that the kidneys are not able to keep up with these increased requirements, leading to relative hypoxia and ischemia, contributing to progression of DKD [105]. ACE inhibitors and angiotensin receptor blockers are thought to primarily reduce kidney disease by decreasing hyperfiltration [110, 116].

Inflammation

Hyperglycemia and insulin resistance lead to the production of advanced glycation end products, which in turn induces production of cytokines [111]. Hyperglycemia also activates protein kinase C, resulting in decreased endothelial nitric oxide synthase leading to further cytokine production and endothelial instability. Glomerular and interstitial infiltration by macrophages is also seen in DKD. These macrophages are then activated by hyperglycemic stress, angiotensin II, and advanced glycation end products, resulting in increased cytokine production and further kidney damage [112].

ESRD

The prevalence of ESRD in pediatric DN differs between countries and ethnic groups. Studies from Canada demonstrate that children with T2DM have a 23-fold increased risk of ESRD and a 39-fold increased risk of dialysis compared with control subjects [113]. In this study, children with T2DM had a fourfold increased risk of renal failure compared to youth with T1DM. Presence of albuminuria was a risk factor associated with ESRD in adolescence [114]. During a 20-year follow-up of 11,681 young patients with T1DM in nationwide population-based study in Sweden, only 127 patients had developed ESRD due to diabetic nephropathy, a presumed reflection of better glycemic control [114]. The cumulative incidence at 30 years of T1DM duration was low, with a male predominance (4.1% [95% CI 3.1–5.3] vs. 2.5% [1.7–3.5]). In addition, a reduced risk, or a delay, in development of ESRD in patients diagnosed with T1DM before the age 5 and 10 years was found [119, 120]. Strict control of the serum glucose concentration, adequate control of elevated blood pressure and dyslipidemia, and use of angiotensin-converting enzyme (ACE)

inhibitor can slow the rate of progression of microalbuminuria or even reduce proteinuria and progressive nephropathy in children with DM [121, 122]. A 5-year, double-blind, placebo-controlled study of candesartan in nonalbuminuric and normotensive young adults with T1DM reported a reduction in mesangial matrix volume and decline in blood pressure with the use of candesartan, suggesting that changes in renal morphology can be prevented or arrested by early intervention [117, 118]. The strongest risk markers for the development of microalbuminuria and hypertension in young adults with T1DM were poor metabolic control after puberty, high daytime systolic blood pressure, and increased glomerular basement membrane thickness at 10 years [119]. Antihypertensive therapy should be targeted to decrease blood pressure values below the 90th percentile for age, gender, and height. Preemptive living donor transplantation before initiation of dialysis is preferred in non-monogenic DM [120]. Screening for mutations associated with monogenic DM should be performed in potential living-related donors for children with known monogenic DM. Family history of T2DM, use of tacrolimus, and hyperglycemia in the first 2 weeks after kidney transplantation are the risk factors for posttransplant DM in children [121].

Screening and Prevention of DM

Screening for T2DM should begin in high-risk children (BMI > 85th percentile for age and sex, family history of T2DM in a first- or second-degree relative, presence of acanthosis nigricans, PCO syndrome, hypertension, dyslipidemia, maternal history of DM or gestational DM, American Indian, Asian/Pacific Islander, African American, or Latino ethnic background) at age of 10 years or at the onset of puberty [1]. The most commonly used screening tests for T2DM include measurement of fasting plasma glucose (FPG) and 2-h plasma glucose during a 2-h OGTT, A1C. A recent randomized controlled trial conducted in overweight or obese children in the United States demonstrated a reduction in the risk of T2DM as estimated by insulin area under the curve from an oral GTT after 13 weeks of 20 or 40 min/day of aerobic training regardless of sex or race [122].

For T1DM, screening for potential complications of the disease (microalbuminuria, retinopathy, dyslipidemia, and neuropathy) is recommended. Annual screening for microalbuminuria should be initiated when the child is 10 years old and has had T1DM for 5 years [123]. The preferred screening strategy for microalbuminuria is measurement of the urine albumin-to-creatinine ratio in an untimed urinary sample. All children who have had T1DM for 3–5 years or more should have an annual ophthalmologic evaluation starting at 10 years of age [55]. A fasting lipid profile should be obtained in prepubertal children (2–10 years), if there is a family history of hypercholesterolemia (defined as total cholesterol >240 mg/dL, [6.2 mmol/L]) and a cardiovascular event before 55 years of age or if the family history is unknown or the child is overweight or obese. Adolescents (puberty or > 10 years of age) should be screened at the time of diagnosis. Testing for vibration (using a tuning

fork) and pressure sensation (using a 10 g monofilament) is recommended at least annually in children older than 10 years of age.

Although no successful strategy for the prevention of T1DM has yet been identified, children who are at high risk for T1DM can be identified using a combination of immune, genetic, and metabolic markers. Genetic markers (e.g., major susceptibility genes for T1DM located in the HLA region on chromosome 6p) may be helpful in assessing the risk of T1DM in close relatives of a patient with T1DM [124]. Measurement of autoantibodies (GAD, IAA, and IA2/ICA512) was reported to prospectively identify all children without familial DM who developed diabetes within 8 years [125]. However, a large proportion of individuals with positive screening test results is found not to have DM upon further diagnostic testing [126]. Determination of the acute (or "first phase") insulin response to glucose (FPIR) during an intravenous glucose tolerance test (IVGTT) and 2-h glucose during OGTT can be used for prediction of DM [115]. In the FPIR test, the rise in serum insulin above baseline is measured during the first 10 min after an intravenous glucose challenge [127]. The response correlates with the functioning β-cell mass. Abnormalities of FPIR and 2-h glucose during OGTT have similar sensitivities for diabetes prediction within 6 months of diagnosis (76% for OGTT [95% CI 60–83%] and 73% for FPIR [95% CI 60–83%]) [2]. Considering the high prevalence of DM with strong evidence for a genetic predisposition, more efforts are needed to promote awareness around familial clustering and primary prevention [106, 128]. Although such parameters as IGF-I, IGFBP3, fasting insulin, glucose, and lipid levels can be measured in LBW or small for gestational age infants to screen for DM, the predictive capacity of these factors as biological markers for later DM or obesity may not be of clinical use [105, 106].

Transition of Adolescents with DM to Adult Healthcare Service

Due to advances in medical care, nearly all children with DM will survive into adult life. Adolescents leave behind their childhood taking new responsibilities and striving to become an independent adult. This coincides with their move from the children's into the adult healthcare service. This transition has a potential to cause instability in the adolescent's already vulnerable state [110, 111, 129]. Therefore, an important role for the healthcare team is to ensure that the transition process will build up and develop a person empowered to become an independent individual. While children's healthcare service may be perceived as family centered, socially oriented, informal, and relaxed, adult service may be perceived as person centered, disease oriented, formal, and direct. Principles of a successful transition should be explained beforehand, allowing the adolescent and family sufficient time to familiarize themselves with the idea that care will be delivered in a different setting and by a different team at some point in the future [130]. The most appropriate time to

introduce this concept is debatable, but it is clear that its introduction at an early stage allows adequate time for preparation such as health education and promotion of independence. The timing of the transfer should take into account adolescent's physical development and emotional maturity, occur at a time of relative stability in their health, and be coordinated with other life transitions [112].

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Part II
Clinical Presentation and Associated Conditions

Chapter 8
Screening, Early Diagnosis, Genetic Markers and Predictors of Progression

Jennifer Tuazon and Janis Cho

Introduction

Chronic kidney disease (CKD) attributed to diabetes occurs in 20–40% of patients with diabetes mellitus (DM) [1]. Diabetic kidney disease typically develops 10 years following a diagnosis of type 1 DM, whereas it may be present at diagnosis in type 2 DM. Progression to end-stage kidney disease (ESKD) requiring dialysis or renal transplantation is the most feared kidney complication and is the leading cause of ESKD in the USA [2]. Thus, screening and early diagnosis may lead to early initiation of therapy that, in turn, may help delay progression of kidney disease.

Screening

The American Diabetes Association (ADA) and the National Kidney Foundation (NKF) recommend at least annual screening for CKD by checking a spot UACR and eGFR in patients with a diagnosis of type 1 DM of >5-year duration and in all newly diagnosed patients with type 2 DM. Patients with a UACR of >30 mg/g

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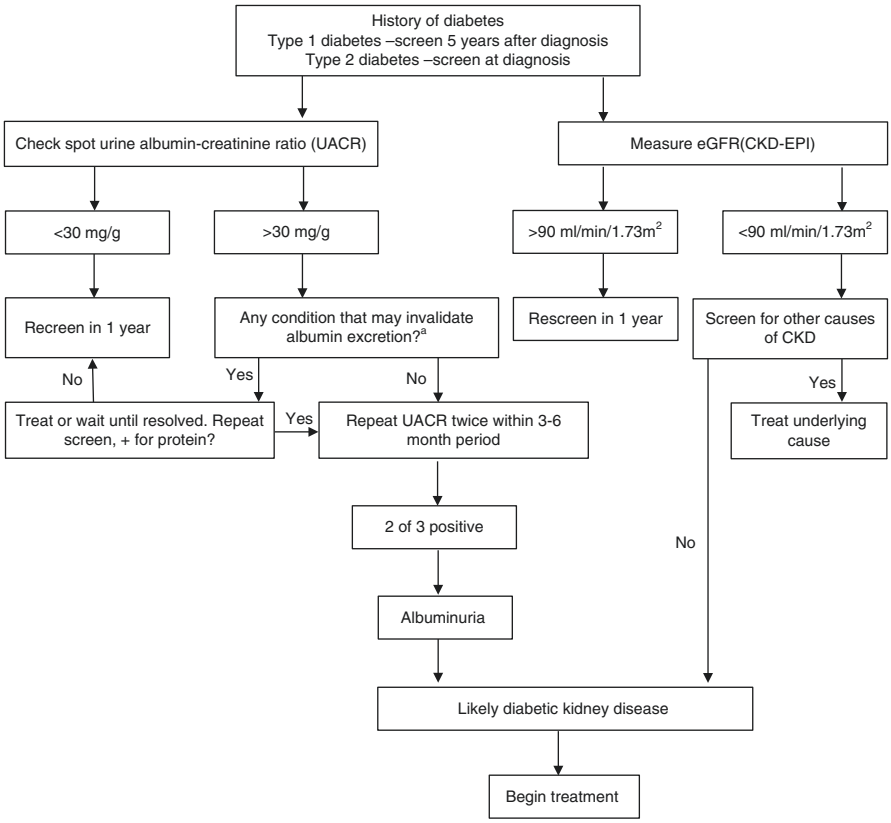

Fig. 8.1 Screening for diabetic kidney disease
[a]Exercise, urinary tract infection, marked hypertension, heart failure, acute febrile illness

creatinine and or eGFR <60 ml/min/1.73m^2 should be monitored twice a year to guide therapy [3, 4]. A suggested screening approach is seen in Fig. 8.1.

Albuminuria

A urinary albumin-to-creatinine ratio is the preferred screening method as this is less cumbersome as compared to 24-hour urine collections. A normal UACR is defined as ≤30 mg/g. Moderately increased albuminuria, used to be called microalbuminuria, is a UACR of 30–300 mg/g Cr, whereas a UACR of >300 mg/g Cr is now designated as severely increased albuminuria (macroalbuminuria) [5].

Albuminuria has been shown to be a risk marker for cardiovascular disease and chronic kidney disease. In a meta-analysis by Perkowitz et al., they found that individuals with microalbuminuria were at 50% greater risk of coronary heart disease (risk ratio 1.47, 95% CI 1.30–1.66) than those without. Those with macroalbuminuria had more than double the risk (risk ratio 2.17, CI 1.87–2.52) [6]. The Chronic

Kidney Disease Prognosis Consortium showed that more severe albuminuria independently predicts mortality and ESKD among individuals with CKD [7].

However, measurement of albuminuria has its limitations. There is high biological variability of >20% between measurements in urinary albumin excretions such that two of three specimens of UACR collected within a 3–6-month period should be abnormal before considering a patient to have albuminuria [8, 9, 10].

There are also several conditions that can lead to albuminuria but not indicative of true renal parenchymal disease. Examples are exercise, fever, infection, and hypertension [11].

Glomerular Filtration Rate

Estimated glomerular filtration rate should be calculated from serum creatinine using a validated formula such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [4]. An eGFR that is persistently below 60 ml/min/1.73m^2 is considered abnormal. However, DKD can also be present with a normal or elevated eGFR, particularly in the early stages. Progressive CKD may be determined best by the slope of sequential GFR estimates, rather than a single estimate.

Diagnosis

Diabetic kidney disease is usually a clinical diagnosis made on the basis of reduced eGFR and persistently increased albuminuria (>300 mg/g creatinine). The typical clinical presentation of diabetic kidney disease is in patients with a prolonged duration of diabetes (>10 years in type 1 diabetes), presence of retinopathy, albuminuria without hematuria, and gradual and progressive loss of GFR. However, in more recent years, the heterogeneity in clinical presentation has become more evident. Large cohort studies have found decreased GFR in diabetics with normoalbuminuria [12, 13]. In a cross-sectional study of adults aged 20 years or older with diabetes mellitus who participated in the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2014, a decrease in prevalence of albuminuria and increase in reduced GFR were found. Whether this data represents undiagnosed CKD from non-diabetic causes, increased use of renin-angiotensin-aldosterone system blockers, or other factors remains uncertain.

It is important to realize that CKD in diabetes does not always represent diabetic kidney disease. Certain clinical features should prompt evaluation for other causes of chronic kidney disease [Table 8.1] [4, 14]. A kidney biopsy may be required to establish a diagnosis especially in cases that may lead to a change in management or to provide prognostic information. In the largest study to date of 620 native renal biopsies performed in patients with diabetes, 37% had diabetic nephropathy alone, 36% had non-diabetic renal disease alone, and 27% had diabetic nephropathy plus non-diabetic renal disease [15]. In those who had non-diabetic renal disease alone found on biopsy, focal sclerosing glomerulosclerosis (FSGS) (22%), hypertensive

Table 8.1 Atypical clinical features that should prompt evaluation for non-diabetic CKD

Active urinary sediment (pyuria, hematuria)
Absence of diabetic retinopathy
Rapidly decreasing eGFR
Rapidly increasing proteinuria or nephrotic syndrome
Signs and symptoms or systemic disease
Short diabetes duration

nephrosclerosis (18%), acute tubular necrosis (ATN) (17%), IgA nephropathy (11%), membranous glomerulonephritis (8%), and pauci-immune glomerulonephritis (7%) comprised 80% of diagnoses.

Other Clinical Predictors of Diabetic Kidney Disease

Aside from albuminuria and eGFR, there are other established clinical risk factors for the development and progression of diabetic kidney disease including age, diabetes duration, Hba1c, systolic blood pressure, and retinopathy status.

There are several studies that looked into predictors of development of diabetic kidney disease. A prospective study by Zoppini et al. of 1682 patients with type 2 diabetes and a baseline eGFR of >60 ml/min/1.73m^2 found that aside from albuminuria, other independent predictors of annual eGFR decline were older age, hypertension, insulin treatment, and lower baseline eGFR [16]. Elley et al., in an analysis of a large multicenter cohort study of type 2 diabetics with baseline median eGFR of 77 ml/min/1.73 m2 followed for up to 11 years, showed that weighted models incorporating sex, ethnicity, age, diabetes duration, albuminuria, serum creatinine, systolic blood pressure, glycemic control, smoking status, and previous cardiovascular disease status fared well in prediction of development of ESKD [17].

Age

Older age has been independently associated with increased risk of progression in diabetic kidney disease in type 2 diabetes in most studies [16] [17] [18]. This is likely related to the observation that there is progressive GFR decline in the general population after age 40. In type 1 diabetes, however, it is suggested that diagnosis before puberty involves a reduced risk or a longer time to development of diabetic nephropathy [19]. A potential explanation is that puberty, which is characterized by rapid growth, hormonal changes, worsening glycemic control, and potentially social factors, hastens processes that lead to chronic complications of diabetes.

Hypertension

In type 1 diabetes, hypertension is typically due to DKD. However, hypertension is found in about a third of patients with type 2 diabetes at diagnosis and is likely caused by a combination of factors including the metabolic syndrome. Regardless of timing of onset of hypertension, high blood pressure has been found to be associated with development and progression of diabetic kidney disease. As an example, the UKPDS (United Kingdom Prospective Diabetes Study) observed that baseline higher systolic blood pressure was independently associated with the development of albuminuria or decreased GFR [20]. In another study, patients with type 2 diabetes were assigned to a target of <150/85 or < 180/105. After a median follow-up of 15 years, a 37% risk reduction of microvascular complications was seen in the lower target group [21].

Hyperglycemia

There are several studies that have shown an association between diabetes control and development of microvascular complications in the kidney. In type 1 diabetics, the DCCT (Diabetes Control and Complications Trial) showed that intensive glycemic control (Hba1c, 7.3%, n = 711) was associated less development of microalbuminuria and macroalbuminuria compared to conventional glycemic control (Hba1c 9.1%, n = 730), over a period of 6.5 years [22]. In the follow-up observational study DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications), the risk for developing a GFR <60 ml/min/1.73 m2 was found to be lower in people who were in the intensive glycemic control group [23].

In type 2 diabetics, the UKPDS demonstrated that participants assigned to intensive glycemic control (Hba1c, 7.0%; n = 2408) vs conventional glycemic control (Hba1c 7.9%; n = 994) had less microalbuminuria or macroalbuminuria at the end of follow-up [24]. Another study involving patients with type 2 diabetes, ADVANCE (Action in Diabetes and Cardiovascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), showed that at Hba1c levels<6.5%, there was no significant increase in risks of development of microvascular events, including macroalbuminuria, doubling of serum creatinine, need for renal replacement, or death due to kidney disease [25].

Diabetic Retinopathy

In type 1 diabetes mellitus, diabetic retinopathy is highly concordant with DKD [26].

However, in type 2 diabetes, the presence of retinopathy is only moderately predictive of diabetic nephropathy. In a meta-analysis by He et al. of 26 studies, the sensitivity of diabetic retinopathy to predict diabetic nephropathy was 0.65 (95% CI 0.62, 0.68) with a specificity of 0.75 (95% CI 0.73, 0.78). The pooled positive and negative predictive values of diabetic retinopathy to predict diabetic nephropathy were 0.72 (95% CI 0.68, 0.75) and 0.69 (95% CI 0.67, 0.72), respectively [27].

Novel Biomarkers

The origin of urinary biomarkers of renal involvement of DM is diverse and comprises constitutive elements of the nephron. Some examples are markers at the epithelial cell/podocyte level such as nephrin and podocalyxin, glomerular basement membrane level (collagen, laminin), endothelial cell level (VEGF), and tubular cell level (NGAL, NAG, and KIM-1) [28–31].

The biomarkers can be classified according to their origin and the pathological processes impairing the nephron: renal dysfunction, inflammatory markers, and oxidative stress [32]. They can also be divided into glomerular, tubular, or others [33].

Although albuminuria is commonly perceived as an early biomarker of glomerular injury, studies suggest that albumin can be a result of early tubular injury due to the absorption by the megalin-cubilin system [34]. Excretion of non-albumin proteins (uNAPs) has been studied as an early marker of tubular injury from diabetes, and some studies have noted that uNAPs may be a better biomarker of early diabetic kidney injury [35–37]. Although previous studies reported uNAPs to be mainly associated with tubular injury only, in diabetic nephropathy, both glomerular and tubular injuries have been observed. For example, urinary kappa and lambda light chains have been reported among uNAPs to be present in urine during early stages of diabetic nephropathy [38]. Other uNAPs include alpha-1-microglobulin, beta-2 macroglobulin, IgG, cystatin C, transferrin, nephrin, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinases-1.

Urinary transferrin was reported to be increased in diabetic patients along with urinary ceruloplasmin and immunoglobulin G and that this preceded albuminuria [39]. Renal hemodynamic changes along with increased glomerular pressure have been postulated as the cause of this finding. Another study showed that people with elevated urinary transferrin often develop microalbuminuria [40, 41]. Similarly, urinary ceruloplasmin excretion correlated positively with albumin excretion rate, and urine ceruloplasmin/creatinine ratio had a sensitivity of 90–91% and a specificity of 61–66% in diagnosing DKD [42, 43].

Type IV collagen constitutes glomerular basement membrane and mesangial matrix [44]. High glucose level is thought to cause increase in collagen production and decrease in breakdown of collagen and contribute to the diffuse glomerulosclerosis. Such processes may explain the reason why increased urinary type IV collagen excretion has been associated with presence of abnormal urinary albumin excretion rate and renal structural lesions even in non-albuminuric patients [45, 46]. It has been suggested that urinary type IV collagen excretion may reflect morphological renal alterations from ongoing extracellular matrix turnover and could play a role in early diagnosis of DKD [47].

Several tubular markers include neutrophil gelatinase-associated lipocalin (NGAL) which is a protein produced by renal tubules in response to structural kidney injury, liver-type fatty acid-binding protein (L-FABP), and kidney injury molecule-1 (KIM-1) [29] [48]. Serum and urinary NGAL is not influenced by age after the fifth year of life, and unlike other markers, it is not a marker of renal dysfunction. Rather, it reflects structural damage of renal cells [49]. In previous studies,

urinary NGAL, along with L-FABP and KIM-1, did not add prognostic value as a marker of injury in type 2 diabetics on top of already established renal factors [50, 51]. However, more recent studies showed that urinary NGAL and KIM-1 levels were high in type 2 diabetics with normal level of albuminuria and increased progressively in patients with microalbuminuria and macroalbuminuria [52]. Another study looked at urinary NGAL and cystatin C in diabetics and prediabetics and found that these markers rise early in DKD. Furthermore, urinary NGAL-creatinine ratio (UNCR) predicted microalbuminuria better than the urinary cystatin C-creatinine ratio (UCCR) [53].

Promising inflammatory markers include tumor necrosis factor alpha (TNF-a), transforming growth factor-B1 (TGF-B1), and orosomucoid. Urinary TNF alpha has been reported to be increased in type 1 diabetics with microalbuminuria, possibly due to hyperfiltration [54, 55]. Upregulation of TGF-B1 expression was reported to be important in fibrosis and tissue remodeling of glomerular tissue [56], and meta-analysis reported association with severity of diabetic nephropathy [57]. Orosomucoid, also named α-1-acid glycoprotein, is another protein associated with the inflammatory process and has been reported to be elevated in non-albuminuric type 1 diabetics compared to controls [58]. Study by Jiang et al. suggested that urinary orosomucoid may be predictive of cardiovascular mortality in type 2 diabetics and that it was independently associated with progression of DKD [59].

Serum cystatin C has superiority over other markers due to its decreased affinity to protein binding and, thus, its ability to be freely filtered across the glomeruli with no or minor tubular excretion. Schwartz et al. have shown previously that reciprocal of cystatin C had strong correlation with GFR [60].

Interleukin-19 (IL-19) is considered an anti-inflammatory interleukin that plays a role in several important pathways in endothelial function. A study by Li et al. showed that IL-19 level correlates to a higher albuminuric state and also positively correlates to hemoglobin A1c level [61]. It is postulated that there is upregulation of IL-19 due to chronic hyperglycemia which in turn stimulates endothelial cells promoting further inflammation and injury [48].

Many of the above markers are lacking in evidence for everyday practical use, and their efficacy in predicting early DKD needs to be further validated. Perhaps, a combination of markers may help with increasing the sensitivity and specificity of these tests. As an example, Yamashita et al. used a panel of six biomarkers including KIM-1 and VEGF-A in diabetic subjects with normoalbuminuria. After a mean follow-up of 6.2, years, the six novel biomarkers appeared to have a better prognostic value for predicting the onset of microalbuminuria [62]. The SUMMIT (Surrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools) investigators assayed 207 biomarkers. Ultimately, 30 biomarkers showed significant association with rapid progression and adjusted for clinical characteristics. Subsequently, a panel of 14 biomarkers (including fibroblast growth factor-21, the symmetric-to-asymmetric dimethylarginine ratio, β2-microglobulin, C16-acylcarnitine, and kidney injury molecule-1) increased the area under the ROC curve from 0.706 to 0.868 [63].

Another study with participants from the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study was conducted to determine whether plasma biomarkers

of kidney injury improve prediction of diabetic kidney disease in adults [64]. They found that several biomarkers (β2-microglobulin, cystatin C, NGAL, and osteopontin) were strongly associated with greater risk of impaired GFR.

A list of biomarker studies on DKD can be found in Table 8.2.

Though promising, further optimization of a panel of the best reported biomarkers can be considered as well as large-scale collaboration to increase power, and generalizability of these tools.

Proteomics

Proteomics is generally described as large-scale experimental analysis of proteins mainly through protein purification and mass spectrometry [29]. Most of the peptide analyses are of collagen fragments, as previously reported by Zurbig et al. [65] One example of mass spectrometry-based method is CKD273 which is developed as a commercial test by Mosaique Diagnostics. This test includes 273 urinary peptides including collagen fragments (compromising 74% of the peptides) as well as various others including uromodulin, clusterin, and polymeric-immunoglobulin complex [66]. Two main trials have used CKD273 to assess risk of disease progression. The initial study was the Diabetic Retinopathy Candesartan Trials-Protect 2 which showed that CKD273 was strongly associated with incident microalbuminuria and that higher baseline CKD273 score was associated with larger reduction in UACR in the spironolactone group versus placebo [51]. The second study, Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephropathy in type 2 diabetic patients with normoalbuminuria (PRIORITY) trial, was a multicenter randomized double-blind controlled trial using CKD273 to risk stratify patients with a high score to receive spironolactone versus placebo [67]. The trial demonstrated that CKD273 predicts development of early kidney disease in diabetes, but the high risk could not be reduced by spironolactone.

More studies are ongoing to assess urinary proteomic panels as a surrogate outcome measure [68]. The innovative use of the proteomics for clinical trials with or without other traditional markers like albuminuria may be one of the first steps in expanding the use of these novel prognostic biomarkers.

Genetic Markers

The development of diabetic nephropathy (DN) was historically thought of as an exclusive result of long-standing poor glycemic control. However, familial clustering suggests a genetic susceptibility to diabetic nephropathy. A study of siblings with type 1 diabetes from the Joslin Clinic showed that there was close to a 50% more risk of developing DN in the sibling if the proband had DKD compared to those who had siblings with diabetes but without DKD [69].

Table 8.2 Studies on biomarkers and DKD

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Single biomarkers or several biomarkers not as a panel						
Hong et al. [75]	*T2D = 30* *T2D DN = 47* *Healthy controls = 30*	Cross-sectional	Proteinuria and CKD	Plasma miR-193a-3p	Upregulated in patients with diabetic nephropathy compared with T2D and healthy controls	No adjustments
Nilavan et al. [76]	*N = 29* *T2D* vs *controls*	Cross-sectional	CKD 2, 4	Pregnenolone sulfate, GA1, PG, and all-trans-Carophyll yellow	Correlated with eGFR	No adjustments
Choi et al. [77]	*T2D n-171* *healthy controls n = 65*	Cross-sectional	Varying levels of albumin excretion	SH3YL1 protein	Protein increased in diabetics but markedly increased in overt proteinuria higher in overt proteinuria	No adjustments
Burns et al. [78]	*N* = 259 (*n* = 194 T1D, *n* = 65 controls)	Cross-sectional	Normoalbuminuria; varying levels of GFR	Urinary angiotensinogen and ACE2 levels, activity of ACE and ACE2	Urinary angiotensinogen and ACE activity associated with ACR	No adjustments
Velho et al. [79]	*N* = 986T1D	Prospective	Varying levels of albumin excretion and GFR	Plasma copeptin	Upper tertiles of copeptin associated with a higher incidence of ESRD	Baseline sex, age, and duration of diabetes
Carlsson et al. [80]	*N* = 607T2D	Prospective	Varying levels of albumin excretion	Plasma endostatin	Endostatin levels associated with increased risk of GFR decline and mortality	Baseline age, sex, eGFR, and ACR

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Dieter et al. [81]	N = 135T2D	Prospective	Proteinuria	Serum amyloid A	Higher serum amyloid A levels predicted higher risk of death and ESRD	UACR, eGFR, age, sex, and ethnicity
Wang et al. [82]	N = 100 (n = 80 with T2D, n = 20 healthy controls)	Cross-sectional	Varying levels of eGFR and ACR	Serum and urinary ZAG	Serum and urinary ZAG associated with eGFR and UACR, respectively	No adjustments
Pikkemaat et al. [83]	N = 161 T2D	Prospective	eGFR >60 ml min^{-1} 1.73 m^{-2}	Copeptin	Copeptin predicted development of CKD stage 3, borderline significant on adjustment for baseline eGFR	Age, sex, diabetes duration, antihypertensive treatment, HbA_{1c}, BMI, SBP
Garg et al. [84]	N = 91T2D (including n = 30 with prediabetes)	Cross-sectional	Varying levels of albumin excretion	Urinary NGAL and cystatin C	NGAL and cystatin C were significantly higher in participants with vs those without microalbuminuria	No adjustments
Viswanathan et al. [85]	N = 78 (n = 65 T2D, n = 13 controls)	Cross-sectional	Varying degrees of albuminuria	Urinary L-FABP	L-FABP inversely associated with eGFR and positively associated with protein-to-creatinine ratio	No adjustments

Panduru et al. [86]	*N* = 1573T1D	Prospective + Mendelian randomization	Varying degrees of albuminuria	Urinary KIM-1	KIM-1 did not predict progression to ESRD independently of AERMendelian randomization supported a causal link between KIM-1 and eGFR	HbA_{1c}, triacylglycerols, AER
Pavkov et al. [87]	*N* = 193T2D	Prospective	Varying levels of albumin excretion,eGFR: ≥60 ml/min in 89% participants	Serum TNFR1 and TNFR2	Elevated concentrations of TNFR1 or TNFR2 associated with increased risk of ESRD	Age, sex, HbA_{1c}, MAP, ACR, and GFR
Fufaa et al. [88]	*N* = 260T2D	Prospective	Varying levels of albumin excretion and eGFR	Urinary KIM-1, L-FABP, NAG, and NGAL	NGAL and L-FABP independently associated with ESRD and mortality	Baseline age, sex, diabetes duration, hypertension, HbA_{1c}, GFR, ACR
Bouvet et al. [89]	*N* = 36T2D	Cross-sectional	Normoalbuminuria and macroalbuminuria	Urinary NAG	Higher NAG levels associated with microalbuminuria	No adjustments
Har et al. [90]	*N* = 142T1D	Cross-sectional	Varying levels of eGFRNormoalbuminuria	Urinary cytokines/ chemokines	Increased urinary cytokine/chemokine excretion according to filtration status with highest levels in hyperfiltering individuals, although not significant after adjustments	Glycemia

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Petrica et al. [91]	$N = 91$ ($n = 70$ T2D, $n = 21$ controls)	Cross-sectional	Normoalbuminuria and microalbuminuria	Urinary α_1-microglobulin and KIM-1 (proximal tubule markers), nephrin and VEGF (podocyte markers), AGE, UACR, and serum cystatin C	Significant association between biomarkers of proximal tubule dysfunction and podocyte biomarkers (independently of albuminuria and renal function)	UACR, cystatin C, CRP
Wu et al. [92]	$N = 462$T2D	Cross-sectional	Varying levels of albumin excretion	Serum klotho, NGAL, 8-iso-PGF2α, MCP-1, TNF-α, TGF-β1	Klotho and NGAL associated with ACR	No adjustments
Sabbisetti et al. [93]	$N = 124$T1D	Prospective	ProteinuriaCKD 1–5	Serum KIM-1	KIM-1 associated with eGFR slopes and progression to ESRD	Baseline ACR, eGFR, and HbA_{1c}
Velho et al. [94]	$N = 3101$T2D	Prospective	Albuminuria	Plasma copeptin	Copeptin independently associated with renal events (doubling of creatinine or ESRD)	Baseline sex, age, diabetes duration, hypertension, diuretics use, HbA_{1c}, eGFR, triacylglycerols, HDL-cholesterol, AER
do Nascimento et al. [95]	$N = 101$($n = 19$ prediabetes, $n = 67$ diabetes [T1D, T2D], and $n = 15$ controls)	Cross-sectional	Varying levels of albumin excretion	Urinary mRNA levels of podocyte-associated proteins (nephrin, podocin, podocalyxin, synaptopodin, TRPC6, α-actinin-4, and TGF-β1)	Urinary nephrin discriminated between the different stages of DKD and predicted increases in albuminuria	No adjustments

Boertien et al. [96]	N = 1328T2D	Prospective	Varying degrees of albuminuria and eGFR	Copeptin	Copeptin associated with change in eGFR independently of baseline eGFR. This association not present in those on RASi	Age, sex, diabetes duration, antihypertensive use, HbA_{1c}, cholesterol, BP, BMI, smoking
Lopes-Virella et al. [97]	N = 1237T1D	Prospective	Normoalbuminuria	Serum E-selectin, IL-6, PAI-1, sTNFR1, TNFR2	TNFR1 and TNFR2 and E-selectin best predictors of progression to macroalbuminuria	Treatment allocation, baseline AER, ACEi/ARB use, retinopathy cohort, sex, age, HbA_{1c}, diabetes duration
Panduru et al. [98]	N = 2454 (n = 2246 T1D, n = 208 controls)	Prospective	Varying degrees of albuminuria	Urinary L-FABP	L-FABP was an independent predictor of progression at all stages of DKD, but L-FABP did not significantly improve risk prediction above AER	Baseline WHR, HbA_{1c}, triacylglycerols, ACR
Araki et al. [99]	N = 618T2D	Prospective	Varying levels of albumin excretion, serum creatinine $\leq 8.8 \times 10^{-2}$ mmol/l	Urinary L-FABP	L-FABP associated with decline in eGFR	Age, sex, BMI, HbA_{1c}, cholesterol, triacylglycerols, HDL-cholesterol, hypertension, RASi use, BP

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Lee et al. [100]	*N* = 380T2D	Prospective	Varying levels of albumin excretion	Plasma TNFR1 and FGF-23	FGF-23 was associated with increased risk of ESRD, only in unadjusted model	Sex, baseline diabetes duration, HbA_{1c}, eGFR, AER
Cherney et al. [101]	*N* = 150T1D	Cross-sectional	Normoalbuminuria	42 urinary cytokines/ chemokines	IL-6, IL-8, PDGF-AA, and RANTES levels differed across ACR tertiles	No adjustments
Conway et al. [102]	*N* = 978T2D	Prospective	Varying degrees of albuminuria and eGFR	Urinary KIM-1 and GPNMB	KIM-1 and GPNMB associated with faster eGFR decline, only in unadjusted modelshigher KIM-1 associated with mortality risk, only in unadjusted models	Baseline eGFR, ACR, sex, diabetes duration, HbA_{1c}, BP
Nielsen et al. [103]	*N* = 177T2D	Prospective	Proteinuria	Urinary NGAL and KIM-1 and plasma FGF23	Higher levels of the biomarkers associated with a faster decline in eGFR, although this was not independent of known promoters	Age, sex, $HbA_{1c,}$ SBP, and urinary albumin
Jim et al. [104]	*N* = 76 (*n* = 66 T2D, *n* = 10 controls)	Cross-sectional	Normoalbuminuria and microalbuminuria	Urinary nephrin levels	Nephrinuria occurred before the onset of microalbuminuria	No adjustments

Gohda et al. [105]	N = 628T1D	Prospective	Normal renal function; normoalbuminuria and microalbuminuria	TNFR1 and TNFR2	TNFR1 and TNFR2 strongly associated with risk for early renal decline	HbA_{1c}, AER, and eGFR
Niewczas et al. [106]	N = 410T2D	Prospective	CKD 1–3	Plasma TNF-α, TNFR1, and TNFR2, ICAM-1, VCAM-1, PAI-1, IL-6, and CRP	TNFR1 and TNFR2 were strongly associated with risk of ESRD	Age, HbA_{1c}, AER, and eGFR
Fu et al. [107]	N = 112 (n = 88 with T2D, n = 24 controls)	Cross-sectional	Varying degrees of albuminuria	Urinary KIM-1, NAG, NGAL	Higher levels of the three markers in T2D than controlspositive association of NGAL and NAG with ACR; negative association of NGAL and eGFR	No adjustments
Nielsen et al. [108]	N = 63T1D	Prospective	Varying levels of albumin excretion and GFR	Urinary NGAL, KIM-1, and L-FABP	Elevated NGAL and KIM-1 were associated with faster decline in GFR, but not after adjustments for known progression promoters	Age, sex, diabetes duration, BP, HbA_{1c}, AER
Kamijo-Ikemori et al. [109]	N = 552 (n = 140 T2D and n = 412 controls)	Cross-sectional and prospective	Varying degrees of albuminuria and GFR	Urinary L-FABP	L-FABP associated with progression of nephropathy	Age, sex, HbA_{1c}, albuminuria status at baseline, BP
Vaidya et al. [110]	N = 697 (n = 659 T1D, n = 38 controls)	Cross-sectional and prospective	Varying levels of albumin excretion	Urinary IL-6, CXCL10/IP-10, NAG, and KIM-1	KIM-1 and NAG both individually and collectively were significantly associated with regression of microalbuminuria	Age, sex, AER, HbA_{1c}, SBP, renoprotective treatment and cholesterol

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Panel of biomarkers/proteomics signatures						
Coca et al. [111]	*N* = 1536 (*n* = 1346 T2D, *n* = 190 controls)	Nested case–control study and prospective	CKD at various stages	TNFR1, TNFR2, and KIM-1	Higher levels of the three biomarkers associated with higher risk of eGFR decline in persons with early or advanced DKD	Clinical variables
Bjornstad et al. [64]	*N* = 527T1D	Prospective	Varying levels of albumin excretion and eGFR	Plasma biomarkers	B2M, cystatin C, NGAL, and osteopontin predicted impaired eGFR	Age, sex, HbA_{1c}, SBP, LDL cholesterol, baseline log ACR, and eGFR
Peters et al. [112]	*N* = 354T2D	Prospective	Varying levels of albumin excretion and eGFR	Plasma ApoA4, ApoC-III, CD5L, C1QB, complement factor H-related protein 2, IGFBP3	ApoA4, CD5L, C1QB, and IBP3 improved the prediction of rapid decline in renal function independently of recognized clinical risk factors	Age, diabetes duration, diuretic use, HDL cholesterol

Mayer et al. [113]	*N* = 1765T2D	Prospective	CKD at various stages	YKL-40, GH-1, HGF, matrix metalloproteinases: MMP2, MMP7, MMP8, MMP13, tyrosine kinase, and TNFR1	Biomarkers explained variability of annual eGFR loss by 15% and 34% (adj *R* [2]) in patients with eGFR ≥60 and < 60 ml min^{-1} 1.73 m^{-2}, respectivelyA combination of molecular and clinical predictors increased the adjusted *R* [2] to 35% and 64% in these two groups, respectively	Sex, age, smoking, baseline eGFR, ACR, BMI, total cholesterol, BP, and HbA_{1c}
Saulnier et al. [114]	*N* = 1135T2D	Prospective	Varying levels of albumin excretion and eGFR	Serum TNFR1, MR-proADM, and NT-proBNP	TNFR1, MR-proADM, and NT-proBNP improved risk prediction for renal function decline	Age, sex, diabetes duration, HbA_{1c}, BP, baseline eGFR, and ACR
Looker et al. [63]	*N* = 307(*n* = 154 T2D, *n* = 153 controls)	Nested case-control	CKD 3	207 serum biomarkers	Panel of 14 biomarkers improved clinical prediction (from 0.706 to 0.868)	Age, sex, eGFR, albuminuria, HbA_{1c}, ACEi and ARB use, BP, weighted average of past eGFRs, diabetes duration, BMI, prior CVD, insulin use, antihypertensive drugs

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Pena et al. [115]	*N* = 82T2D	Prospective	Normoalbuminuria and macroalbuminuria	Plasma peptides	18 peptides (related to PI3K-Akt, VEGF, mTOR, MAPK, and p38 MAPK, Wnt signaling) improved risk prediction for transition from micro- to macroalbuminuria (C statistic from 0.73 to 0.80)	Baseline albuminuria status, eGFR, RASi use
Pena et al. [116]	*N* = 82T2D	Prospective	Varying levels of albumin excretion and eGFR	28 biomarkers	MMPs, tyrosine kinase, podocin, CTGF, TNFR1, sclerostin, CCL2, YKL-40, and NT-proCNP improved prediction of eGFR decline when combined with established risk markers	Baseline smoking, sex, SBP, eGFR, use of oral diabetic medication
Foster et al. [117]	*N* = 250T2D	Prospective	Unselected but 54% albuminuric	β-Trace protein and B2M	β-Trace protein associated with ESRD	GFR, albuminuria, age, sex, diabetes duration, hypertension, cholesterol

Agarwal et al. [118]	*N* = 87 (*n* = 67 T2D, *n* = 20 controls)	Prospective	CKD 2–4varying levels of albumin excretion	17 urinary and 7 plasma biomarkers	Urinary C-terminal FGF-2: Strongest association with ESRDplasma VEGF associated with the composite outcome of death and ESRD	Baseline albuminuria and eGFR
Siwy et al. [119]	*N* = 165T2D	Prospective	Wide ranges of eGFR and urinary albumin	Urinary CDK273	Validation of this urinary proteome-based classifier in a multicenter prospective setting	Albuminuria
Verhave et al. [120]	*N* = 83T1D and T2D	Prospective	Overt diabetic nephropathy	Urinary IL-1β, IL-6, IL-8, MCP-1, TNF-α, TGF-β1, and PAI-1	MCP-1 and TGF-β1 were independent and additive to proteinuria in predicting the rate of renal function decline	Albuminuria
Bhensdadia et al. [121]	*N* = 204T2D	Prospective	eGFR stages 1–2 and normo–/ macroalbuminuria	Urine peptides	Haptoglobin-to-creatinine ratio: Best predictor of early renal function decline	Albuminuria, ACEi use
Merchant et al. [122]	*N* = 33T1D	Prospective	Microalbuminuria	Small (<3 kDa) plasma peptides	Plasma kininogen and kininogen fragments associated with renal function decline	No adjustments but stratum matched for eGFR and albuminuria
Roscioni et al. [123]	*N* = 88T2D	Prospective	Normoalbuminuria and microalbuminuria	CKD273 (urine)	Able to detect progression from normo- to micro- and micro- to macroalbuminuria	Baseline albuminuria status, eGFR, RASi use

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Zürbig et al. [124]	*N* = 35T1D and T2D	Prospective	Normoalbuminuria; normal eGFR	Urinary CKD273	Early detection of progression to macroalbuminuria: AUC 0.93 vs 0.67 for urinary albumin	Albuminuria
Titan et al. [125]	*N* = 56T2D	Prospective	Macroalbuminuria	Urinary RBP and serum and urinary cytokines (TGF-β, MCP-1, and VEGF)	Urinary RBP and MCP-1: Independently related to the risk of CKD progression	Creatinine clearance, proteinuria, BP
Schlatzer et al. [126]	*N* = 465T1D	Nested case-control	CKD 1Normoalbuminuria	Panel of 252 urine peptides	A panel including Tamm-Horsfall protein, progranulin, clusterin, and α-1 acid glycoprotein improved the AUC from 0.841 (clinical variables) to 0.889	Age, diabetes duration, HbA_{1c}, BMI, WHR, smoking, total and HDL cholesterol, SBP, ACR, uric acid, cystatin C, BP/ lipid treatment
Metabolomics						
Niewczas et al. [127]	*N* = 158T1D	Prospective	Proteinuria and CKD 3	Global serum metabolomic profiling	7 modified metabolites were associated with renal function decline and time to ESRD	Baseline HbA_{1c}, ACR, eGFR, BP, BMI, smoking, uric acid levels, RASi use, other antihypertensive treatment, and statins

Klein et al. [128]	*N* = 497T1D	Prospective	Normoalbuminuria	Multiple plasma ceramide species and individual sphingoid bases and their phosphates	Increased plasma levels of very long-chain ceramide species associated with reduced macroalbuminuria risk	Treatment group, baseline retinopathy, sex, HbA_{1c}, age, AER, lipid levels, diabetes duration, ACEi/ARB use
Pena et al. [129]	*N* = 90T2D	Case-control and prospective	Normoalbuminuria and macroalbuminuria	Plasma and urinary metabolomics	Urine hexose, glutamine and tyrosine and plasma histidine, and butenoylcarnitine associated with progression from micro- to macroalbuminuria	Albuminuria, eGFR, RASi use
Niewczas et al. [130]	*N* = 80T2D	Prospectivenested case-control study	CKD 1–3	78 plasma metabolites (uremic solutes) and essential amino acids	Abnormal levels of uremic solutes and essential amino acids associated with progression to ESRD	Albuminuria, eGFR, HbA_{1c}
Sharma et al. [131]	*N* = 181 (*n* = 114 T2D, *n* = 44 T1D, *n* = 23 controls)	Cross-sectional	Different CKD stages	13 urine metabolites of mitochondrial metabolism	Differences in urine metabolome between healthy controls and diabetes mellitus and CKD cohorts	Age, race, sex, MAP,BMI, HbA_{1c}, diabetes duration
Hirayama et al. [132]	*N* = 78T2D	Cross-sectional	Varying levels of albumin excretion	19 serum metabolites	Able to discriminate presence or absence of diabetic nephropathy	No adjustments

(continued)

Table 8.2 (continued)

Author, ref.	Sample size and population	Study design	DKD stage	Biomarkers	Main results	Adjustments
Van der Kloet et al. [133]	*N* = 52T1D	Prospective	Normoalbuminuria	Metabolite profiles of 24-h urines	Acylcarnitines, acylglycines, and metabolites related to tryptophan metabolism were discriminating metabolites for progression to micro- or macroalbuminuria	No adjustments
Ng et al. [134]	*N* = 90T2D	Cross-sectional	Varying levels of eGFR	Octanol, oxalic acid, phosphoric acid, benzamide, creatinine, 3,5-dimethoxymandelic amide, and *N*-acetylglutamine	Able to discriminate low vs normal eGFR	Age at diagnosis, age at examination, baseline serum creatinine
Han et al. [135]	*N* = 150 (*n* = 120 T2D, *n* = 30 controls)	Cross-sectional	Varying levels of albumin excretion	35 plasma nonesterified and 32 esterified fatty acids	Able to discriminate albuminuria status	No adjustments

Adapted from Colhoun, H.M., Marcovecchio, M.L. Biomarkers of diabetic kidney disease. *Diabetologia. 2018;***61:**996–1011

The indirect diagnostic measures of diabetic kidney disease (albuminuria, eGFR) and the heterogeneity of risk factors have complicated the definition of DKD as a phenotype in genetic analysis and have probably contributed to limited and inconsistent findings [70].

However, in recent years, a few large-scale genome-wide association studies (GWAS) have been done in attempt to further identify genes that are associated with diabetic kidney disease.

The first GWAS to identify genome-wide significant loci was reported by the Genetics of Nephropathy – An International Effort (GENIE) consortium in 2012 [71]. This was a meta-analysis of genome-wide association studies (GWAS) of type 1 diabetes with diabetic nephropathy comprising ~2.4 million single nucleotide polymorphisms (SNPs) in 6691 individuals. There were two SNPs that were found to be associated with ESRD: rs7583877 in the *AFF3* gene ($P = 1.2 \times 10^{-8}$) and an intergenic SNP on chromosome 15q26 between the genes *RGMA* and *MCTP2*, rs12437854 ($P = 2.0 \times 10^{-9}$). Data suggest that *AFF3* influences renal tubule fibrosis via the transforming growth factor-beta (TGF-β1) pathway. For the phenotype of diabetic nephropathy, a strong association was found for an intronic SNP in the *ERBB4* gene which has been purported to be involved in renal fibrosis as well.

The largest GWAS on DKD was published by the Diabetic Nephropathy Collaborative Research Initiative (DNCRI) led by the GENIE consortium in 2019 [72]. Data from over 19,000 individuals with type 1 diabetes with and without kidney disease were analyzed. There were 16 new loci identified that were associated with diabetic kidney disease at genome-wide significance. The strongest signal was from a missense coding variant (rs55703767) in *COL4A3*, a gene that encodes a component of the glomerular basement membrane that, when mutated, causes the progressive inherited nephropathy Alport syndrome.

For DKD in type 2 diabetes, a GWAS was conducted by the Surrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools (SUMMIT) consortium [73]. The principal dichotomous analysis involved 5717 type 2 diabetes subjects (T2D), 3345 with DKD. The strongest signal was identified near GABRR1 (rs9942471, $P = 4.5 \times 10^{-8}$) which is associated with microalbuminuria in European T2D patients. However, no replication of this signal was observed in Asian subjects with T2D or in the equivalent type 1 diabetes analysis. The authors concluded that despite challenges in addressing phenotypic heterogeneity, access to increased sample sizes may continue to provide more robust inference regarding risk variant discovery for DKD.

In African Americans, who are disproportionately affected with ESKD, an analysis was performed on 3432 T2D-ESKD and 6977 non-diabetic non-nephropathy controls [74]. Six independent variants located in or near *RND3/RBM43*, *SLITRK3*, *ENPP7*, *GNG7*, and *APOL1* achieved genome-wide significant association ($P < 5 \times 10^{-8}$) with T2D-ESKD.

A summary of genome-wide association studies loci reaching genome-wide significance for diabetic kidney disease is presented in Table 8.3.

Table 8.3 Genome-wide association studies loci reaching genome-wide significance for diabetic kidney diseases

SNP	Reported gene	*P* value	Reported phenotype (total *n* or cases vs controls)	Diabetes population	References
rs7583877	*AFF3*	1.2×10^{-8}	ESKD (1399 vs 5253)	T1D	[56]
rs12437854	15q26 intergenic – *RGMA*, *MCTP2*	2.0×10^{-9}	ESKD (1399 vs 5253)	T1D	[56]
rs4972593[a]	2q31 intergenic – *SP3*, *CDCA7*	3.9×10^{-8}	ESKD (688 vs 2009)	T1D	[136]
rs1564939[b]	*GLRA3*	4.3×10^{-10}	24-h urinary albumin excretion rate (3612)	T1D	[137]
rs12523822[c]	6q25 intergenic – *SCAF8*, *CNKSR3*	1.3×10^{-8}	DKD (5226 vs 8510)	T1D + T2D (not all controls had diabetes)	[138]
rs13329952[d]	*UMOD*	2.5×10^{-8}	eGFR (16,477)	T1D + T2D	[139]
rs56094641[e]	*FTO*	7.7×10^{-10}	Diabetic nephropathy (4022 vs 6890)	T2D	[140]
rs9942471	*GABRR1*	4.5×10^{-8}	Microalbuminuria (1989 vs 2238)	T2D	[58]
rs72858591[f]	*RND3/RBM43*	4.5×10^{-8}	ESKD (3432 vs 6977)	T2D cases vs non-diabetic controls	[59]
rs58627064[f]	*SLITRK3*	6.8×10^{-10}	ESKD (3432 vs 6977)	T2D cases vs non-diabetic controls	[59]
rs142563193[f]	*ENPP7*	1.2×10^{-8}	ESKD (3432 vs 6977)	T2D cases vs non-diabetic controls	[59]
rs142671759[f]	*ENPP7*	5.5×10^{-9}	ESKD (3432 vs 6977)	T2D cases vs non-diabetic controls	[59]
rs4807299[f]	*GNG7*	3.2×10^{-8}	ESKD (3432 vs 6977)	T2D cases vs non-diabetic controls	[59]
rs9622363[f]	*APOL1*	1.4×10^{-10}	ESKD (3432 vs 6977)	T2D cases vs non-diabetic controls	[59]

rs55703767	*COL4A3*	5.3×10^{-12}	Diabetic nephropathy (4948 vs 12,076), all vs control (7247/12,053), CKD + diabetic nephropathy (2897/11,766), macroalbuminuria (2751/12,124)	T1D	[57]
rs12615970	*COLEC11*	9.4×10^{-9}	CKD (4266 vs 14,838)	T1D	[57]
rs142823282	*TAMM41*	1.1×10^{-11}	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs145681168	*HAND2-AS1*	5.4×10^{-9}	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs118124843	*DDR1*	3.4×10^{-8}	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs77273076	*MBLAC1*	1.0×10^{-8}	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs551191707	*PRNCR1*	4.4×10^{-8}	ESKD vs macroalbuminuria (2187 vs 2725)	T1D	[57]
rs144434404	*BMP7*	4.7×10^{-9}	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs115061173	*LINC01266*	4.1×10^{-8}	ESKD vs control (2187 vs 12,101)	T1D	[57]
rs116216059	*STAC*	1.4×10^{-8}	ESKD vs non-ESKD (2187 vs 17,219)	T1D	[57]
rs191449639	*MUC7*	1.3×10^{-8}	Diabetic neuropathy (4948 vs 12,076)	T1D	[57]
rs149641852	*SNCAIP*	1.4×10^{-8}	CKD extreme (2235 vs 14,993)	T1D	[57]
rs183937294	*PLEKHA7*	1.7×10^{-8}	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs61983410	14q12 intergenic – *STXBP6*, *NOVA1*	$3.1 \times 10^{-8-}$	Microalbuminuria (2447 vs 12,113)	T1D	[57]
rs113554206	*PAPLN*	8.5×10^{-9}	Macroalbuminuria (2751 vs 12,124)	T1D	[57]
rs185299109	chr18p11intergenic – *LINC00470*, *METTL4*	1.3×10^{-8}	CKD (4266 vs 14,838)	T1D	[57]
rs149131600[g]	*HPN*	$P_{diabetes} = 3.5 \times 10^{-8}$	UACR (554,659 general population, 46,939 individuals with diabetes)	Unspecified	[141]
rs6688849[g]	1p33 intergenic – *FOXD2*, *TRABD2B*	$P_{diabetes} = 4.1 \times 10^{-9}$	UACR (564,135 general population, 51,215 individuals with diabetes)	Unspecified	[65]
rs74375025[g]	*CUBN*	$P_{diabetes} = 1.1 \times 10^{-24}$	UACR (558,518 general population, 50,641 individuals with diabetes)	Unspecified	[65]
rs790093h	*GCKR*	$P_{diabetes} = 1.5 \times 10^{-13}$	UACR (563,291 general population, 51,515 individuals with diabetes)	Unspecified	[65]

(continued)

Table 8.3 (continued)

SNP	Reported gene	*P* value	Reported phenotype (total *n* or cases vs controls)	Diabetes population	References
rs59825600[h]	*KAZN*	$P_{diabetes} = 3.6 \times 10^{-8}$	UACR (549,562 general population, 40,668 individuals with diabetes)	Unspecified	[65]
rs6706313[h]	*MIR4432HG-BCL11A*	$P_{diabetes} = 2.8 \times 10^{-8}$	UACR (564,068 general population, 51,162 individuals with diabetes)	Unspecified	[65]
rs17137004[h]	*FOXP2*	$P_{diabetes} = 2.7 \times 10^{-8}$	UACR (563,167 general population, 51,294 individuals with diabetes)	Unspecified	[65]
rs4258701[h]	*CDH2*	$P_{diabetes} = 1.1 \times 10^{-8}$	UACR (564,246 general population, 51,328 individuals with diabetes)	Unspecified	[65]

CKD, chronic kidney disease; DKD, diabetic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio

Adapted from Cole, J.B., Florez, J.C. Genetics of diabetes mellitus and diabetes complications. Nat Rev. Nephrol. 2020;16:377–390

[a]Female specific. [b]Replicated in Finnish cohort but not in other cohorts of European ancestry. [c]Trans-ethnic meta-analysis [d]Also significant in the primary analysis in the general population. [e]Genome-wide association study in Japanese cohort, not replicated in European cohort. [f]Remained significant after removing loci with $P < 0.05$ with T2D. [g]Trans-ethnic meta-analysis; significant in the primary meta-analysis in the general population but with a larger effect in diabetes subset and replicated in other studies. [h]Trans-ethnic meta-analysis; not significant in the primary meta-analysis in the general population

Conclusion

Biomarkers other than UACR and eGFR have potential for early detection of diabetic kidney disease but have not yet reached clinical practice. Further studies are needed to investigate the utility and practicality of either a single or a panel of biomarkers. Several genome-wide association studies have identified loci that are associated with DKD using larger sample sizes. However, genetic studies in diverse populations for fine mapping and population-specific associations are needed.

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Chapter 9
Atypical Presentations

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Overview of Traditional and Nontraditional Concepts in Diabetic Kidney Disease

Diabetic nephropathy (DN) develops in approximately 40% of patients who are diabetic and remains the leading cause of end-stage renal disease (ESRD) in the world. Diabetes mellitus results from a group of anomalies that are caused by altered efficiency in the synthesis and release of insulin and resistance to the action of insulin and mediated by autoimmune and hereditary as well as environmental factors that induce local mutations. The diverse clinical manifestations include atherosclerotic vascular disease, heart disease, neuropathy, retinopathy, hypertension, dyslipidemia, and renal insufficiency. The metabolic disturbances associated with diabetes lead to glomerular hypertrophy, hyperfiltration (HF), intra-glomerular hypertension, accumulation of advanced glycated proteins, expression of reactive oxygen species (ROS), proliferative cytokines, microvascular disease, glomerulosclerosis, tubulointerstitial inflammation, fibrosis, and progressive diabetic nephropathy.

The natural history of "typical" diabetic nephropathy in type 1 diabetes mellitus (T1DM) has been classically described in stepwise stages, during which

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pathophysiologic and clinical changes develop over extended periods of time. The first 5–10 years after the onset of T1DM are associated with "silent" changes in renal structure and function, which include glomerular hypertrophy, hyperplasia, increased kidney size, hyperfiltration (HF) with increased glomerular filtration rate (GFR), and onset of microalbuminuria defined as 30–300 mg of albumin/24 h or 20–200 ug/min. The "typical" pathologic changes include mesangial cell hypertrophy, hyperplasia, increased mesangial matrix, thickening of the glomerular basement membrane (GBM), and tubular basement membrane (TBM), as well as varying degrees of tubulointerstitial injury and fibrosis. After the "silent" changes in the kidneys, microalbuminuria traditionally transitions into the macroalbuminuric ranges of >300 mg albumin/24 h with gradually decreasing GFR in the ensuing years. It has become apparent that about 25% of patients develop diabetic nephropathy in a nontraditional manner without manifesting the traditional transition from micro- to macroalbuminuria with gradual decrease in GFR. This chapter will focus on "atypical" aspects of the diabetic kidney and highlighting areas where most significant advances have been made in the recent past.

Hyperfiltration and Increased GFR Herald the Onset of Diabetic Kidney Disease

Glucose is normally transported in the proximal convoluted tubule (PCT) by sodium-glucose cotransporters SGLT-2 in the most proximal S1 segment and SGLT-1 in the terminal S2 and S3 segments of the PCT. These two transporters reabsorb approximately 97% and 3% of the filtered load of glucose, respectively. At normal serum glucose levels, any filtered glucose is completely reabsorbed and is thus absent from urine. As serum glucose progressively increases, glucose appears in the urine when the filtered load of glucose exceeds the maximum resorptive capacity of the cotransporters at serum glucose levels that exceed 180 mg/dl.

The typical pathophysiology of diabetic kidney disease starts within 3 days after the onset of hyperglycemia when there is glucose-induced overexpression of ornithine decarboxylase (ODC), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) which induce hypertrophy and hyperplasia of the proximal tubule cells in the S1 segment with increased expression of SGLT-2 [1]. In this setting, the increase in filtered load of glucose is cotransported with sodium to decrease sodium delivery to the distal tubule. Eventually less filtered sodium is delivered to the macula densa which activates the tubulo-glomerular feedback mechanism, resulting in dilatation of the glomerular afferent arteriole via nitric oxide-.

mediated inhibition of adenosine to increase glomerular blood flow (to correct a "perceived" decrease in filtered sodium) and initiates a PDGF-mediated increase in glomerular size, which in combination with the increased hydrostatic glomerular pressure results in HF to increase the GFR of both kidneys [2]. The supernormal

GFR is a precursor to a progressive decline in GFR as the diverse pathologic mechanisms affect the renal architecture.

Counterintuitively an increase in salt intake will eventually overwhelm the PCT threshold for sodium-glucose transport, increase delivery of sodium distally to inhibit the macula densa, and constrict the afferent arteriole to eliminate the HF, which is referred to as the "salt paradox" to decrease glomerular HF in diabetes [3]. Ironically, the SGLT-2 inhibitors block proximal sodium glucose cotransport to deliver more sodium to the macula densa to mimic the "salt paradox" by constricting the afferent arteriole to reduce intra-glomerular pressure and eliminate the HF while reducing serum glucose.

Because SGLT-2 inhibitors lack the dose-limiting adverse effects of other therapies (such as hyperkalemia, renal dysfunction, and hypotension), they provide an additional tool in the prevention and treatment of CKD among patients with type 2 diabetes mellitus (T2DM). However, the protective/beneficial effects of SGLT-2 inhibitors on cardiorenal outcomes may be exerted by mechanisms that are not directly related to a reversal of the HF. When SGLT-2 inhibitors are first administered, there is increasing amount of glucose in urine that initially overwhelms the downstream SGLT-1 transporters in the S3 segment of the PCT to increase sodium and glucose delivery to the macula densa, which activates the tubulo-glomerular feedback to constrict the afferent arteriole, eliminate the hyperfiltration, and normalize GFR.

The administration of an SGLT-2 inhibitor to a normal nondiabetic subject initially increased glucose excretion substantially to 94% of the filtered glucose. However, fractional glucose reabsorption (FGR) does not decrease by 97% but eventually decreasing to ~40–50%, suggesting there is a compensatory increase in SGLT-1 activity downstream or incomplete inhibition of SGLT-2 [4, 5]. The renoprotective effects of SGLT-2 inhibition relate to decreased proximal convoluted tubule reabsorption of Na-glucose-water, as well as to an additional effect of impeding the sodium-hydrogen exchanger (NHE) [6]. More filtrate with sodium chloride, glucose, and water is delivered to the macula densa which initiates the tubuloglomerular feedback mechanism to restrict "further excessive filtration," constricting the afferent arteriole to reduce intra-glomerular filtration pressure and GFR. An initial reduction in GFR after instituting SGLT-2 inhibition is functional and reversible, often returning to near baseline in diabetic patients with eGFR <60 ml/min/1.73 m^2 [7].

It is becoming apparent that the cardiorenal protection offered by the SGLT-2 inhibitors is not completely due to the modest decrease in serum glucose, and transient elimination of HF. Research is ongoing to discover the pleiotropic effects of the SGLT-2 inhibitors, which will be discussed in greater detail in a separate chapter. These other actions may include reductions in plasminogen activator inhibitor-1 (PAI-1), a pro-thrombotic agent, inhibition of the sodium-hydrogen ion exchanger, or increasing glucagon levels by activating SGLT-1 in alpha cells of the pancreas [8, 9, 10, 11]. Amelioration of DN by SGLT-2 inhibitors in mice has been attributed to the stabilization of mesangial cells that is independent of its glucose-lowering effect

[12]. It is known that high glucose levels stimulate de novo synthesis of diacylglycerol (DAG), which depends on excess glucose entry into cells via glucose transporters, which is followed by protein kinase-C (PKC) activation and subsequent nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway-driven ROS overproduction in various vascular cells [13, 14, 15, 16].

DAG-PKC activation by elevated glucose in mesangial cells (MCs) increases expression of NOX-4 (also known as NADPH oxidase) and produces superoxide free radicals as well as increased expression of transforming growth factor-β (TGF-β) and fibronectin and possibly overproduction of extracellular matrix by MCs [17, 18]. Maki confirmed the presence of SGLT-2 in mouse MCs and found that SGLT-2 inhibitors (canagliflozin, ipragliflozin) inhibited glucose consumption in the medium under high-glucose conditions, inhibited PKC-NADPH oxidase pathway-induced ROS production, and inhibited the expression of TGF-β1 and fibronectin, all of which have been associated with mesangial expansion in diabetic kidneys. It had previously been reported that impaired contractility of MCs induced by a high-glucose or diabetic state could cause glomerular HF [12, 19].

The benefits of empagliflozin were reported in the EMPA-REG outcome study, which demonstrated a 38% relative risk reduction in death from cardiovascular (CV) cause [20]. In the "Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction" trial, the risk of worsening heart failure or death was lower by 26% in dapagliflozin-treated patients versus controls, irrespective of the presence or absence of diabetes mellitus [21].

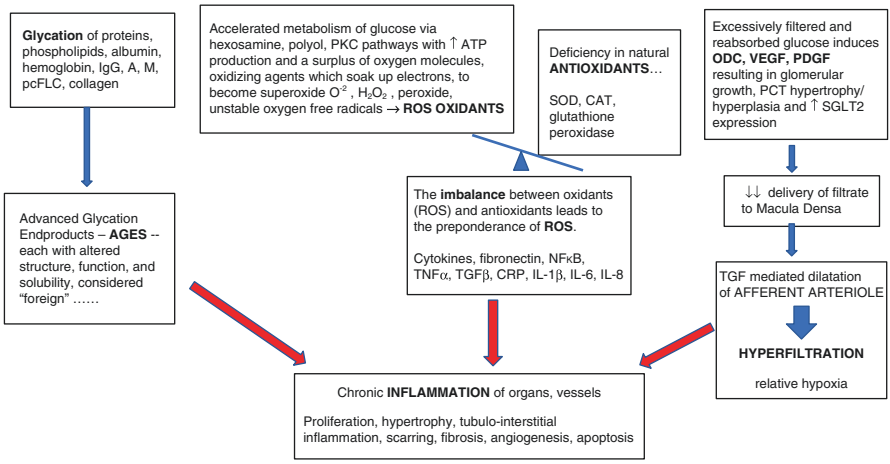
The CREDENCE study was a double-blind trial in 4401 patients who were treated with canagliflozin or placebo. The mean age of patients was 63 yrs. old, all having T2DM for an average of 15.8 years and had GFR between 30 and 90 cc/min, all had albuminuria, and all were treated with angiotensin-converting enzyme inhibitors (ACE inhibitors, or ACEi). The composite of outcomes included (a) progression to ESRD (dialysis or transplant); (b) doubling of serum creatinine; and (c) renal or CV death. The relative risk (RR) of ESRD was 32% lower in the canagliflozin group. Among secondary end points, the risks of CV death, myocardial infarction, or stroke (HR, 0.80; 95% CI, 0.67–0.95; $P = 0.01$) and for hospitalization for heart failure (HR, 0.61; 95% CI, 0.47–0.80; $P < 0.001$) were lower among those taking canagliflozin. In conclusion, among patients with T2DM and kidney disease, those in the canagliflozin group had a lower risk of kidney failure and CV events than those in the placebo group during a median follow-up of 2.62 years. The study was stopped early after a planned interim analysis [22]. In the Declare-Timi 58 study, T2DM patients with CV risk were treated with dapagliflozin vs. placebo. Dapagliflozin significantly reduced the proportion of patents with "fast-declining eGFR" (estimated glomerular filtration rate) defined as a decrease in eGFR of at least 3 mL/min/1.73m^2; dapagliflozin-treated patients experienced a 28.6% "fast decline" in GFR as compared to 37.1% of placebo-treated patients [23].

The Roles of Glucotoxicity, Oxidative Stress (OS), and Inflammation in Diabetic Kidney Disease

Biological oxidation is an energy-producing reaction at the cellular level when one organic compound transfers a negative electron to another compound or to oxygen. A compound is oxidized when it loses an electron and is reduced when it gains an electron. These "redox" reactions are driven by donor oxidoreductase "dehydrogenases" and receptor reductases such as "oxidases" in which case O2 is the acceptor. These reactions are the main source of cellular energy. A free radical is an oxygen molecule that has lost an electron. Since it is now in an unstable state, it consumes energy as it attempts to steal an electron from another molecule. The amount of energy created depends on the redox potential difference between the electron donor and the electron acceptor. OS represents an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects by antioxidants. OS can be induced by many different mechanisms such as infections, trauma, ingestions, altered bowel flora, and glucose intolerance – the initial insult may stimulate excessive oxidation with a predominance of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [combined abbreviation for ROS and RNS is RONS], which collectively create unstable reactive free radicals [24]. Oxidation and subsequent inflammation are crucial in defense mechanisms against infections, but if not properly regulated, they may initiate several deleterious effects such as cytokine overproduction and an increase in pro-inflammatory and oxidative stress mediators [25]. The normally low amounts of pro-oxidative agents, which have important defensive roles, are inactivated, and kept in balance by natural intracellular antioxidants, or "scavenger" enzyme systems such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) which interact with the unstable free radicals to neutralize their ability to damage the vasculature/endothelium and nearby cells. There is ongoing research to elucidate their potential role in promoting cell regeneration [26, 27].

The hyperglycemia-mediated increase in ROS includes peroxides, superoxide, singlet oxygen, and H_2O_2 which can corrupt the cellular machinery, redirecting the cells to overproduce pro-inflammatory cytokines and pro-carcinogenic genes, causing damage to proteins, and forming advanced glycation end products (AGEs). The ROS may alter DNA with modification of base pairs, creating covalent cross-links and single- and double-stranded breaks and impairing cellular function by redirecting transcription factors to the point where nearby cells are destroyed or proliferate. The consequences include injury to the pancreas, the renal microcirculation, the endothelium (atherosclerosis), the heart, autoimmunity, and the nervous system and the induction of tumors. And the ROS further enhance the inflammatory response by triggering other pro-inflammatory mediators such as activating nuclear factor-kappa B (NFκB). Biological oxidation can be considered the analogy of rusting (adding oxygen to iron and getting rust), i.e., the aging process of the body occurring at the cellular level [28]. (See Table 9.1)

Table 9.1 Chronic HYPERGLYCEMIA



Hyperglycemia suppresses the monocyte membrane receptor (CD-33) which normally downregulates cytokine production, resulting in increased production of tumor necrosis factor-α (TNFα), interleukin IL-1β (IL-1β), and interleukin-8 (IL-8) [29]. In addition, hyperglycemia leads to glycolysis and mitochondrial overproduction of superoxide (O_2^-) and other ROS which directly activate PKC and NFκB. PKC increases the production of extracellular matrix, vascular permeability, and vascular cell proliferation, leading to thickening of the GBM, tubulointerstitial fibrosis, glomerulosclerosis, and microvascular disease in the kidneys and eyes [30, 31, 32, 33].

The renal ROS are produced by the mitochondrial respiratory chain enzymes, such as NADPH oxidase (NOX). The upregulation of NOX isoforms (NOX-1, NOX-2, NOX-4, and NOX-5) is mainly responsible for the oxidative stress that induces endothelial damage and fibrosis in diabetic nephropathy [34, 35, 36]. The unstable superoxide anion (O_2^{--}) and peroxynitrite ($ONOO^{--}$) are derived from reactive nitrogen species (RNS), generated by the reduction of molecular oxygen through the action of the NOX enzyme complex. As soon as O2- is formed, it is converted into the highly toxic hydrogen peroxide H_2O_2.

Diabetic nephropathy is also susceptible to other "atypical coconspirators" such as gut-derived toxins (indoxyl sulfate (IS), p-cresol (PC), and p-cresol sulfate (PCS)) which increase OS and inflammatory markers C-reactive protein (CRP), NFκB, IL-6, IL-1, cyclooxygenase-2, TNFα, and inducible nitric oxide synthase (iNOS) [37, 38]. Viral and/or bacterial infections can contribute to inflammatory injury of tissues by increasing oxidative stress and cause DNA damage in the host [39]. Since high OS triggers the formation of ROS and AGEs, it follows that diabetes and conditions of chronic high OS will further accelerate this spontaneous process [40, 41].

AGEs, Oxidative Stress and the Impact on the Diabetic Kidney

Endogenous AGEs

The impact of diabetes on various organs is strongly related to hemoglobin A1c [HgbA1c, glycated hemoglobin]. Glycation of hemoglobin is a nonenzymatic condensation reaction between glucose and β-chain N terminal, which produces an unstable Schiff base, which in turn rearranges to form 1-deoxyfructose, an Amadori product known as HgbA1c or referred to as an advanced glycation end product (AGE) [42, 43]. Chronic hyperglycemia in diabetes causes increased glycation of hemoglobin to produce HgbA1C and proteins which contribute to diabetic nephropathy, retinopathy, neuropathy, and microvascular damage [44]. HgbA1c is utilized clinically to evaluate the degree of glycemic control in a diabetic patient, its level reflecting a 3-month average of serum glucose concentrations [45].

Reducing the level of HgbA1c to <7.5% with intensive insulin therapy blunted the decrease in GFR in T2DM with typical diabetic glomerular lesions [46].

Extensive evidence demonstrates that AGEs, including HgbA1C, can cause tissue injury, causally linking them to long-term diabetic complications [47, 48, 49]. Other proteins also become glycated, including albumin, apolipoprotein B, IgG, IgA, and IgM, which are proatherogenic [50, 51, 52]. Various proteins (and likely their glycated counterparts) appear in the urine and are reabsorbed/endocytosed via the megalin-cubilin multi-receptor complex [53]. Glomerular ultrafiltration of excessive amounts of plasma-derived proteins (as well as glycated proteins) incites an inflammatory and fibrogenic response in the tubulo-interstitium leading to renal functional loss [54]. AGEs can bind to cellular receptors for AGEs (RAGEs) and cause OS, increasing the production of intracellular free radical intermediates (especially H_2O_2) as well as activating inflammatory pathways in vascular endothelial cells [55, 56, 57, 58]. The RAGEs are a multiligand member of the immunoglobulin superfamily of cell surface receptors that binds AGEs and other molecules including β-amyloid peptides and β-sheet fibrils [59]. This leads to activation of NFκB and transcription of many pro-inflammatory genes in addition to initiating a self-renewing vicious cycle, which perpetuates pro-inflammatory signaling [60]. The RAGE-mediated uptake of AGEs can promote cell and tissue injury, cell differentiation, senescence, and tumorigenesis in specific cell types [61, 62, 63]. AGEs also accumulate in the retinal pericytes to induce growth retardation and apoptosis while stimulating VEGF expression, which may play a significant role in the pathogenesis of proliferative diabetic retinopathy [64].

One of the most abundant endogenous proteins to be glycated is collagen, and this leads to skin aging [65, 66]. Accumulating AGEs become entrapped in kidney cells and initiate structural and physiological changes that contribute to DN.

AGE-affected proteins have altered conformation, function, charge, and solubility which lead to molecular dysfunction and disrupted interactions with other local

proteins and cells, which can lead to inflammation and damage to tissues and vasculature [67, 68, 69, 70]. Intact immunoglobulins and/or light chains can undergo glycosylation which alters their biological activity and pathogenicity [71, 72, 73]. Accumulation of glycated polyclonal free light chains (pcFLCs) in the kidney may contribute further to DN in addition to injuring the kidney in a manner that is similar to that induced by non-glycated monoclonal free light chains.

Exogenous AGEs

In addition to endogenous formation of AGEs, exogenous dietary AGEs are absorbed during digestion, circulate, and eventually get deposited in various tissues. Exogenous, dietary, low molecular weight AGEs are absorbed in the gastrointestinal (GI) tract. They are present in foods that have been "processed" which includes heating, cleaning, colorizing, cooking, drying, salting, grilling, frying, toasting, smoking, and pickling. These exogenous AGEs can accumulate when ingested in excess, and correlate with indicators of inflammation and oxidative stress, including NFκB, TNFα, and CRP [74]. The destructive effects of RAGE-mediated uptake of AGEs can be blocked by other cell surface receptors, advanced glycated end-product receptor-1, advanced glycated end-product receptor-2, and advanced glycated end-product receptor-3 (AGER-1, AGER-2, and AGER-3), which regulate endocytosis and degradation of AGEs and counteract the deleterious effects of RAGE-mediated uptake of AGEs [75, 76, 77, 78]. Oral AGEs can promote insulin resistance and diabetes by depleting the antioxidant defense provided by AGER-1 [79]. Alternatively, an AGE-restricted diet can sustain a higher level of AGER-1-mediated antioxidant activity and may mitigate insulin resistance [47].

Role of Polyclonal Free Light Chains (pcFLCs) in Diabetic Nephropathy

The demonstration of increased circulating pcFLCs in diabetes raises the interesting possibility that they might be similarly putative as monoclonal free light chains (mcFLCs). It may be possible that pcFLCs are glycated and behave similarly to other AGEs, causing inflammation and tissue injury. There is ample evidence that mcFLCs from patients with multiple myeloma are endocytosed via cubilin-megalin receptors in the PCT cells and activate NFκB, which induces the production and release of inflammatory cytokines including interleukins IL-6 and IL-8, ROS, and monocyte chemoattractant protein-1 (MCP-1) to induce tubulointerstitial inflammation, fibrosis, and renal injury [80].

The concept of the putative nature of mcFLCs inducing inflammation and fibrosis was further demonstrated and strengthened by utilizing an in vivo model of

infusing mcFLCs in 5/6 nephrectomized mice which is superior to in vitro systems where variables can be controlled without permitting potential competing variables to affect outcomes. This inflammatory response to mcFLC has been shown to be as much as a fivefold greater than equimolar concentration of albumin, which has been used to support the concept of protein trafficking to induce inflammation and fibrosis of kidneys [81].

The endocytosis of peptides via the cubilin-megalin axis in the PCT may be a common pathway for other proteins such as the pcFLCs to initiate inflammation and renal fibrosis. pcFLCs serve as a biomarker for an active innate immune activity and evidence of increasing organ dysfunction [82].

It is known that urinary pcFLCs increase early in the course of DN and progressively increase in the serum as GFR progressively declines [83, 84]. pcFLCs are derived from normal B-cells/plasma cells and are produced in excess of intact immunoglobulins in response to antigenic challenge [85]. Light chains, independent of their source, bind to cubilin and megalin glycoprotein receptors in the proximal renal tubule and are endocytosed [86]. Dispenzieri et al. showed that a non-clonal elevation of combined FLC (sum of FLC) predicted an inferior overall survival in a general population, independent of renal function, sex, and age [87].

In a study by Kalara et al., 822 patients with stages 3–5 CKD (non-dialysis) were recruited to evaluate the effect of cFLC on outcomes in CKD. They concluded that increased IgFLC levels (non-paraprotein derived, and in a normal ratio) were an independent risk factor for mortality and progression to ESRD [88]. The mechanism by which cFLC (as a biomarker of inflammation) predicts progression of CKD or survival is unknown. It may be possible that chronic inflammation, overwhelming the antioxidant capacities of the patient, induces overproduction of pcFLC. They appear in the filtrate and after endocytosis may initiate cytokine production, local inflammation, and injury to glomerulus or tubules, and represent a nontraditional risk for CKD progression.

pcFLCs are not "inert." Redegeld reported that pcFLCs elicit immediate hypersensitivity-like responses, with mast cell degranulation, plasma extravasation, and cutaneous swelling similar to the induction of immediate hypersensitivity reactions by intact IgE and IgG [89]. It is uncertain whether pcFLCs are only a marker of poor outcomes or possess a pathogenic role in causing cellular dysfunction. The metabolism of pcFLCs occurs in many organs including the kidney, liver, intestines, spleen, and muscle – all organs expressing the neonatal Fc receptor (FcRn). Renal megalin, cubilin, and FcRn form an endocytic protein complex to internalize filtered albumin and IgG proteins as well as FLC which are then transported from endosomes to lysosomes where they are degraded [90, 91, 92]. FcRn reduces lysosomal degradation of endocytosed albumin and pcFLCs so they can be recycled to the central circulation [93]. In the absence of intracellular FcRn, the endocytosed pcFLCs undergo lysosomal proteolytic degradation [94]. After endocytosis excessive amounts of proteins can accumulate in the lysosomes and induce inflammation and fibrogenesis in the interstitium [95]. Glucotoxicity and OS stimulate plasma cells to produce more immunoglobulin free light chains (IgFLC) and contribute to the so-called light chain theory of DN. pcFLCs are a marker of the activity of the

innate immune system, and excessive pcFLCs indicate an underlying chronic inflammatory state and may represent a marker of chronic inflammation in the diabetic patient [96]. Groop suggested that urinary glycation of kappa light chains resulted in their aggregation into high molecular weight polymers which could interfere with the normal tubular reabsorptive processes and lead to chronic inflammation [97]. Increased intratubular protein content causes changes in the tubule cells and interstitium, possibly induced by an overexpression of an isoform of VEGF, an inflammatory response protein [98, 99, 100].

Studies have shown that pcFLCs can target cells in a range of autoimmune and inflammatory diseases affecting the colon, neurons, and lung alveolar cells [101, 102, 103]. It appears that pcFLCs, like intact immunoglobulin molecules, initiate a chain of events such as opsonization, phagocytic recruitment, complement activation, antibody-dependent cell-mediated activity, agglutination, and hypersensitivity reactions. The combined total of pcFLC, which includes kappa and lambda light chains, appears to serve as a biomarker for increased immune activity and evidence of increasing organ dysfunction. Ritchie evaluated 872 patients with stage 3–5 CKD, measuring cFLC, and showed a strong independent relationship between high cFLC levels, mortality, and progression to ESRD [88]. High levels of cFLC have been determined to be an independent risk factor for death in a study from the United Kingdom, as well as a predictor of prognosis in heart failure, concluding that cFLC levels represent a nontraditional biomarker of CKD which is superior to CRP [104, 82].

It appears that pcFLCs are not innocent "bystanders" and may be co-opted or altered in chronic inflammatory states and then contribute to the inflammation, vascular disease, and renal parenchymal changes in DN. The combination of increased pcFLCs and increased mortality as well as progressive kidney disease suggests a role for FLCs in the pathogenesis of DN, and that the level of pcFLC is not merely a marker of inflammation.

Antioxidants and Inhibition of Inflammation

Natural antioxidants are currently being investigated for their ability to possibly induce vascular cell regeneration by impacting stem cells to differentiate into functional endothelial cells and smooth muscle cells. Besides the presence of natural antioxidants in vascular cells, natural antioxidants are also found in fruits, vegetables, legumes, and medicinal plants that interact with unstable free radicals ROS and RONS, neutralizing their oxidative damage on vascular cells, by possible downregulation of cyclin-dependent kinase (CDK) inhibitors and allowing upregulation of antioxidants such as CDK2, CDK4, and CDC2. These effects may prevent widespread vascular diseases including coronary arteries and the microvasculature. Other environmental antioxidants include carotenoids – carotenoids are found in colored fruits and green vegetables and include β-carotene, lutein, zeaxanthin,

astaxanthin, and lycopene. β-Carotene and lycopene have been shown to decrease TNFα-mediated ROS generation at the.

endothelium and increase the bioavailability of the vasodilator nitric oxide (NO) [105, 106]. Autophagy is a natural, highly regulated process that regulates proliferation and differentiation of endothelial progenitor cells (EPCs) that line blood vessels, recycling cytoplasm and disposing of excess or defective organelles. However, glucose-mediated OS disproportionately increases autophagy which leads to endothelial cell dysfunction and premature death. In vivo diabetic animal studies revealed that EPC functions of mobilization, differentiation, and tube formation are disrupted. In the diabetic patient, AGEs increase endothelial progenitor cell (EPC) autophagy which, in vitro, is inhibited by lycopene treatment of EPCs, increasing their proliferation and reducing their apoptotic tendencies [32].

Vitamin D – Vitamin D may derive from the diet or be synthesized cutaneously. Vitamin D2 is produced by plants, and vitamin D3 is produced in the skin. Both are inert and require conversion to 25-hydroxy vitamin D in the liver and then to the biologically active 1,25-dihydroxy vitamin D. 1,25-dihydroxy vitamin D restores normal vascular function by reendothelialization of the damaged arterial wall. Vascular cells including endothelial cells, smooth muscle cells (SMCs), and pericytes express vitamin D receptors (VDR) [107]. VDR activation by vitamin D also reduces renal inflammation in experimental DN and suppresses inflammation and fibrosis by inhibiting several inflammatory pathways [108]. 1,25-dihydroxy vitamin D deficiency is common in CKD due to reduced availability of 1α-hydroxylase activity.

Vitamin E – Tocopherols are fat-soluble antioxidants found in vegetable oils, α-tocopheroxyl being the most abundant, which preserves endothelial integrity, inhibits vascular SMC proliferation, and regulates endothelial function [109, 110].

Selenium – Selenium contributes to the physiological balance of ROS and antioxidants, increasing ROS, and enhances the differentiation of human embryonic stem cells (ESC) to vascular progenitor cells. The reprogramming of iPSCs (induced pluripotent stem cells) is associated with generation of high ROS levels [111]. Several reports showed that, in comparison with somatic precursor cells, iPSCs exhibit the following criteria: (1) marked protection against nuclear and mitochondrial DNA (mtDNA) damage and (2) significantly lower levels of ROS due to upregulation of intrinsic antioxidant enzymes [112, 113]. A physiological level of ROS or oxidative optimum is needed for proper differentiation of stem cells, especially for proper cardiogenesis and vasculogenesis [114]. Selenium is a cofactor for glutathione peroxidases (GSH-Px) which are synthesized in the kidney and are essential for ROS metabolism. A restricted protein diet in advancing CKD often leads to selenium deficiency, and reduced synthesis of the antioxidant GSH-Px. However, as CKD progresses the imbalance between ROS and antioxidants is exacerbated by the loss of nephrons producing GSH-Px rather than a deficiency of selenium. Thus, selenium supplementation should be considered early on in patients

with diabetic nephropathy because a damaged kidney is unable to synthesize GSH-Px, even after supplementation with selenium [115].

Copper – Copper has a significant effect on vascular cell types, reducing apoptosis, increasing vascular endothelial nitric oxide synthase-3 (eNOS), and inhibiting vascular SMC migration and proliferation into the aortic intima of the artery in animal models [116].

Vitamin C – Vitamin C inhibits VSMC proliferation by promoting endothelial cell proliferation in the presence of CAT enzyme, inhibiting free radicals, upregulating the eNOS and SOD activities, and downregulating NADPH oxidase in the aortic wall [117, 118, 119, 120]. NADPH oxidase is normally a dormant membrane-bound enzyme which increases the production of a superoxide free radical when activated by stimuli such as bacterial products and cytokines. Excessive production of this ROS in vascular cells causes cholesterol-laden macrophages (foam cells) to adhere to the artery wall forming the cholesterol plaque [121]. Another role for vit C is suggested in cardiac and vascular regeneration through enhanced reprogramming of iPSCs that can differentiate into various vascular cell lineages, cells that have been shown to differentiate into vascular SMCs and endothelial cells [122, 119].

Polyphenols – Resveratrol is a natural polyphenol, found in many plant species, especially in grapes' skin, as well as in red wines. Resveratrol has beneficial pleiotropic effects including antioxidant activity, antitumor activity, blood pressure (BP) lowering, and increased proliferation and functional activity of endothelial progenitor cells [123, 124, 125].

There are many more plant-derived metabolites which have been associated with beneficial effects in CKD by having direct ROS scavenging properties, downregulation of profibrotic cytokines, and attenuation of renal macrophage infiltration that are beyond the scope of this chapter.

Treatment with RAAS Inhibitors

The maladaptive circulatory response which results in hyperfiltration is the basis for the use of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) which lower intra-glomerular pressure by dilating the efferent arteriole and lowering systemic pressure in the afferent arteriole. In 1993, the Collaborative Study Group reported a significant slowing of the rate of decline in GFR in patients with T1DM and diabetic nephropathy taking captopril versus placebo-controlled patients, as well as a 59% reduction in the risk of combined end points of death, dialysis, and transplantation. The protective effect was independent of blood pressure control [126]. Another ACE inhibitor, enalapril, was shown to attenuate the decline in renal

function and reduced albuminuria in normotensive, normoalbuminuric patients with T2DM [127]. In the RENAAL trial, losartan significantly reduced the incidence of doubling of serum creatinine, ESRD, or death by 16% compared with placebo in combination with "conventional" antihypertensive treatment (i.e., alpha-blockers, beta-blockers, calcium channel blockers, diuretics, and other centrally acting agents) [128]. In a post hoc analysis, the incidence of ESRD was higher in Hispanic and Asian patients than in white and black patients [129]. In a study of 3577 patients with diabetes, aged 55 years or older, who had a previous cardiovascular event but absence of clinical proteinuria, heart failure and low ejection fraction were randomly assigned to take ramipril (10 mg/day) or placebo in the Heart Outcomes Prevention Evaluation study. All the primary outcomes, which included myocardial infarction, stroke, cardiovascular death, total mortality, and revascularization, were significantly reduced, including a 24% reduction in overt nephropathy that was independent of BP control [130]. Although much data suggests a beneficial effect of ACEi or ARBs in the treatment of diabetic nephropathy, the RASS trial of 285 patients with normotensive T1DM and normoalbuminuria, treatment with losartan or enalapril did not slow progression of DN measured as a change in glomerular mesangium volume. The authors suggested that early treatment may possibly be renoprotective but remains to be proven in a prospective trial [131].

It appears that many studies support using ACEi or ARBs early in the treatment of diabetes, for their role in reducing proteinuria, and the progression of DN.

Attention was directed to combine ACEi and ARB, so-called dual RAAS blockade, which failed to show any advantage over unilateral blockade [132, 133].

Clinical studies may be susceptible to the duration of diabetes before entry into the study by duration of the study, dosing of the study medication, concurrent medications, genetic tendencies, concomitant glomerular disease, age, comorbidities, gender, ethnicity, or other unknown confounders which may yield different results. This has resulted in a dearth of studies with different conclusions. However, inhibition of the RAAS in diabetic patients at risk, whether hypertensive or normotensive, with or without albuminuria, appears to reduce the progression of DN [134].

Aldosterone Blockade and Protection Against Diabetic Nephropathy

Elevated glucose activates oxidative stress, leading to kidney damage, but overactivation of the mineralocorticoid receptor (MR) leads to inflammation and fibrosis in the vasculature of the heart, kidney, and brain. Aldosterone production is largely dependent on angiotensin II, but the phenomenon of "aldosterone breakthrough" where serum aldosterone levels return to or exceed baseline levels after initiation of RAAS blockade mitigates the effect of ACEi/ARBs on BP control [135].

Plasma aldosterone concentrations and mineralocorticoid receptor overactivation are associated with an enhanced risk of CV injury by exerting inflammation and fibrosis in multiple organs and tissues including the heart, vessels, kidneys, brain, and peripheral vasculature in preclinical investigations [136, 137]. The interaction between aldosterone and endothelin, together with their regulation on inflammation, OS, and fibrosis contributes to the progression of DN. Death related to cardiovascular (CV) causes is the main competing outcome to development of ESRD in patients with CKD. For patients with CKD stage 3, where eGFR is ≤60.

mL/min/1.73 m2, the risk of death, mainly due to CV events, is over 10 times higher than the risk of progressing to ESRD [137]. Subgroup analyses of previous studies with the two steroidal MRAs spironolactone and eplerenone showed that MR antagonism decreases the risk of CV events and sudden death in patients with HFrEF and impaired kidney function [138]. Similar morbidity and mortality benefits might also accrue in T2D patients with CKD [139].

Spironolactone is associated with gynecomastia and breast pain, which is alleviated by eplerenone. Finerenone is a new nonsteroidal mineralocorticoid receptor antagonist (MRA) with higher selectivity for the MR than spironolactone and stronger binding affinity than eplerenone in vitro [140]. The higher affinity of finerenone to the MR will more effectively inhibit recruitment of transcriptional coactivators involved in the expression of hypertrophic and profibrotic genes as compared to steroidal MRAs [141]. Unlike spironolactone and eplerenone, which reach higher concentrations in renal tissue in comparison with cardiac tissue [31], finerenone is distributed relatively equally between the heart and the kidneys, at least in rodents [142]. In the Antagonist Tolerability Study-Diabetic Nephropathy study, finerenone at a dose of 20 mg daily reduced UACR by 38% in addition to retarding progression of CKD, greater reductions in blood pressure of 3–5 mm Hg, and increasing potassium by only 0.2 mEq/L. The authors concluded that addition of finerenone to the use of an ACEi or ARB among patients with DN had further reductions in urinary albumin-creatinine ratio [143]. In a systematic review, the authors suggested that the beneficial cardiorenal effects of MRAs, including CV risk reduction and delaying CKD progression, may result from the direct antifibrotic and anti-inflammatory effects of finerenone or from the combined improvement in the function of both end organs [144, 145].

Allopurinol

In the last few years, several studies have evaluated allopurinol for its potential role in mitigating the progression of CKD. Studies investigating the use of allopurinol vs. placebo in patients with type 1 DN, stages 1–3, and in patients who had stage 3 or 4 CKD with rapid decline in their estimated GFR or clinically significant proteinuria at baseline have demonstrated no significant effect on the rate of GFR decline [146, 147].

Conclusion

Diabetic kidney disease results from the interplay of several pathologic pathways, starting with hyperfiltration, glucose-induced oxidative stress, oxidative stress-mediated AGE formation, the vicious cycle of AGE-mediated oxidative stress and inflammation, the potential role of reactive pcFLCs, and the ever-present genetic and environmental contributors. Targeted interventions may mitigate some of the ravages of diabetes. A cautionary note to providers who are involved in the care and management of the diabetic patient is to be aware of concomitant medications that the patient is taking. Commonly used medications such as proton pump inhibitors, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and allopurinol may cause allergic tubulointerstitial nephritis and contribute to further renal inflammation in the diabetic patient [148, 149]. Renal injury may occur within 3 days to 3 months. When patients begin taking these and other medications, routine surveillance of serum creatinine seems a prudent approach to prevent nondiabetic CKD.

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Chapter 10
Albuminuria and Proteinuria

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Healthy subjects excrete <150 mg of protein in a 24-h period. Of this protein, only 10–20% is albumin, and the remaining portion is composed of immunoglobulins, enzymes, low-molecular-weight proteins, and peptides as well as Tamm-Horsfall proteins. Thus, normal albumin excretion is extremely small. Routinely used dipsticks measure albumin only, but its detection is not evident until the concentration of albumin exceeds 300 mg. Therefore, routine testing for urinary albumin requires either a chemical method or a dipstick that recognizes only albumin at very low concentrations.

In recent years, the leading cause of proteinuria (albuminuria) in the United States and Europe is diabetic kidney disease (DKD) or superimposed glomerular disease rather than primary glomerular diseases [1, 2]. Proteinuria of glomerular origin represents the most important, singular sign of kidney disease and heralds the onset of clinical DKD. *Not proteinuria but albuminuria is more specific, and is commonly used to define the earliest stages of DKD*. In particular, raised urinary albumin levels between 30 and 300 mg/day are considered pathognomonic of DKD both in type 1 and in newly diagnosed type 2 diabetic subjects. Albuminuria <30 mg/day is considered normal, and its prognostic significance in the progression of DKD is less clear. It should be noted that proteinuria may be an early manifestation of an isolated nondiabetic kidney disease or nondiabetic renal disease superimposed on typical DN, in nearly 35–50% of patients with type 2 and less commonly with type 1 diabetes [3–5].

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Definitions of Proteinuric States in Diabetic Kidney Disease

The preferred measure of proteinuria in diabetic patients is urine albumin excretion or albuminuria in the diagnosis of DKD [6]. Effective potential therapeutic interventions at the earlier stages of albuminuria are available with complete, partial, or no reversal/resolution in DKD. The latter usually correlates with nondiabetic renal diseases, particularly in the absence of diabetic retinopathy, which may require specific therapies [5]. Early studies have shown that diabetic patients, particularly with type 1 diabetes, demonstrate various levels of albuminuria-proteinuria during the evolution of DKD. This evolutionary course has been divided into various stages for proper management of DKD [7, 8].

Stages 1 and 2 develop within the first 5 years and refer to normoalbuminuric state defined as albumin excretion rate in urine up to 30 mg/24 h.

Stage 3, also known as incipient DKD, generally occurs in 35–40% of patients after 6–15 years of onset of diabetes. This stage is characterized by albumin excretion 30–300 mg/24 h (20–200 μg/min), which is defined as microalbuminuria. Microalbuminuria represents the earliest clinical sign of DKD and is significant in predicting further deterioration of renal function and development of hypertension without adequate metabolic and blood pressure control. This transition from normo- to microalbuminuria is a crucial step in the evolution of DKD, as 35–44% of diabetic patients may progress to renal failure between 15 and 25 years.

The stage 4 is overt DKD, which occurs between 15 and 25 years and is qualified by proteinuria of >500 mg/24 h or albuminuria >300 mg/24 h, detectable by routine urinalysis by dipstick along with hypertension and decline in estimated glomerular filtration rate (eGFR).

The magnitude of proteinuria may increase with progression of kidney disease to nephrotic range (3–3.5 g/day) or nephrotic range albuminuria (2.2 g/day), within the next 5–10 years, leading to end-stage kidney disease (ESKD) in a fraction of cases in type 1 diabetes. However, several studies have shown that regression of microalbuminuria is more common than progression to overt (clinical) proteinuria or ESKD in some type 1 diabetic patients [9]. In type 2 diabetic patients, the progression to ESKD is faster but varied depending on ethnicity, age, male gender, presence of retinopathy, and increased baseline albumin excretion [9].

It should be noted that kidney impairment can occur in both type 1 and type 2 diabetic patients without albuminuria, or without progression from microalbuminuria to overt proteinuria [10].

Justification of the Term “Albuminuria-Proteinuria”

Some investigators [11, 12] and a consensus panel [13] propose that the use of terms microalbuminuria and overt proteinuria should not be used, and replaced by such terms as albuminuria or albuminuria-proteinuria. Their proposal is

based on the observations from several studies that reported the occurrence of cardiovascular events even in the presence of extremely low urinary albumin excretion rate [11–15]. Also, albuminuria is a continuous variable that should be regarded as a significant marker of endothelial dysfunction, causing systemic complications. Some investigators believe that microalbuminuria is a misnomer, and implies "small size" albumin molecule rather than small quantity of albumin in the urine.

The use of the term "albuminuria-proteinuria" appears to be the more meaningful terminology than microalbuminuria [12], as most of the clinicians routinely measure proteinuria than albuminuria in their management of nondiabetic kidney disease. The clinicians, however, order the urine albumin measurement only in diabetics, but they follow protein-to-creatinine ratio in nondiabetic patients. Therefore, the use of the term "albuminuria-proteinuria" is justified.

It should be noted that almost all therapeutic trials were conducted in diabetic patients either with normoalbuminuria, microalbuminuria, or overt proteinuria. In this chapter, we will continue to use this terminology in place of new terminology as proposed by the 2012 KDIGO guideline [16]. This guideline categorizes albuminuria into stage 1, stage 2, and stage 3 albuminuria to replace normo-, micro-, and macro or overt proteinuria, respectively (see Table 10.2).

Measurement of Urinary Albumin

Urine Collection Most of the studies suggest that the first morning void urine specimen provides the best results of albuminuria with little variability. If the first voided sample is not available, second morning void sample can be used.

Urine Storage Determination of albumin is preferred in a fresh sample. However, it is not possible in clinical studies with large number of samples. It is suggested that the urine samples can be kept at 4 °C for at least 1–2 weeks before analysis, or at –80 °C for prolonged period of time. Albumin seems to be stable at these temperatures.

Current Methods for Albumin Determination There are several methods to determine small amounts of albumin in the urine. In the laboratory, a large number of samples can be analyzed in a few hours, which is cost-effective. The most commonly used techniques are radioimmunoassay, immunoturbidimetry, laser immunonephelometry, enzyme-linked immunosorbent assay, and single radial immunodiffusion assay. High-performance liquid chromatography (HPLC) method seems to measure both the fragments and the entire albumin molecule, and is the suggested methodology for urine albumin determination. Therefore, urine albumin concentrations by HPLC method are higher than with other routine immunoassay methods, resulting in much higher incidence rates of albuminuria in diabetic patients.

In the office setting, a number of dipsticks were developed to test for albumin. These dipsticks take only a few minutes for analysis, but they are expensive. Several dipsticks have been developed over the years to detect low-grade albuminuria, and are useful in the primary care setting and diabetes clinics. Table 10.1 shows various in-office albumin tests.

Reporting Urinary Albumin Historically, urinary albumin is expressed as mg/24 h. Since collection of urine for 24 h is not feasible in all patients, it has become a common practice to express as the ratio of urinary albumin to urinary creatinine (ACR) in a spot urine sample. However, confusion arises from reporting results in units of "mg albumin/mmol creatinine," "mg albumin/g creatinine," "μg albumin/mg creatinine," "g albumin/mol creatinine," or "mg albumin/mg creatinine" [13]. The 2012 KDIGO guideline simplified the expression of reporting albuminuria for the physician, as shown in Table 10.2.

Significance of Albuminuria in Type 1 Diabetic Patients

Several prospective studies from various laboratories have demonstrated that an elevation in albumin excretion rate without clinical proteinuria predicts the risk of developing clinical DKD later in life [17–21]. From Table 10.3, it is evident that higher percentage of microalbuminuric patients progress to clinical proteinuria than patients with normoalbuminuria.

Table 10.1 Albumin tests in the office and clinics

Name	Test description
Micral test strips	Color match strips with results in 1 min
Clinitek microalbumin two reagent strips	Provides albumin, creatinine, and albumin-creatinine results in 1 min
ImmunoDip microalbumin strips	Color match strips with results in 3 min
HemoCue albumin 201	Urine sample is drawn into the cuvette and read in an analyzer with the result in 90 s

Table 10.2 Categories of albuminuria

Category	Albumin excretion rate (mg/24 h)	Albumin-to-creatine ratio		
		(mg/mmol)	(mg/g)	Terms (description)
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased
A3	>300	>30	>300	Severely increased

Table 10.3 Predictive value of microalbuminuria for the development of diabetic kidney disease in type 1 diabetic patients with normo- or microalbuminuria

Study (ref)	Patients (no.)	Follow-up period (years)	Cutoff UAE (μg/min)	Patients progressed to clinical proteinuria (%)
Viberti et al. [17]	63	14	>30 <30	87 4
Parving et al. [18]	23	6	>28 <28	75 13
Mogensen and Christensen [19]	43	10	>15 <15	86 0
Mathiesen et al. [20]	71	6	>70 <70	100 5
Almdal et al. [21]	118	5	>20 <20	19 2

Significance of Albuminuria in Type 2 Diabetic Patients

The renal prognostic value of microalbuminuria in type 2 diabetes is not as clear as in type 1 diabetes. This is probably related to several factors, including the onset of diabetes, coexisting hypertension, obesity, and hyperinsulinemia. It is generally accepted that type 2 diabetics demonstrate either micro- or macroalbuminuria at the time of diagnosis. Also, the majority of the patients are either hypertensive, obese, or hyperinsulinemic at the onset of diagnosis. In addition, some of the "so-called" type 2 diabetics may have a nondiabetic kidney disease causing heavy proteinuria. Despite the above limitations, several studies have shown that microalbuminuria can predict the later development of overt proteinuria in type 2 diabetic patients (Table 10.4).

A study by Berhane and colleagues [32] confirmed the observations shown in Table 10.4, who evaluated the predictive value of albuminuria and eGFR for ESKD in 2420 Pima Indians with type 2 diabetes. Based on ACR, the patients were classified into normoalbuminuric (ACR <30 mg/g), microalbuminuric (ACR 30–300 mg/g), and macroalbuminuric (≥300 mg/g) groups. During a mean follow-up of 10.2 years, 287 patients developed ESKD. The incidence of ESKD increased with increasing albuminuria, and the highest incidence was associated with macroalbuminuria. Also, low GFR was associated with the highest incidence of ESKD. Combined albuminuria and eGFR had a complementary effect on the development and progression to ESKD. A meta-analysis of general and high-risk population cohorts also confirmed that both albuminuria and estimated GFR predicted an additive risk for ESKD [33]. Thus, albuminuria can predict the development of ESKD.

Table 10.4 Progression of microalbuminuria to kidney disease in patients with type 2 diabetes

Author (ref)	No.	Observation period (year)	Patients developing clinical proteinuria (%/year)
Mogensen et al. [23]	59	9	2.4
Nelson et al. [24]	50	4	9.3
Ravid et al. [25]	49	5	8.4
Ahmad et al. [26]	51	5	4.8
Gæde et al. [27]	80	4	5.8
Estacio et al. [28]	150	5	4.0
HOPE Study Group [29]	1140	4.5	4.5
Parving et al. [30]	201	2	7.5
Parving et al. [31]	86	5	7.0

Adapted from Ref. [22]

Mechanisms of Albuminuria in Diabetes

The mechanisms responsible for albuminuria-proteinuria in diabetes have been thoroughly studied. Hemodynamic alterations, hyperglycemia, hormones, size and charge-selective properties of the glomerular capillary wall, alterations in the glomerular basement membrane (GBM) composition, reactive oxygen species, glycation of proteins, and altered glomerular epithelial/podocyte biology have been implicated. Mesangial cell pathophysiology has long been considered central to the development of albuminuria and glomerulosclerosis in diabetes. In recent years, however, the participation of podocytes in proteinuria and glomerulosclerosis has been extensively studied at the molecular level [34–40]. We, therefore, focus our discussion on podocyte biology in albuminuria-proteinuria of diabetes.

Podocyte Biology In order to reach the Bowman space, the ultrafiltrate passes through the fenestrae of the endothelium, the GBM, and the slit pore or slit diaphragm of the podocytes. These podocytes are highly specialized cells with primary, secondary, and complex tertiary cellular processes, the latter being the foot processes which interdigitate with adjacent epithelial foot processes and anchor firmly on the basement membranes. Since they are terminally differentiated cells, they are incapable of being replaced by compensatory proliferation of the adjacent epithelial cells.

The slit diaphragms lie between two foot processes of the podocyte, and form the final barrier to filtration of water and solutes. Although low-molecular-weight proteins may pass through these barriers easily, proteins such as albumin are not easily filtered, partly also related to a negatively charged selective barrier composed of glycosaminoglycans.

Studies have shown that the slit diaphragms contain a number of proteins that restrict the passage of albumin into the Bowman space. The first protein to be identified was nephrin. Mutations in the gene encoding nephrin (NPHS1) cause congenital nephrotic syndrome of the Finnish type. The other slit diaphragm proteins

include P-cadherin, Neph1 and 2, FAT1 (fatty acid transporter tumor suppressor homolog-1), and FAT2. The foot processes are not static, but they contain a contractile cytoskeleton. This cytoskeleton contains actin, α-actinin-4, synaptopodin, myosin-II, talin, and vinculin. The cytoskeleton of the foot processes connects to both the GBM and the slit diaphragm. The slit diaphragm proteins are connected to the cytoskeleton by various proteins, including podocin, CD2AP (CD2-associated protein), ZO-1 (zonula occludens-1), and densin. Podocin seems to play a key role in nephrin signaling and also in activating TRPC6 (transient receptor potential cation channel subfamily C, member 6). The foot processes are attached to the GBM via $\alpha_3\beta_1$-integrin and dystroglycan. The integrin dimers specifically interconnect TVP (talin, paxillin, vinculin) complex to laminin 11 of the GBM.

In addition to several proteins, the podocytes express receptors for angiotensin II and many other cytokines and growth factors. Therefore, drugs aimed at blocking these receptors may prevent proteinuria and glomerulosclerosis.

In diabetes, podocyte injury plays an important role in DKD. Abnormalities in podocyte-specific proteins have been reported. For example, nephrin, P-cadherin, and ZO-1 expressions are reduced in diabetic glomeruli and podocytes [41–44]. Decreased synthesis or loss of these proteins has been shown to cause proteinuria. Combined structural and functional changes have been observed in these podocytes, as a result of injury, even in the earlier stages of DKD. The structural changes are best visualized by electron microscopy demonstrating decreased podocyte number and/or density, via apoptosis or varying degrees of podocyte detachment and broadening of the foot processes, leading to diminished width of the slit diaphragm as well as reduced nephrin protein and significant loss of negative charge [41–44]. Podocyte or foot process denudation from the GBM has been attributed to suppression of anchor protein integrin-α_3 and overexpression of β_1-integrin in response to high glucose levels and angiotensin II. Furthermore, other actin-binding proteins in the podocytes, such as α-actinin-4, synaptopodin, and surface anionic protein podocalyxin, were all downregulated, contributing toward podocyte damage and dysfunction. These structural and molecular changes of the podocytes have been shown to promote albuminuria-proteinuria in both experimental and human studies [41–44]. Concurrent activation of the growth factors and cytokine systems by hyperglycemia, glycated proteins, hypertension-induced mechanical stress, and high renal angiotensin II induced transforming growth factor-beta 1 (TGF-β1), and increased vascular endothelial growth factor A (VEGF-A) and other signaling pathways contribute to podocyte injury [43–48]. Furthermore, perturbations in lipid metabolism in diabetes mellitus and DKD also render podocytes to be susceptible to injury, specifically via mitochondrial dysfunction and mitochondrial lipid alterations [49]. Thus, podocytes play an important role in the development of albuminuria and glomerulosclerosis in diabetes. The consequences of podocyte injury and subsequent loss (podocytopenia) are also enhanced by gradual glomerular extracellular matrix alterations in composition, structure, and thickening, as a result of hyperglycemic and hypertensive effects. Additionally, pathologic parameters that include severe podocyte injury leading to collapsing glomerulopathy (frequently accompanied by microvascular obliterative changes and ischemia-related podocytopathy), segmental

glomerulosclerosis, and extracapillary hypercellularity in DKD have been associated with new-onset or enhanced proteinuria, often up to nephrotic range, as well as markers of poor prognosis [50, 51].

Based on the premise that a clinical diagnosis of DKD hinges on the identification of microalbuminuria, often occurring after the first 5 years following the onset of diabetes which can be variable, particularly in the setting of type 2 diabetes mellitus, a suggestion to assess the histological damage at the time by obtaining a routine kidney biopsy is made [52]. This may detect the various pathological features including nondiabetic glomerular/renal lesions at an earlier stage that may be amenable for intervention and prevent progression. The advent of more advanced mass spectrometry and molecular approaches using urine and tissue samples in these DKD patients has identified multiple pathways of cellular insults, which serve as targets for novel therapies [53, 54].

Extrarenal Manifestations of Albuminuria

There are several associated extrarenal abnormalities in patients with albuminuria or microalbuminuria. The microalbuminuric patients are at a higher risk not only for cardiovascular and other microvascular diseases such as retinopathy and neuropathy than normoalbuminuric diabetic patients as well. The mechanisms responsible for increased cardiovascular mortality in microalbuminuric patients are poorly understood. However, microalbuminuria seems to be a marker for widespread endothelial dysfunction, and a number of cardiovascular risk factors are present in microalbuminuric patients. Table 10.5 summarizes some of the abnormalities (associations) that are found in microalbuminuric patients, which predispose them to increased early morbidity and mortality from cardiovascular disease (CVD).

Albuminuria and Cardiovascular Disease

Albuminuria is a risk factor for CVD [56]. Even normal albumin excretion rates, i.e., below 30 mg/24 h, are associated with CVD complications. Following meta-analysis it has been emphasized that microalbuminuria carries substantially more CVD complications [15]. In earlier studies, it has been shown that the relative mortality from CVD is increased 40-fold in type 1 diabetic patients with proteinuria as compared with the general population [57]. Subsequently, follow-up studies in type 1 diabetic patients for 10, 18, or 23 years suggested that microalbuminuria is a strong risk factor for early death, particularly CV death (reviewed in Ref. [47]). In another cross-sectional study [58], 476 type 1 adult diabetic patients were followed for a 5-year period. During this follow-up, 19 patients died and 30 developed CV or renal disease, such as myocardial infarction ($N = 8$), stroke ($N = 3$), amputation ($N = 6$), and renal insufficiency ($N = 13$). Urinary albumin concentration in a single

Table 10.5 Extrarenal manifestations of microalbuminuria in both types of diabetic patients

Functional parameter	Change
Hemodynamic	
Blood pressure	↑
Left ventricular function	↓
Left ventricular mass	↑
End-diastolic volume	↓
Maximal oxygen uptake	↓
Cardiovascular risk factors	
Total cholesterol	↑
VLDL cholesterol	↑
LDL cholesterol	↑
Apolipoprotein B	↑
HDL cholesterol	↓
Plasma fibrinogen	↑
Endothelial cell function	
Von Willebrand factor	↑
PAI	↑
Adhesion molecules	↑
Function of nitric oxide	↓
$TER_{albumin}$	↑
$TER_{fibrinogen}$	↑
ACE level	↑
Homocysteine level	↑
Microvascular disease	
Proliferative retinopathy	↑
Peripheral neuropathy	↑

Adapted from Ref. [55]
↑ increase, ↓ decrease, *PAI* plasminogen activator inhibitor, *TER* transcapillary escape, *ACE* angiotensin-converting enzyme

early morning urine sample was found to be a strong prognostic marker for the development of CVD or death.

The relationship between the degree of albuminuria and CV risk was examined by the investigators of the Heart Outcomes Prevention Evaluation (HOPE) study [59]. This was a cohort study conducted between 1994 and 1999 with a median follow-up of 4.5 years. The prevalence of microalbuminuria in diabetic patients was 32.6% as compared with 14.8% in patients without diabetes. The results suggest that any degree of albuminuria is a risk factor for CV events, such as myocardial infarction, stroke, and CV death, or hospitalization for congestive heart failure. The risk of CVD increases with an increase in ACR, starting well below the microalbuminuria cutoff. This study is thus consistent with many other previous studies [55].

Dinneen and Gerstein [60] critically analyzed the literature linking microalbuminuria with total and cardiovascular morbidity and mortality in type 2 diabetic patients. A total of 11 cohort studies were selected from 264 citations for analysis.

These 11 studies included a total of 2138 patients with a mean follow-up of 6.4 years. Duration of diabetes ranged from newly diagnosis to 13 years. The prevalence of microalbuminuria ranged from 20% to 36% in the 8 cohorts that excluded patients with clinical proteinuria. All studies reported significant association between microalbuminuria and total mortality or cardiovascular morbidity and mortality. The authors concluded that microalbuminuria is a strong predictor of total and cardiovascular morbidity and mortality in patients with type 2 diabetes. The observation that a reduction in albuminuria parallels an improvement in CVD prognosis supports the concept that microalbuminuria is a strong risk factor for CVD.

Albuminuria and Hypertension

As shown in Table 10.5, one of the concomitant abnormalities in microalbuminuric patients is elevated blood pressure. Studies have shown that microalbuminuria precedes the increase in systemic blood pressure during the development of diabetic kidney disease in type 1 patients. Also, a significant correlation was found between arterial blood pressure and albumin excretion rate in microalbuminuric patients [61]. The prevalence of hypertension was greater than 80% in both male and female patients with overt proteinuria.

The association between ambulatory blood pressure monitoring (ABPM) and microalbuminuria has been studied in normotensive type 1 diabetic patients by several investigators, in order to define the variability in blood pressure and albumin excretion rate (reviewed in Ref. [55]). These studies have shown that 24-h blood pressure is significantly higher in micro- than in normoalbuminuric patients. Furthermore, the physiological nocturnal fall in systolic blood pressure was blunted. Some of these studies found a correlation between microalbuminuria and ABPM and not with casual or office blood pressure readings. The conclusion from all these studies is that 24-h blood pressure recording is a useful technique in detecting abnormalities in blood pressure that are not apparent in casual blood pressure measurement in normotensive type 1 diabetic patients.

Table 10.6 summarizes ABPM in normotensive adult type 1 diabetic patients with normo- and microalbuminuria. Also, the ambulatory blood pressure recordings

Table 10.6 Ambulatory blood pressure (mm Hg) recordings in normotensive type 1 diabetic patients with or without microalbuminuria

	Daytime		Nighttime		24 h		Office	
Subjects	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Controls	122	72	114	60	118	68	116	68
Normoalbuminuria	122	75	112	63	118	70	118	71
Microalbuminuria	128	79	121	70	126	75	122	74

Adapted from Ref. [55]
SBP systolic blood pressure, *DBP* diastolic blood pressure

were compared with office or clinic blood pressures in these diabetics and matched healthy controls.

Determinants of Albuminuria

Several factors can influence albuminuria or microalbuminuria. The most important determinants are hyperglycemia and blood pressure. Determinants such as familial predisposition to proteinuria, duration of diabetes, age, endothelial cell dysfunction, lipid abnormalities, and probably smoking may be involved in the development and progression of microalbuminuria.

Screening for Albuminuria

A routine urinalysis should be performed in all patients before screening for microalbuminuria. If the dipstick is positive for proteinuria, there is no need to screen for microalbuminuria because the patient already has overt proteinuria. If the dipstick is negative, then screening for microalbuminuria is indicated. The consensus is that the screening should begin from puberty and 5 years after the diagnosis of type 1 diabetes. Urine samples can be collected over a 24-h period, early morning specimen, or a random spot collection, whichever is convenient to the patient, and follow the criteria shown in Table 10.1 to define albuminuria.

Before albuminuria is established in any patient, it is essential to rule out other causes that increase or decrease albumin excretion (Table 10.7). Also, two of the three collections done in a 3–6-month period should show elevated albumin levels before the diagnosis of microalbuminuria is entertained. A suggested schema for screening type 1 or type 2 patients for microalbuminuria is shown in Fig. 10.1.

Table 10.7 Clinical conditions associated with increased or decreased albumin excretion

Increase	Decrease
Urinary tract infection	Nonsteroidal anti-inflammatory drugs
Blood in urine	ACE inhibitors, or angiotensin receptor blockers
Fever	Malnutrition
Exercise within 24 h	Low-protein diets
Uncontrolled hyperglycemia	Inadequate 24-h urine collection
Uncontrolled hypertension	Overnight urine collection
Congestive heart failure	
High protein intake	
Excessive diuresis	
Upright posture	
Menstrual and vaginal bleeding	

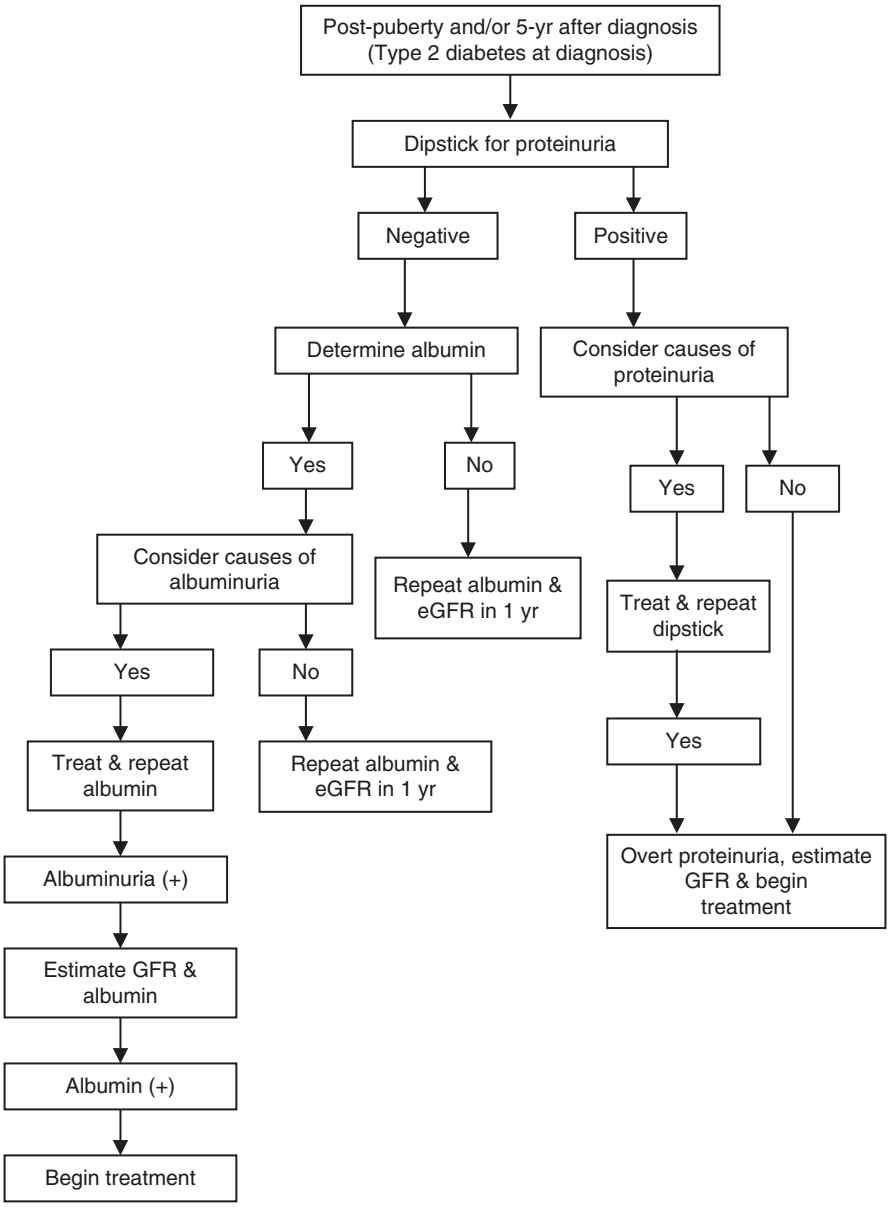

Fig. 10.1 Screening for albuminuria and estimated GFR (eGFR) in type 1 and type 2 diabetic patients

Proteinuria of Nondiabetic Origin

Occasionally, patients with established diabetes present with dipstick positive or heavy proteinuria that is not expected for the duration or control of hyperglycemia. Also, unexpected deterioration in renal function is seen. Such atypical presentation is more common in type 2 diabetic than type 1 diabetic patients [3–5]. These patients require a thorough clinical workup of proteinuria. Such patients usually undergo a kidney biopsy to establish DKD and its various stages, but also to document existence of a nondiabetic renal disease alone or superimposed on DKD. In addition to a definitive diagnosis, the histopathologic findings provide pertinent prognostic information as well as a direction for appropriate therapy and management. The current indications for kidney biopsy are shown in Table 10.8.

When kidney biopsies were performed in patients with atypical presentation, as shown in Table 10.8, a variety of nondiabetic kidney diseases were observed. Such renal lesions were present either alone or superimposed on DKD, making management more difficult. The following glomerular lesions have been documented:

Minimal change nephrotic syndrome/focal segmental glomerulosclerosis
Membranous glomerulonephritis
Crescentic glomerulonephritis
Postinfectious glomerulonephritis
IgA nephropathy primary/secondary
Lupus nephritis
HCV-associated glomerulonephritis
Fibrillary glomerulonephritis
Monoclonal immunoglobulin-mediated diseases
Collapsing glomerulopathy

It is, therefore, suggested that the nephrologist should include nondiabetic renal lesions in the differential diagnosis of abnormal proteinuria. Table 10.9 shows clinical features of various glomerular diseases with proteinuria that may be helpful for appropriate management.

Table 10.8 Indications for kidney biopsy in diabetic patients with renal disease

1. Proteinuria or nephrotic syndrome of sudden onset, appearing less than 5–10 years of type 1 DM
2. Proteinuria and/or impaired renal function in the absence of retinopathy in type 1 DM[a]
3. Proteinuria associated with a nephritic syndrome characterized by micro- or macrohematuria and renal insufficiency with RBC casts in type 1 and 2 DM
4. Unexplained renal failure with or without proteinuria
5. Presence of a systemic disease with abnormal serologic findings and clinical renal disease
6. Abnormal imaging studies such as ultrasonography and Doppler studies, after excluding renovascular disease
7. Absence or urologic disease or infection

[a]The prevalence of retinopathy less predictable for DN in type 2 DM

Table 10.9 Differential diagnosis of diabetic and non-diabetic kidney diseases

Diagnosis	Proteinuria	Hematuria	Creatinine	S Alb	Serology	BP	Systemic symptoms
Diabetic nephropathy	Variable	Cr 30%	Gradual increase	Nl or low	Negative	Variable	Long duration >10 years, nonspecific
Minimal change disease	NRP	None	Normal	Low	Negative	–	–
Focal segmental sclerosis	NRP	None	Normal	Low	Negative	–	–
Membranous GN, primary	NRP	<20%	Normal	Low	PLA2R abs	–	
Membranous GN, secondary	NRP	None-1+	Normal	Low	Depending on systemic disease	–	Disease specific
Post-infectious GN	Mild to moderate	1–3+	Elevated	Nl or low	+ or neg blood cultures	Variable	Evidence of infection
IgAN	Mild	1–3+	Variable	Nl or low	Negative	Variable	Some cases with MRSA infection
Crescentic GN	Mild	3+	Elevated	Nl	ANCA, antiGBM	–	Rash, lung symptoms
Lupus nephritis	Variable to NRP	1–3+	Variable	Nl or low	ANA+	Variable	SLE symptoms
HCV/HBV infection	Variable to NRP	1–3+	Variable	Low	HBV+, HCV+	–	Extrarenal or hepatic disease
Fibrillary GN	Mild to NRP	1+	Variable	Low	Negative	–	–
Monoclonal protein disease	Mild to NRP	1–3+	Variable	Nl or low	M-spike	–	Depending on type of disease
Collapsing GP	Often NRP	None	Elevated	Variable	Negative	Variable	–

NRP Nephrotic range proteinuria >3gm/24 h, *Nl* normal, *Neg* negative, *Variable* creatinine levels may depend on active/proliferative GN or chronic sclerosing changes

Treatment of Albuminuria-Proteinuria

A detailed review of treatment of albuminuria is beyond the scope of this chapter. Only generalizations are presented here. Almost all studies recommend an angiotensin-converting enzyme inhibitor (ACE-I), or an angiotensin receptor blocker (ARB) as an initial drug of choice for albuminuria. In addition, control of

glucose to achieve HbA1c ≤7% in type 1 and type 2 diabetic patients has an independent positive effect in reducing albuminuria. Lowering blood pressure and controlling glucose have an additive effect in preventing the progression of albuminuria and renal dysfunction.

ACE-Is provide a selective benefit over other antihypertensive agents in both delaying the progression of albuminuria and decline in GFR in patients with high levels of albuminuria. Also, the use of ACE-Is has been shown to reduce major CV events, such as stroke, myocardial infarction, and death, in diabetic patients. In normoalbuminuric type 2 diabetic patients, ACE-Is have been shown to delay the onset of microalbuminuria. ARBs seem to have minimal effect in preventing onset of albuminuria in normotensive type 1 and type 2 diabetic subjects. However, ARBs have been shown to reduce the progression from micro- to macroalbuminuria as well as the development of ESKD in type 2 diabetic patients. Furthermore, the CV events were prevented by ARBs in type 2 diabetics.

A combination of an ACE-I and an ARB is not suggested at this time, although such a combination has been shown to have an additive effect in reducing proteinuria in both types of diabetics in the past. Also, addition of renin inhibitor is not suggested at this time. An additive benefit in terms of proteinuria can be achieved with a combination of an ACE-I or an ARB and an aldosterone blocker in patients with eGFR >60 mL/min. Even in these patients, serum potassium levels may be slightly elevated. Therefore, close monitoring of serum potassium is warranted with this combination therapy.

Other antihypertensive drugs such as calcium channel blockers, diuretics, or β-blockers have been shown to lower proteinuria, and these can be used as additional drugs to lower blood pressure who are on either ACE-Is or ARBs. These drugs can be used as first-line therapy in selected individuals who cannot tolerate either ACE-Is or ARBs. Serum electrolytes, creatinine, and lipid panel should be obtained periodically in patients on diuretics.

Recent studies have shown that glucose-lowering agents such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors may have renoprotective effects. In a meta-analysis of 15 randomized clinical trials (n = 15,382 patients) evaluating albuminuria using albumin-to-creatinine ratio, SGLT-2 inhibitors were found to significantly reduce albuminuria in type 2 diabetic patients. Also, a reduction in proteinuria was reported [62].

Also, other oral hypoglycemic agents such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 analogues have expanded the options not only to control glycemia and blood pressure in patients with type 2 diabetes but also improve CV and/or renal outcomes.

Low-protein diet (0.8 g/kg/day) can be used in selected diabetic patients whose proteinuria is progressing despite good glucose and blood pressure control and on adequate dosage of an ACE-I or ARB.

Several other therapies have been applied to improve both proteinuria and eGFR. Table 10.10 summarizes the therapies that have been tried with variable success.

Table 10.10 Medical management of diabetic kidney disease

Proven benefit	Probable benefit	Benefit to be proven[a]
Blood glucose control	Control of hyperlipidemia	Aldose reductase inhibitors
Blood pressure control	Smoking cessation	Inhibitors of AGE
Low-protein diet	Low-salt diet	Antiplatelet and related therapy
		Antioxidants
		PKC inhibitors Sulodexide
		Growth factor inhibitors
		Gene therapy

[a]Need large human studies; *AGE* advanced glycation end products, *PKC* protein kinase C, *GAG* glycosaminoglycans

Table 10.11 Potential therapies for treatment of diabetic kidney disease

Therapeutic agent	Proposed mechanism
Pirfenidone	Inhibition of TGF-β1, TNF-α, collagen synthesis
Tranilast	Inhibition of TGF-β1
Doxycycline	Inhibition of matrix metalloproteinase activity
Pentoxifylline	Inhibition of proinflammatory cytokines
Connective tissue growth factor (CTGF) antagonist	Inhibition of matrix production and TGF-β1
Anti-TGF-β1	Inhibition of matrix formation
Bardoxolone	Decrease in oxidative stress
Bosentan	Endothelin (ET)-a and b antagonist
Atrasentan	ET-a selective receptor antagonist
Avosentan	ET-a antagonist
Paricalcitol	Inhibition of pro-fibrotic cytokines
Allopurinol	Inhibition of xanthine oxidase
B vitamin (folic acid, B_6, B_{12})	Decrease in oxidative stress and glycation
Adiponectin	Activation of an energy-sensing enzyme, AMPK
Rapamycin	Inhibition of mTOR (mammalian target of rapamycin)
Finerenone	Mineralocorticoid receptor antagonist

In recent years, a number of new therapeutic drugs have been tried in animals and humans for diabetic kidney disease. These therapeutic drugs are summarized in Table 10.11 [63–68].

Podocyte-Specific Drugs

As discussed under "Mechanisms of Proteinuria," either decreased synthesis or mutations in genes that encode the podocyte proteins cause albuminuria. Therefore, development of podocyte-specific drugs is clearly indicated. In diabetic animal models, a number of pharmaceutical strategies have been tried with success. These studies are summarized in Table 10.12 [67–69].

Table 10.12 Podocyte-specific drugs

Vehicle	Target	Result
PKCα inhibitor	Prevents nephrin loss	↓proteinuria
Low-molecular-wt heparin	Binding to RAGE and inactivates its actions	↓albuminuria
RAGE antibody	Inactivation of RAGE	↓albuminuria
BMP7	Podocyte overexpression	↓albuminuria
	Podocyte preservation of BMP7	↓albuminuria
BMP7 injection	Counteracts CTGF action	↓albuminuria
CTGF-AS-ODN	Podocyte overexpression	↓albuminuria
sFlt-1	Inhibits binding of prorenin to its receptor	↓proteinuria
Handle region peptide (a decoy peptide)		

BMP7 bone morphogenetic protein 7, *CTGF-AS-ODN* connective tissue growth factor antisense oligodeoxynucleotide, *PKC* protein kinase C, *RAGE* receptor for advanced glycation end product, *sFlt-1* soluble fms-like tyrosine kinase1 (or soluble vascular endothelial growth receptor-1)

Conclusions

The presence of albuminuria-proteinuria in diabetic patients is an indication of early kidney disease and signifies systemic endothelial dysfunction. Even a small amount of albuminuria (<30 mg/day) carries a risk for CVD. Abnormalities in podocyte-specific proteins and other forms of podocyte injury seem to be the underlying mechanisms for albuminuria-proteinuria. Whenever a diabetic patient presents with significant albuminuria-proteinuria, the nephrologist should consider the coexistence of nondiabetic primary glomerular diseases. An expanded role for a kidney biopsy is considered to identify kidney damage secondary to DKD as well as nondiabetic renal disease (Table 10.8).

The screening for albuminuria should begin from puberty and 5 years after the diagnosis of diabetes in type 1 patients. Urine samples can be collected over a 24-h period, early morning specimen, or a random spot collection, whichever is convenient to the patient. Albumin-to-creatinine ratio in a morning-voided specimen is usually the standard way of expressing the excretion of albuminuria in the outpatient setting. Reagent strips for documenting the minute quantities of albuminuria are available in the office setting and diabetes clinics. Screening for albuminuria should begin during the first visit in type 2 diabetic patients.

ACE-Is or ARBs are the drugs of choice for the treatment of albuminuria. Prevention of albuminuria delays the progression of kidney disease as well as CVD. Combination of an ACE-I and an ARB is not recommended; however, a combination of either one of these drugs and an aldosterone antagonist seems to have an added benefit in the prevention of renal and CV diseases. Several new medications targeting podocytes are being evaluated in animals and humans to prevent albuminuria-proteinuria in diabetic and nondiabetic patients. It is hoped that their introduction into the clinical practice is expected to decrease the morbidity and mortality in patients with albuminuria-proteinuria.

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Chapter 11
Hypertension and Diabetes

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Introduction

Hypertension (traditionally diagnosed after two office blood pressures ≥140/90 mm Hg) is currently the most common chronic condition for which Americans obtain medical care [1]. The age-adjusted prevalence of hypertension in the USA had been relatively stable at about 30% from 1992 to 2016 [2], but increased to 46% on 13 NOV 17, when an American College of Cardiology/American Heart Association task force reduced the threshold for this diagnosis to ≥130/80 mm Hg [3]; this definition has been rejected by both The American Association of Family Physicians and The American College of Physicians. Diabetes mellitus (diagnosed since 1997 after two fasting blood glucose measurements are >125 mg/dL, but more recently if A1c is >6.5% [4]), especially the more common type 2, also has a prevalence that is strongly influenced by age and obesity; multiple datasets suggest there has been a near doubling of the incidence of diabetes in the last 4 decades in the US. The age- and gender-dependence of the prevalence of hypertension and diabetes in the US (derived from the National Health and Nutritional Examination Surveys, NHANES, 2013–2016 [1, 5]) are shown in Fig. 11.1 and Table 11.1.

The burden of hypertension, diabetes, and their combination, is substantial. For example, in data from NHANES 2013–2016, 42.8% of American women and 49% of American men over age 20 years had hypertension; the corresponding proportions for diabetes were 12% for women and 14% for men. These figures are likely to be underestimates, because, in NHANES 2013–2016, 36.3% of those with blood pressures ≥130/80 mm Hg claimed to be unaware of the diagnosis of hypertension [1], and undiagnosed diabetes was estimated to affect 2.8% of Americans [4].

Hypertension and diabetes are just two of the all-too-commonly clustered cardiovascular risk factors in many Americans, which also include obesity and

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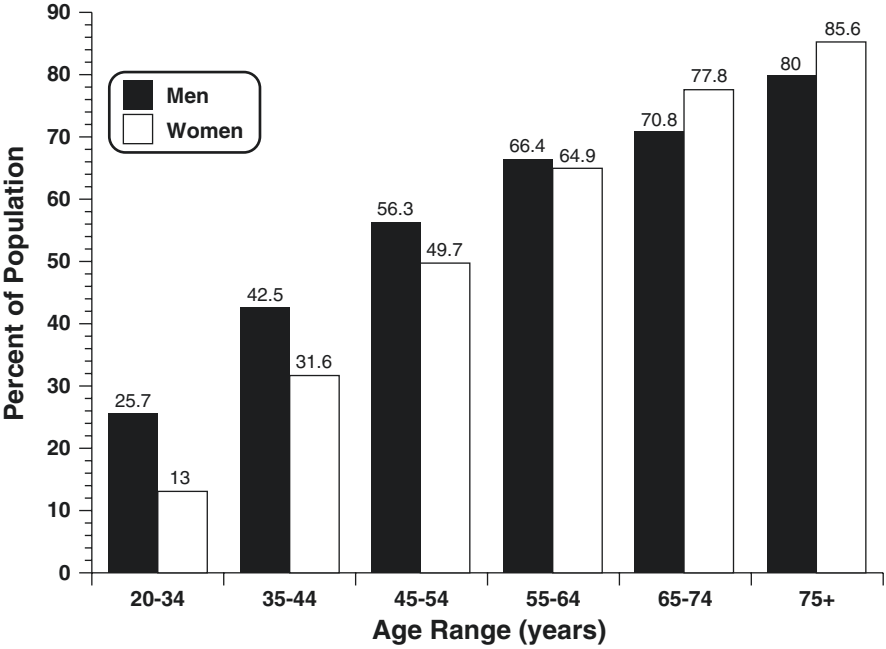

Fig. 11.1 Age- and gender-specific prevalence of hypertension (blood pressure ≥130/80 mm Hg, or taking antihypertensive medication) in the US, according to the National Health and Nutrition Examination Surveys 2013–2016. (Data from Ref. [1]). Traditionally, men had a higher prevalence of hypertension than women until about age 60, after which the reverse has been true. Whether this can be appropriately attributed to a survivorship effect is not clear

Table 11.1 Estimated prevalence (and 95% confidence intervals) for diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults 18 years of age or older, United States, 2013–2016

Parameter	Diagnosed diabetes (%)	Undiagnosed diabetes (%)	Total diabetes (%)
Total (age-adjusted)	10.2 (9.3–11.2)	2.8 (2.4–3.3)	13.0 (12.0–14.1)
Age range (years)			
18–44	3.0 (2.6–3.6)	1.1 (0.7–1.8)	4.3 (3.4–5.0)
45–64	13.8 (12.2–15.6)	3.6 (2.8–4.8)	17.5 (15.7–19.4)
65+	21.4 (18.7–24.2)	5.4 (4.1–7.1)	26.8 (23.7–30.1)
Gender			
Men	11.0 (9.7–12.4)	3.1 (2.3–4.2)	14.0 (12.3–15.5)
Women	9.5 (8.5–10.6)	2.5 (2.0–3.2)	12.0 (11.0–13.2)
Race/ethnicity			
White, non-Hispanic	9.4 (8.4–10.5)	2.5 (1.9–3.3)	11.9 (10.9–13.0)
Black, non-Hispanic	13.3 (11.9–14.9)	3.0 (2.0–4.5)	16.4 (14.7–18.2)
Asian, non-Hispanic	11.2 (9.5–13.3)	4.6 (2.8–7.2)	14.9 (12.0–18.2)
Hispanic	10.3 (8.1–13.1)	3.5 (2.5–4.8)	14.7 (12.5–17.3)

Adapted from Table 1a of Ref. [4]

dyslipidemia (especially elevated serum levels of triglycerides and, perhaps more importantly, low-density lipoprotein cholesterol). A summary of the estimated prevalence of these inter-related risk factors, based on recent national survey data, extrapolated from the entire US adult population [1–4] (and for their overlap in a 60-year old person, the closest age of the average American with diabetes, from the Framingham Heart Study [6]), is shown in Fig. 11.2. One of the more important features of this Figure is the 67–90% overlap of diabetes with hypertension (depending on age, body-mass index, and kidney function), which provides a very strong impetus for population-based strategies to improve or prevent clinical adverse outcomes in diabetics (see below).

Across the globe, both diabetes and hypertension contribute strongly to death and disability. Worldwide, raised systolic blood pressure was identified as the largest (and most important) risk factor for the Global Burden of Disease (GBD) study in 2017, accounting for 30% of deaths attributable GBD risk factors and 18% of the global disability-adjusted life years, edging out smoking (20.8% and 15%), high fasting plasma glucose (19% and 14%), and high body-mass index (13.8% and 12.2%, respectively) [7]. This was a huge change from 1990, when childhood infectious diseases were more often fatal, and reflects the increasing incidence of cardiovascular disease (and its risk factors) across the earth. An earlier analysis estimated that 26.4% (or about 972 million) of the world's population had hypertension in 2000, with 29.2% (or 1.56 billion) projected to have the condition by 2025. Most of the growth was expected to occur in developing nations [8]. The International

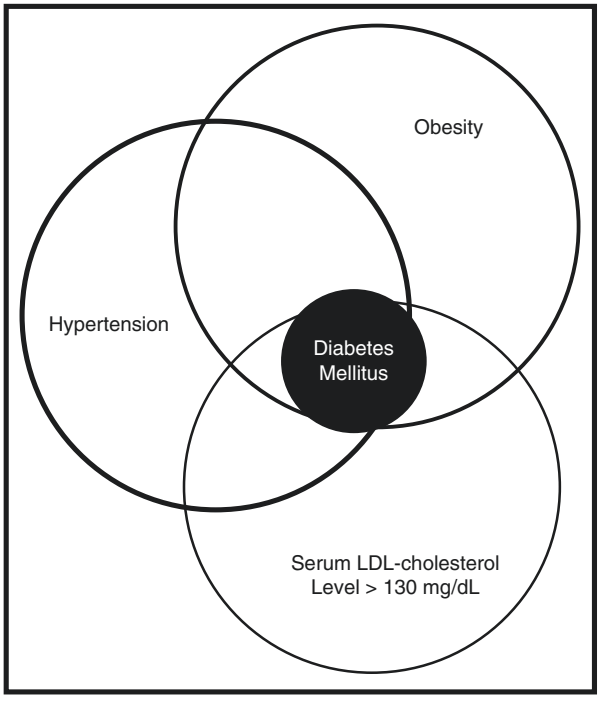

Fig. 11.2 Venn diagram representing the prevalence (and strong overlap) of hypertension (33%), diabetes (11.8%), obesity (34.6%), and elevated serum low-density lipoprotein cholesterol level (>130 mg/dL, 31.1%) in the civilian, non-institutionalized US adult population (represented by the area within the square box) in recent National Surveys that included the year 2010 [1]. (The overlap proportions are taken from either national survey data (when available), or Ref. [5])

Diabetes Federation estimates that 463 million people had diabetes in 2019, which will increase to 700 million by 2045, because the prevalence of type 2 diabetes is increasing in every country surveyed. Perhaps because nearly 80% of people with diabetes live in low- and middle-income countries, about half of those with diabetes have not yet been diagnosed. Reflecting its importance as a risk factor for mortality (with 4.2 million deaths in 2019), the prevalence of diabetes is greatest worldwide between the ages of 40 and 59 years [9].

Pathophysiology of Hypertension in Diabetics

Although perhaps something of an oversimplification, one of the most important factors in the co-development of hypertension and diabetes is insulin resistance. This problem can be most directly studied using insulin-clamp techniques that are most appropriate in a research setting, but surrogates have been developed, including fasting and post-prandial serum insulin levels that lend themselves to large studies, including clinical trials. The results of such studies suggest that more than 50% of Americans with primary hypertension have insulin resistance. Genetics have also been implicated, because first-degree relatives of patients with hypertension also have an increased risk of insulin resistance and dyslipidemia, even if they are normotensive. Probably more important for most Americans are environmental factors, like high-fat and high-calorie diets and sedentary lifestyles that lead to central adiposity and ectopic lipid deposition. These factors probably combine with the increased risk of insulin resistance to cause inflammatory and oxidative stress, which has many negative effects. In addition to enhancing the activity of the renin-angiotensin-aldosterone and sympathetic nervous systems, and causing sodium/water retention, many maladaptive derangements occur in blood vessels. These include an increase in vascular smooth muscle cell proliferation, arterial stiffness, and vascular tone, and endothelial dysfunction, a decreased ability to vasodilate in response to appropriate stimuli (e.g., nitric oxide) [9]. Some of these effects (especially closely linked to hyperinsulinemia) appear to be mediated by an elevation in intracellular calcium concentrations within vascular smooth muscle cells; which has, in turn, been recently linked to abnormal vitamin D levels and metabolism [10]. Some believe that better understanding of these pathophysiological links between hypertension and diabetes has implications for better treatment of either condition, as antihypertensive drug classes may have differential effects on incident diabetes, and some hypoglycemic drugs may increase blood pressure (see below).

Hypertension and Type 1 Diabetes Mellitus

Type 1 diabetes (characterized by a complete lack of insulin) currently affects only about 6–8% of Americans with diabetes, with the other 92–94% having type 2 diabetes (characterized by peripheral insulin insensitivity). Most affected patients are

children or adolescents, who, because of their young ages, are at low risk for hypertension. Therefore, they are also at low risk for competing causes of death (compared to their type 2 diabetic counterparts, discussed below), so a larger proportion of type 1 diabetics develop chronic kidney disease (compared to type 2 diabetics) over their lifetimes. Most type 1 diabetic patients develop "moderately increased albuminuria" (albumin:creatinine ratio 30–300 mg/gm; formerly, "microalbuminuria"), proteinuria and subsequently renal disease before hypertension (see Chaps. 3, 6, and 7 of this book for more details). However, elevated blood pressure accelerates the disease processes in these relatively younger individuals, and greatly increases their risk of both macrovascular and microvascular manifestations of diabetes. For this reason, *early*, intensive antihypertensive therapy is often recommended, particularly with an inhibitor of the renin-angiotensin system (for which there are copious clinical trial data using severely increased albuminuria (albumin:creatinine ratio: >300 mg/gm, formerly, "microalbuminuria") as the endpoint) [4]. Typically, beta-blockers are best avoided as antihypertensive therapy for type 1 diabetics, as such patients are more prone to hypoglycemia, signs and symptoms of which can be diminished and even masked by beta-blockade [2, 4]. Otherwise considerations about blood pressure management in type 1 diabetics are quite similar to those for the much more common type 2 diabetics, which have been more extensively studied (see below).

Hypertension and Type 2 Diabetes

We have far more data, and thus much stronger evidence (even including some from randomized clinical trials, see below), for the role of blood pressure as a major contributor to the risk of both cardiovascular and renal disease in type 2 diabetics. Nearly all epidemiological studies, starting with the Framingham Heart Study, have consistently identified hypertension as an independent risk factor for heart disease, stroke, cardiovascular death, and end-stage renal disease, whether the subject was initially diabetic or not. Perhaps the most specific literature on the prognostic importance of hypertension in diabetics comes from a roughly 4-year follow-up study of 1145 Framingham participants after the new diagnosis of diabetes, of whom 125 died and 204 experienced a cardiovascular event [11]. After appropriate adjustments for demographic and other clinical variables, hypertension was associated with a highly significant 72% increase in the risk of mortality, and a similarly significant 57% increase in the risk of cardiovascular event in individuals with newly-diagnosed diabetes. Hypertension carried a far greater population-attributable risk than diabetes for both death (30% vs. 7%) and cardiovascular event (25% vs. 9%) in these subjects. Some would argue that conclusions drawn from observational studies are inherently weaker than observations made about primary analyses of clinical trials. Fortunately, we have abundant data from clinical trials in both diabetic subjects treated with antihypertensive drug therapy (compared to those who did not receive such therapy) [12, 13], and hypertensive subjects who were or were not diabetic (at baseline) that consistently show significant benefits of lowering blood pressure to prevent major cardiovascular and/or renal endpoints.

Cardiovascular Outcomes in Hypertensive Diabetics vs. Hypertensive Non-Diabetics

The Blood Pressure Lowering Treatment Trialists' Collaboration published their compiled data comparing outcomes in clinical trials of antihypertensive drug therapy in diabetics vs. non-diabetics in 2005 [14]. Although their original intent was not to directly compare risks among diabetics and non-diabetics, but instead to identify the benefits of similar blood pressure-lowering treatments in these groups, their data about fatal or non-fatal myocardial infarctions ("Coronary Heart Disease") can be rearranged as in Fig. 11.3. Random-effects meta-analysis of these data shows that diabetics consistently have a higher risk of coronary heart disease events than non-diabetics, even when treated with similar, if not identical, antihypertensive regimens. On average, diabetics in these trials (who were generally well-treated with all appropriate other therapies at the times the trials were executed) experienced an 88% (95% confidence interval, CI: 83–99%) increased risk of fatal or non-fatal myocardial infarction ($P << 0.0001$), compared to non-diabetics. Similar calculations indicate that the risk of fatal or non-fatal stroke in clinical trials of antihypertensive agents is highly significantly increased by 43% (95% CI: 38–52%) in

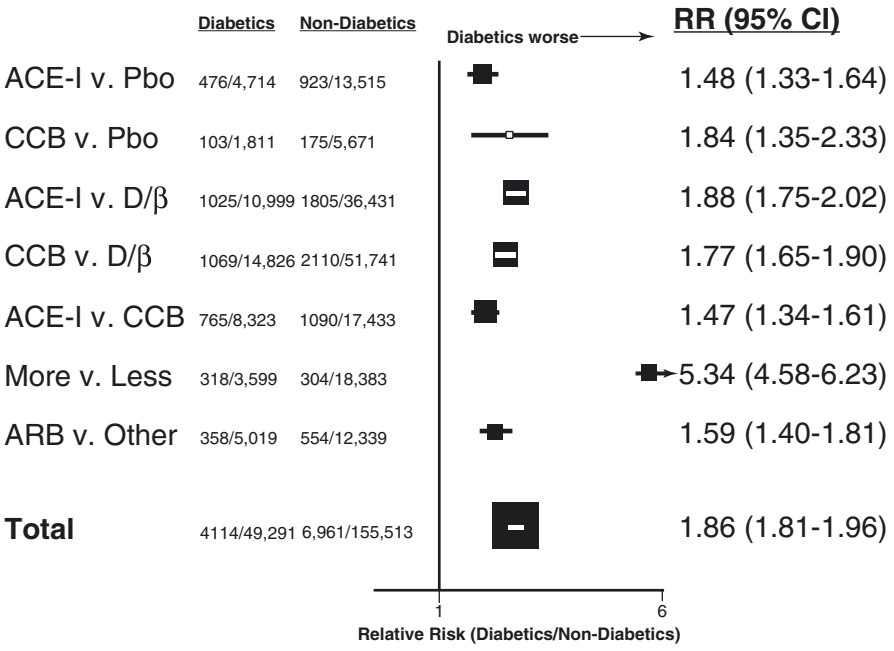

Fig. 11.3 Meta-analysis of coronary heart disease (fatal or non-fatal myocardial infarction) in randomized clinical trials comparing antihypertensive drug regimens in hypertensive diabetics vs. hypertensive non-diabetics. (Data from Ref. [14]). The summary odds ratio for coronary heart disease across 186,620 subjects was 1.88 (95% confidence interval: 1.83–1.99) for diabetic compared to non-diabetic hypertensives

diabetics, compared to non-diabetics. Similarly, cardiovascular death was significantly increased by 90% (95% CI: 84–101%) for diabetics compared to non-diabetics. These estimates are in substantial agreement with many other datasets, including those from large epidemiological studies, indicating that diabetes roughly doubles long-term cardiovascular risk, in both hypertensive and non-hypertensive individuals.

Renal Outcomes in Hypertensive Diabetics

Although there are fewer data from randomized clinical trials for renal vs. cardiovascular endpoints, many lines of evidence strongly implicate hypertension as a major risk factor for end-stage renal disease and progressive renal disease in diabetics. Perhaps most tragic are the data collected for each patient who starts renal replacement therapy in the USA on the "Intake Form," which are summarized annually by the United States Renal Data Systems [15]. According to the report for the year 2019, 58,372 of the 124,369 (or 46.9%) of individuals who were diagnosed with end-stage renal disease in 2017 had diabetes as the primary reason for their fate; a further 28.8% had hypertension as the primary cause of kidney failure. However, these data are likely biased, because the Intake Form allows only a single answer to a typically complex question, and the options are given alphabetically (putting "Diabetes" ahead of "Hypertension" in the list). The Intake Form was modified once, in 2001, to allow identification of more than one condition that resulted in renal replacement therapy. In that year, 15% of those reaching end-stage renal disease had diabetes alone as the cause, 33% had hypertension alone, and 39% had both hypertension and diabetes checked on the Intake Form. These data, which have not been replicated, suggest that, even (or perhaps especially) among diabetics, hypertension is a major contributor to the risk of end-stage renal disease.

In addition to these population-based epidemiological data about the risk of end-stage renal disease being significantly higher in hypertensive diabetics, many longitudinal databases also show a highly significant increase in the risk for several renal endpoints in hypertensive (compared to normotensive) diabetics. Interestingly, the Framingham Heart Study has not contributed extensively to this literature, primarily because they originally enrolled only 5209 subjects in their study, and it is far more likely that these individuals died of cardiovascular causes before they developed end-stage renal disease. However, large databases from the Multiple Risk Factor Intervention Trial [16], the Department of Veterans Affairs Medical Centers [17], and the Kaiser Permanente of Northern California Health Plan [18] have consistently shown that hypertension is a major, significant contributor to both chronic kidney disease and end-stage renal disease, even (or perhaps especially) among diabetics. Similar conclusions have been reached in long-term follow-up of populations from Finland [19], China [20], and Norway [21].

Perhaps even more compelling than epidemiological data about the importance of elevated blood pressures in diabetics in preventing kidney disease are the large

number of successful clinical trials, summarized in detail below, that have shown major benefits in retarding the progression of kidney disease, and sometimes even preventing or delaying the onset of end-stage renal disease.

Hypertension Treatment Strategies in Diabetics

Lifestyle Modifications

Few would argue that intensive non-pharmacological intervention, typically starting with diet and exercise, should not be highly recommended for diabetics with elevated blood pressures [4]. Recent clinical trial data supporting these interventions in hypertensive diabetics, however, are scarce, as it is probably unethical now to randomize diabetic hypertensive patients to a strategy that does not include diet and exercise. A summary of the effects of dietary modifications (typically to lower both calories and sodium) on blood pressure can be found in an excellent review [22]. Many other lifestyle modifications have a salutary effect on blood pressure, but those highlighted in an American Heart Association Scientific Statement [23] included increased physical activity (typically aerobic exercise) and device-guided breathing. The benefits of aerobic exercise in hypertensive diabetics probably derive from both weight loss (with or without a diet plan) and improved insulin sensitivity. The best data on this point come from a large epidemiological study in Finland [24], and the Finnish Diabetes Prevention Study [25], which showed that overweight subjects with impaired glucose tolerance experienced a 58% reduction in the risk of diabetes over an average of 3.2 years after being randomized to individualized counseling about reducing weight, total and saturated fat, and increasing dietary fiber and physical activity; the benefits were directly related to successful achievement of these goals.

A beneficial lifestyle modification that should not really require much discussion is tobacco avoidance [1, 4]. Cigarettes and other forms of tobacco use increase the risk of atherosclerotic cardiovascular disease, independently of blood pressure and diabetes. Although the “evidence-base” for tobacco avoidance in diabetics, hypertensives, or the combination is lacking (primarily because it would be unethical to recommend that smokers with these problems continue using tobacco), all current guidelines recommend cessation of tobacco use, which has been shown in long-term epidemiological studies to significantly decrease the risk of most of the chronic complications of hypertension and diabetes (including cardiovascular death, myocardial infarction, stroke, and amputations).

Effects of Antihypertensive Drugs on Incident Diabetes

Although lowering elevated blood pressure is highly beneficial in preventing both cardiovascular and renal endpoints in individuals with hypertension, different classes of antihypertensive agents have disparate effects on glucose tolerance (and

incident diabetes). It has been known since the late 1950s that thiazide diuretics may increase insulin requirements in diabetics, or increase the risk of incident diabetes in those who are not yet diabetic. Data on this point are confounded by the fact that hypertension itself increases these risks, presumably due to both the higher risk of overweight/obesity, and increased insulin resistance. Some beta-blockers have been noted to increase both these risks, perhaps by limiting exercise tolerance and decreasing peripheral arterial flow (and glucose uptake by large skeletal muscles). On the other hand, both angiotensin converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown in randomized clinical trials to improve insulin sensitivity, and reduce the risk of incident diabetes. Network meta-analyses have been used to compare the risks of incident diabetes across all antihypertensive drug classes (including placebo/no treatment) in long-term randomized clinical trials in hypertensive individuals [26]. The most recent of these is summarized in Fig. 11.4 [27].

The clinical implications of these data are controversial [26, 28]. The Multiple Risk Factor Intervention Trial [29], the population-based Finnish Monitoring of trends and determinants in cardiovascular disease experience [30], the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) [31], and the long-term follow-up of the Systolic Hypertension in the Elderly Trial [32] all showed no significant increase in cardiovascular risk among individuals who were not diabetic at baseline, but who developed it during afterward, compared to those who maintained euglycemia during follow-up. This conclusion can be easily faulted, however, because the duration of follow-up, particularly in clinical trials, was relatively short (e.g., in ALLHAT, the protocol called for initial testing for incident diabetes at 2 years of follow-up, and therefore limited the time for development of subsequent cardiovascular disease to 2.9 years, on average). A population-based observational study from Italy suggested (based on 11 outcome

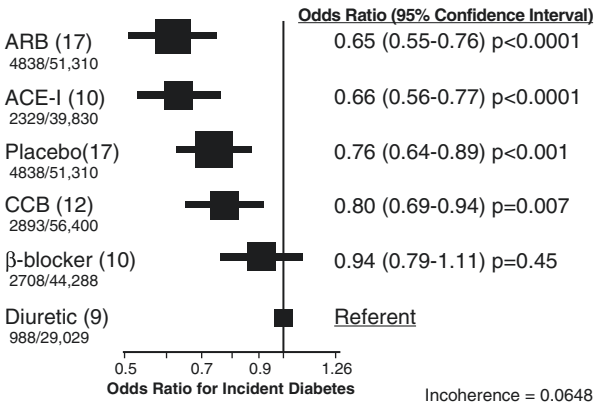

Fig. 11.4 Results of network meta-analysis of incident diabetes in 34 clinical trials involving antihypertensive drugs (and placebo/no treatment). The numbers in parentheses after each class of drug are the frequency of use in clinical trials; the numbers separated by the slash below the drug class correspond to the number of incident diabetics/number of subjects at risk. (Data from Ref. [27])

events in the new diabetic population) that new-onset diabetes was associated with a significantly higher risk of cardiovascular events (compared to non-diabetics), which did not differ from cardiovascular event rates over 13 years in those who were diabetic at baseline [33]. A population-based study from Gothenberg, Sweden concluded that it took 9 years for the cardiovascular risk of new-onset diabetes to achieve statistical significance [34]. The Framingham Heart Study also concluded that the cardiovascular risk associated with incident diabetes was time-dependent, and became significant after more than a decade for coronary heart disease, but only ~7 years for coronary heart disease death [35]. This experience was similar to that seen in the Valsartan Long-term Use Evaluation (VALUE) trial, in which the 1298 patients who developed diabetes during follow-up had a cardiac morbidity that was intermediate (hazard ratio 1.43, 95% confidence interval: 1.16–1.77) between those who were diabetic at randomization (hazard ratio 2.20, 95% confidence interval: 1.95–2.49), compared to the referent group who remained euglycemic throughout [36].

There is little doubt that, in large populations, the increased risk of incident diabetes associated with diuretics or beta-blockers (even though statistically significant), is vastly outweighed by the overwhelmingly beneficial effects of blood pressure lowering. Even if the cardiovascular and/or renal risk of incident diabetes does not increase significantly for a decade, the short-term incremental costs involved in routine medical care for diabetics will be substantial: monitoring blood glucose (and A1c twice yearly), intensifying lipid-lowering drug therapy, monitoring renal function (albuminuria and serum creatinine), and ophthalmological and podiatric screening [4]. These types of considerations have led to the common recommendation to begin antihypertensive drug therapy for most diabetics with either an ACE-inhibitor or an ARB, as they are least likely to increase plasma glucose levels or insulin requirements, and they delay the progression of albuminuria (see below) [4].

Pharmacological Treatment of Hypertension in Diabetes

Overview

Essentially all authorities agree that controlling blood pressure is beneficial for diabetics [4], but controversy exists regarding which class of antihypertensive agent should be preferred as first-line drug therapy, and what the target blood pressure should be. The American Diabetes Association still recommends either an ACE-inhibitor or an angiotensin receptor blocker for all diabetics with urinary albumin:creatinine ratio >30 mg/gm [4]. In 2005, the Blood Pressure Lowering Treatment Trialists' Collaboration found "comparable" differences across four initial types of antihypertensive drugs (ACE-inhibitor, ARB, calcium antagonist, diuretic/beta-blocker) vs. placebo for preventing total major cardiovascular events in diabetics, and "limited evidence" that lower blood pressure goals produced larger

reductions in total major cardiovascular events in diabetics [12]. This last conclusion was similar to the non-significant trend seen in the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Blood Pressure trial, regarding the primary outcome comparing systolic BPs of <120 and <140 mm Hg [37]. Some have suggested that the argument about a "preferred" initial antihypertensive drug therapy in diabetics is (or should be) moot, as nearly all diabetics (in clinical trials, as well as in general clinical practice) have required two or more blood pressure-lowering agents to achieve even the currently recommended blood pressure target of <140/90 mm Hg [4].

The numbers of diabetics with major cardiovascular events (composite of cardiovascular death, stroke, or myocardial infarction) observed (or estimated) in 28 randomized clinical trials of antihypertensive drugs involving 78,754 subjects, are summarized in Table 11.2. The results from a network meta-analysis of these data are shown in Fig. 11.5 [38]. These data support (and extend) the 2005 analyses of the Blood Pressure Lowering Treatment Trialists' Collaboration [14], as well as those of the 2015 meta-analysis [12], both of which suggested that there were few important (or statistically significant) outcome differences across randomized initial therapies for hypertensive diabetics. These data are confounded by the fact that most placebo-treated patients in these studies received other antihypertensive agents, in addition to the randomized drug, which dilutes the protective effect of the active agent. Most authorities now hold that most differences in such analyses are more likely due to issues related to statistical power, study design, and other technical factors, rather than a clear superiority of one drug class over another for all diabetic hypertensive subjects.

ARBs

Angiotensin II receptor blockers offer many advantages for the treatment of hypertension in type 2 diabetics. They are generally effective in lowering blood pressure (particularly when combined with a diuretic or calcium antagonist), are well tolerated (even better than placebo in several comparative trials in non-diabetics), reduce both the incidence and severity of proteinuria or albuminuria, prevent major cardiovascular and renal events, and are contraindicated only in patients immediately before or during pregnancy, with known renovascular hypertension, or prior allergy to the specific agent. All ARBs (except azilsartan) are now generically available, and at least 3 (losartan, valsartan and irbesartan) are on most $9/month drug lists.

Probably the best clinical trial evidence for an angiotensin receptor blocker to prevent major cardiovascular events comes from the type 2 diabetic subgroup enrolled in the Losartan Intervention For Endpoint (LIFE) reduction trial [39]. Critics will argue that this study enrolled only patients with very strict criteria for left ventricular hypertrophy, and therefore its results may not and should not be generalizable to other patients without such abnormalities. Two years after its publication, the first author of this very report pointed out that atenolol, the initial comparator agent in LIFE, is a suboptimal once-daily antihypertensive agent [40].

Table 11.2 Major cardiovascular events observed (or estimated[a]) in outcome-based clinical trials of antihypertensive drugs in diabetics

Trial acronym	Drug class	Events/at risk	Drug class	Events/at risk	Drug class	Events/at risk
SHEP[a]	Diuretic	39/283	Placebo	58/300		
ABCD	CCB	47/235	ACE	29/235		
FACET	CCB	23/191	ACE	14/189		
UKPDS	ACE	94/400	Beta-blocker	72/358		
NORDIL	CCB	44/351	Beta-blocker[a]	44/376		
Syst-Eur[a]	CCB	13/252	Placebo	31/240		
MICRO-HOPE	ACE	277/1808	Placebo	351/1769		
Syst-China[a]	CCB	5/51	Placebo	10/47		
INSIGHT[a]	CCB	46/649	Diuretic	49/653		
PROGRESS	ACE	82/394	Placebo	91/368		
IDNT	ARB	138/579	Placebo	144/569	CCB	128/567
RENAAL	ARB	124/751	Placebo	118/762		
IRMA-2[a]	ARB	11/194	Placebo	18/201		
LIFE	ARB	103/586	Beta-blocker	139/609		
ALLHAT	Diuretic	906/5393	CCB	555/3214	ACE	521/3129
CONVINCE	CCB	101/1616	Beta-blocker	116/1623		
INVEST[a]	CCB	463/3169	Beta-blocker	450/3231		
SCOPE	ARB	46/313	Placebo	51/284		
PERSUADE	ACE	103/721	Placebo	130/781		
DIAB-HYCAR	ACE	282/2443	Placebo	276/2469		
DETAIL	ACE	12/130	ARB	150/120		
ASCOT	CCB	246/2565	Beta-blocker	257/2572		
ADVANCE	ACE	480/5569	Placebo	520/5571		
CASE-J	ARB	68/1011	CCB	70/1007		
ONTARGET	ARB	568/3246	ACE	558/3146		
ACCOMPLISH	CCB	170/3347	Diuretic	203/3468		
PRoFESS	ARB	498/2840	Placebo	511/2903		
TRANSCEND	ARB	211/1059	Placebo	211/1059		

SHEP Systolic Hypertension in the Elderly Program [64], *ABCD* Appropriate Blood pressure Control in Diabetes (N Engl J Med. 2000;343:1969), *FACET* Fosinopril Amlodipine Cardiovascular Events Trial (Diabetes Care. 1998;21:1779–1780), *UKPDS* United Kingdom Prospective Diabetes Study #39 [63], *NORDIL* Nordic Diltiazem study (Lancet. 2000;356:359–365), *Syst-Eur* Systolic hypertension in Europe trial (N Engl J Med. 1999;340:677–684), *MICRO-HOPE* Microalbuminuria, Cardiovascular and Renal Outcomes-Heart Outcomes Prevention Evaluation [52], *Syst-China* Systolic Hypertension in China study (Arch Intern Med. 2000;160:211–220), *INSIGHT* International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment

(continued)

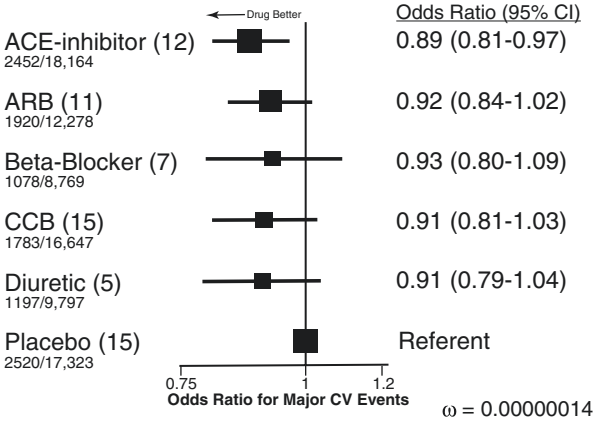

Fig. 11.5 Results of a network meta-analysis comparing the risk of major cardiovascular events (cardiovascular death, myocardial infarction, or stroke) in 78,754 diabetic subjects across all randomized drug classes (placebo, diuretic, beta-blocker, calcium antagonist, ACE-inhibitor, angiotensin II receptor blocker) in 28 clinical trials of antihypertensive drugs (excluding the combination arms of ONTARGET, adapted from Ref. [38]). Numbers in parentheses are the number of trials using this randomized drug class. Horizontal bars indicate the 95% confidence limits; the boxes represent the odds ratios (drawn with area proportional to available statistical information). *CI* confidence interval, *ACE-inhibitor* angiotensin converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *CV* cardiovascular. Numbers separated by the slash below the drug class represent the numbers of diabetics with major cardiovascular events/numbers randomized across all trials

(Hypertension. 2003;41:431–6), *PROGRESS* Perindopril Protection against Recurrent Stroke Study (Blood Press. 2004;13:7–13), *IDNT* Irbesartan Diabetic Nephropathy Trial [41], *RENAAL* Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan [42], *IRMA-2* Irbesartan in patients with type 2 diabetes and Microalbuminuria study #2 [44], *LIFE* Losartan Intervention For Endpoint reduction trial [36], *ALLHAT* Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial [53], *CONVINCE* Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (JAMA. 2003;289:2073–2082), *INVEST* International Verapamil-trandolapril Study (Hypertension. 2004;44:637–642), *SCOPE* Study on Cognition and Prognosis in the Elderly (Blood Press. 2005;14:31–37), *PERSUADE* Perindopril Substudy in coronary Artery disease and Diabetes (Eur Heart J. 2005;26:1369–1378), *DIAB-HYCAR* Diabetes, Hypertension, microalbuminuria or proteinuria, Cardiovascular events And Ramipril study (BMJ. 2004;328:495, erratum 686), *DETAIL* Diabetics Exposed to Telmisartan And Enalapril Study [50], *ASCOT* Anglo-Scandinavian Cardiac Outcomes Trial [61], *ADVANCE* Action in Diabetes and Vascular disease: preterAx® and diamicroN-MR® Controlled Evaluation (Lancet. 2007;370:829–840), *CASE-J* Candesartan Antihypertensive Survival Evaluation in Japan (Hypertens Res. 2010;33:600–606), *ONTARGET* Ongoing Telmisartan Alone or in combination with Ramipril Global Endpoint Trial [56], *ACCOMPLISH* Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension [62], *PRoFESS* Prevention Regimen for Effectively Avoiding Second Strokes (N Engl J Med. 2008:359:1225–1237), *TRANSCEND* Telmisartan Randomised Assessment Study in angiotensin Converting Enzyme-inhibitor intolerant subjects with cardiovascular Disease (Lancet. 2008;371:1174–1183)

Despite these objections, however, the 1195 subjects in LIFE all had hypertension, type 2 diabetes, and electrocardiographic evidence for left ventricular hypertrophy, and were randomized to initial antihypertensive therapy with either losartan or atenolol, followed by hydrochlorothiazide, and other antihypertensive drugs, as needed. Blood pressures fell from an average of 177/96 mm Hg at randomization to 146/79 mm Hg in the losartan group, compared to 148/79 mm Hg in the atenolol group. The primary composite endpoint was the first occurrence of cardiovascular death, stroke, or myocardial infarction, and was significantly reduced in the group randomized to losartan (relative risk: 0.76, 95% confidence interval: 0.58–0.98, P = 0.031), even after statistical adjustment for both baseline Framingham risk score and the degree of left ventricular hypertrophy. This unusual, *post-hoc*, step was prespecified in the LIFE data analysis protocol, to reduce the probability of a Type II statistical error, which was most likely to have arisen from an unbalanced randomization process. Both all-cause and cardiovascular mortality were also significantly reduced in the losartan group (by 39% and 37%, respectively). These data were consistent with a suggestion, popular from 1995 to 2005, that how blood pressure was lowered might be an important determinant of outcomes [41]; today, most authorities agree that lowering blood pressure is more important than which agent is selected to start the process [42, 43].

Two classic, placebo-controlled, multicenter, prospective, randomized clinical trials have made type 2 diabetic nephropathy a "compelling indication" for an ARB, resulting in two FDA-approvals for this condition. Many are not aware that in both the Irbesartan Diabetic Nephropathy Trial (IDNT) [44] and the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Trial [45], potentially-eligible type 2 diabetics had their blood pressures treated with diuretics, beta-blockers, and/or other antihypertensive drugs, before randomization to an ARB, placebo (or amlodipine in IDNT). The entry criteria for the two studies were only slightly different: IDNT required type 2 diabetics between 30 and 70 years of age, a blood pressure >135/85 mm Hg, >900 mg/day of proteinuria, and a serum creatinine between 1 and 3 mg/dL in women, or 1.2–3.0 mg/dL in men. For RENAAL, type 2 diabetics had to be 30–70 years old, with urinary albumin/creatinine ratios of >300 mg/gm, and serum creatinine levels between 1.3 and 3.0 mg/dL. The results, published back-to-back in the *New England Journal of Medicine*, were astonishingly similar. Blood pressure was reduced in IDNT from 159/87 mm Hg at randomization, to 140/77 mm in the group randomized to irbesartan, 141/77 mm Hg in the group randomized to amlodipine, and 144/80 mm Hg in the group randomized to placebo. In RENAAL, blood pressures were reduced from 152/82 mm Hg at randomization, to 140/74 mm Hg in the losartan group, and 142/74 mm Hg in the placebo group (at the end of the study). Not only was the primary composite endpoint for both trials identical (first occurrence of doubling of serum creatinine, end-stage renal disease, or death), but also the final P-value comparing the incidence of the primary endpoint across the ARB and placebo was exactly 0.02 for each trial! The results of traditional meta-analyses summarizing these two landmark trials are shown in Fig. 11.6. It is probably not surprising that there was no overall effect on mortality, as the average age of the

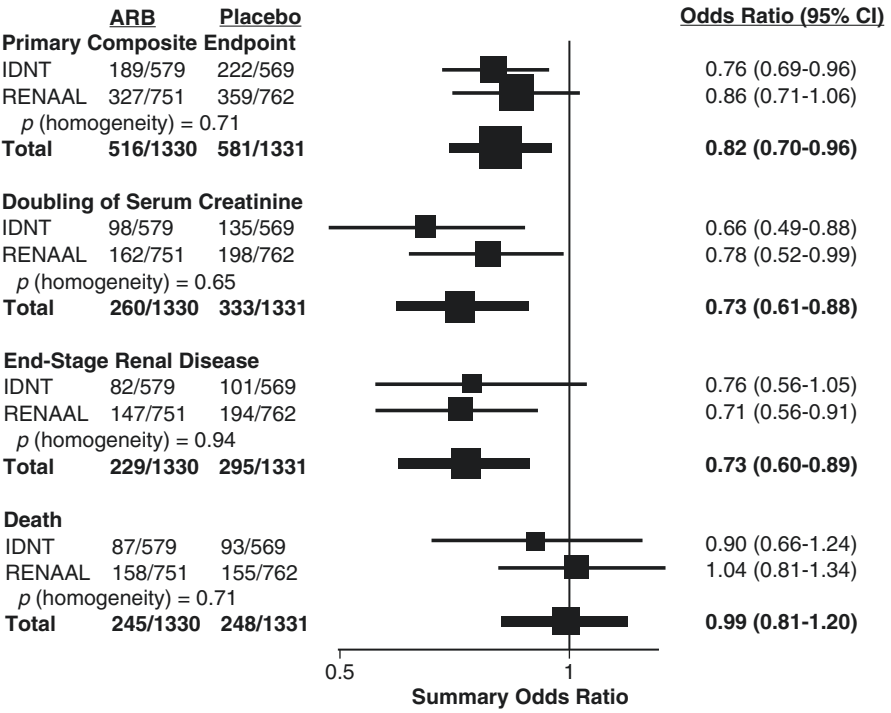

Fig. 11.6 Results of traditional Mantel-Haenzsel meta-analyses of comparisons of an angiotensin receptor blocker (irbesartan or losartan) vs. placebo in two landmark trials of type 2 diabetic nephropathy. (Data from Refs. [44, 45]). Horizontal bars correspond to the 95% confidence limits for each comparison; solid boxes are drawn in proportion to the number of subjects experiencing each endpoint (compared to the referent primary composite endpoint). *ARB* angiotensin receptor blocker, 95% CI = 95% confidence interval, *IDNT* Irbesartan Diabetic Nephropathy Trial, *RENAAL* Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan. Note that these analyses ignore otherwise valid data from the amlodipine arm of IDNT

diabetic subjects was nearly 60 years, and nearly two-thirds had retinopathy at randomization. However, the overall highly significant delay of the primary endpoint, and the significant reduction in the number of people requiring renal replacement therapy were impressive. Pharmacoeconomic analyses of these and similar outcomes studies indicate that ARBs (even at pre-generic prices!) are cost-saving within 2 years of institution of therapy in patients with either early or late diabetic nephropathy [46].

Although not recognized by the US FDA as a valid surrogate endpoint, albuminuria and/or proteinuria have been extensively studied in both type 1 and type 2 diabetics. In nearly all trials, ARBs are quite effective in both reducing albuminuria in the short-term, and preventing its development in the longer term (typically 2–4 years). Perhaps the most famous trial of this type was the Irbesartan Microalbuminuria trial [47], published simultaneously with IDNT and RENAAL. In

this prospective trial, 610 type 2 hypertensive diabetics with "microalbuminuria" (then defined as 20–200 μg/min) were randomized to placebo or low or high dose irbesartan for 2 years, and followed for the development of frank proteinuria (≥ 288 mg/d, and an increase from baseline of ≥15%). Blood pressures were barely different across the groups (145/84 mm Hg with placebo, 143/84 mm Hg with 150 mg/d, and 142/84 mm Hg with 300 mg/d of irbesartan), and there were fewer adverse effects and discontinuations in the drug-treated groups. After 2 years, only the group receiving irbesartan at 300 mg/d showed a significant (70%) reduction in the incidence of proteinuria; the lower dose had only a non-significant trend at 39%. A subsequent meta-analysis suggested that renin-angiotensin-aldosterone system inhibitors significantly reduced albuminuria in both type 1 and type 2 diabetics, with a larger effect on those with higher levels of baseline albuminuria [48].

Several of the many objections to albuminuria as a valid or useful surrogate endpoint in kidney disease in diabetics can be documented by conclusions of important studies. Especially in type 1 diabetes, the degree of albuminuria varies considerably, depending on recent blood pressure control, volume status, dietary sodium intake, and other factors. One prospective study of 75 normotensive type 1 diabetics without albuminuria at baseline suggested that patients with an increase in blood pressure during sleep predicted the development of microalbuminuria [49]. This issue can presumably be overcome by requiring two successive determinations above threshold (e.g., as in the Irbesartan Microalbuminuria trial [47]). Secondly, a 3.2-year clinical trial that enrolled 4447 type 2 diabetics without albuminuria, comparing 40 mg of olmesartan vs. placebo showed a slightly lower office blood pressure (by 3.1/1.9 mm Hg), a slowing of the rate of onset of microalbuminuria (by 23%, 95% CI: 6%–37%, P = 0.01), no difference in nonfatal cardiovascular events (P = 0.37), but an increase in cardiovascular death (15 vs. 3, P = 0.01) in the olmesartan group [50]. Although the excess death rate has been attributed to chance, an imbalance in the numbers of patients with known coronary heart disease, and other factors, many would argue that it takes far longer than 3.2 years for the disease process in hypertensive diabetics to progress from microalbuminuria to clinical cardiovascular events, suggesting that this study was underpowered to detect a significant difference in the "hard endpoints" of stroke, myocardial infarction, or cardiovascular death. The role of albuminuria as an outcomes effect modifier in chronic kidney disease is likely to remain controversial for some years to come [51].

ACE-Inhibitors

ACE-inhibitors share many of the advantages of ARBs for the treatment of diabetics with hypertension, but carry the added risk of chronic, nonproductive cough (~13%) and angioedema (0.7%). Perhaps because they were the first available agents that directly inhibited the renin-angiotensin system, they have been well tested in clinical trials that included diabetics. Perhaps the most illustrative is the Captopril Collaborative Study Group's comparison of captopril vs. placebo in type 1 diabetics with nephropathy [52]. This trial enrolled 409 type 1 diabetics with urinary protein

excretion >500 mg/d and serum creatinine <2.5 mg/dL, and used doubling of serum creatinine as the primary endpoint. After a 3-year median follow-up period, blood pressure differences between the groups were <2/4 mm Hg; significantly fewer patients in the captopril-treated group experienced doubling of serum creatinine (25 vs. 43, P = 0.007), or the secondary composite (but clinically important) endpoint of death, dialysis or transplantation (23 vs. 42, P = 0.006).

This landmark study made it difficult to justify doing similar placebo-controlled renal outcome trials in type 2 diabetics, as it was widely assumed that similar benefits should accrue. One head-to-head comparison of an ARB with an ACE-inhibitor has been done in type 2 diabetics, but it used the surrogate endpoint of decline in glomerular filtration rate (measured by iohexol clearance) as its primary outcome measure, and was successful in establishing statistical "non-inferiority" of telmisartan with enalapril in a 5-year study of 250 type 2 diabetics [53]. Many feel that this endpoint was not as robust as those used in previous renal outcome studies, and may have been unduly influenced by lack of a final measurement in 14% of the telmisartan- and 13% of the enalapril-treated subjects. Many other trials have established ACE-inhibitors as being particularly valuable for reducing proteinuria and delaying the progression of chronic kidney disease in patients without diabetes [54].

ACE-inhibitors have also been studied extensively to prevent cardiovascular disease events in diabetics. Perhaps the most optimistic effects were seen with ramipril in the 3677 diabetics randomized in the Heart Outcomes Prevention Evaluation (HOPE) [55]. Although stopped 6 months earlier than planned, the diabetics randomized to rampril enjoyed a highly significant 25% relative risk reduction for the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke, as well as significant reductions in each of its components, as well as a 24% reduction in all-cause mortality and development of >300 mg/d of proteinuria. Later trials enrolling large numbers of diabetics and non-diabetics, that compared placebo with either perindopril or trandolapril were not nearly as positive, probably because of more extensive and appropriate treatment of other risk factors in both randomized groups (including antiplatelet agents, beta-blockers in subjects with a history of myocardial infarction, and lipid-lowering agents). The overwhelmingly positive results of HOPE and its diabetic substudy might be attributed to the reluctance of the Data Safety and Monitoring Board to halt the trial, which would be far more likely today (for many reasons) than in 1999.

It is important to balance the perhaps uniquely positive results of HOPE and its diabetic substudy by contrasting it with the results of the clinical trial that enrolled the largest number of type 2 diabetics ever, the Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial (ALLHAT) [56], discussed further below. In their enrolled cohort of 13,101 diabetics, lisinopril was not superior to chlorthalidone in preventing any type of cardiovascular event, and may have been significantly worse in preventing stroke in black subjects (diabetic or not).

Many small studies in diabetes, heart failure, chronic kidney disease, and other conditions suggested that combining an ACE-inhibitor and an ARB might be beneficial. This seemed especially promising for reduction of albuminuria in diabetics [57], or prevention of death or rehospitalization in patients with systolic heart

failure [58]. However, when the large trial (with 25,620 randomized subjects) was undertaken combining full doses of telmisartan + ramipril, there was a slightly lower blood pressure in the group given the combination, but no improvement in cardiovascular events, significantly more hyperkalemia and renal dysfunction [59], and a significantly greater risk of the composite of doubling of serum creatinine, end-stage renal disease, or death [60]. Among the 9612 enrolled diabetics, similar (non-significant) trends were observed for these important endpoints. These data suggested that there were few differences between full doses of an ACE-inhibitor and an ARB, and that the combination might be harmful to the kidney. More recently, losartan (100 mg/d) was given to 1448 type 2 diabetics with an albumin/creatinine ratio of >300 mg/gm and a baseline estimated glomerular filtration rate (*e*GFR) between 30 and 89.9 mL/min/1.73 m^2, to which was added either placebo or lisinopril (10–40 mg/d). Although originally intended to compare regimens with regard to a "hard renal endpoint" (a composite of the first occurrence of: decline in *e*GFR ≥30 mL/min/1.73 m^2 if baseline *e*GFR was ≥60 mL/min/1.73 m^2, decline in *e*GFR of ≥50%, end-stage renal disease, or death), the trial was terminated early (despite a non-significant 12% reduction in the primary composite endpoint) because of excess hyperkalemia (6.3 vs. 2.6 events per 1000 person-years in the combination vs. monotherapy arms) and acute kidney injury (12.2 vs. 6.7 events per 1000 person-years) [61]. These data confirmed the potential harms of combining an ACE-inhibitor + ARB in type 2 diabetics, which increased the risk of shared toxicities (e.g., hyperkalemia, acute kidney injury), with no major benefit on cardiovascular or renal outcomes.

Renin Inhibitor(s)

The newest method of interfering with the renin-angiotensin system attacks the rate limiting step: hydrolysis of angiotensinogen to angiotensin I, by directly inhibiting renin. Aliskiren, the original renin inhibitor, was launched in 2007, and seemed to have many of the advantages of an ARB: dose-dependent blood pressure reductions, excellent tolerability profile, and contraindications only for pregnancy and renal artery disease. The initial trial in hypertensive type 2 diabetics with an early morning albumin/creatinine ratio between 300 and 3499 mg/gm compared losartan 100 mg/d, with or without aliskiren force-titrated from 150 mg/d for 3 months, to 300 mg/d, for another 3 months [62]. The results were quite promising: only a little (and non-significant) lowering of blood pressure, quite similar adverse effects, and a 20% overall reduction in albumin/creatinine ratio, with aliskiren + losartan, compared to losartan alone. This led to high expectations about the "hard outcomes study" that compared adding aliskiren (300 mg/day) to either an ACE-inhibitor or an ARB in 8561 diabetics with either chronic kidney disease, cardiovascular disease, or both. Although blood pressure and albuminuria were slightly lower in the group given aliskiren, the study was stopped prematurely because of significantly higher risk of hyperkalemia, hypotension, or adverse effects requiring discontinuation of drug therapy in the aliskiren group [63]. After the announcement of the trial's

early termination, other trials of aliskren in diabetics and marketing efforts for all dose forms of the aliskiren + valsartan combination were halted, and the FDA-approved product information for aliskiren was updated to include a contraindication for combining aliskiren with either an ARB or ACE-inhibitor in diabetics, and a warning against using aliskren in patients with an estimated glomerular filtration rate <60 mL/min/1.73 m^2, if the patient is already taking an ACE-inhibitor or ARB.

A *post-hoc* analysis of the trial comparing the combination of telmisartan + ramipril to monotherapy with either in type 2 diabetics also showed a higher risk of hypotension, hyperkalemia, and the need for acute dialysis in those receiving dual inhibitors of the renin-angiotensin system [64]; excess risk was also observed in the losartan + lisinopril-treated group of the more recent trial funded by the Department of Veterans Affairs [61]. Taken together, these data indicate that monotherapy should be more advantageous than combining two drugs that interfere at different sites of the renin-angiotensin-aldosterone cascade.

Calcium Antagonists

Both dihydropyridine and non-dihydropyridine calcium antagonists have been used to lower blood pressure in many diabetic patients, based on a number of clinical trials. Early studies of non-dihydropyridine calcium antagonists showed mild-to-moderate reductions in proteinuria, which are often additive to those of renin-angiotensin system inhibitors, whereas "naked" dihydropyridine calcium antagonist tend to increase proteinuria, and were significantly inferior to an ARB in IDNT in preventing its renal endpoints [44]. As a result, most physicians now use calcium antagonists in combination with a renin-angiotensin-system inhibitor, as was commonly the case in RENAAL [45]. Calcium antagonists have no major adverse effect on glucose or cholesterol metabolism, are reasonably well tolerated, and have plentiful outcomes data from randomized clinical trials in both diabetic and non-diabetic hypertensives.

Two trials are especially illustrative of the potential benefits of calcium antagonists in diabetics: the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH). The former compared amlodipine (with perindopril, as needed) and atenolol (with bendroflumethiazide, as needed), with fatal or non-fatal myocardial infarction as the primary endpoint. Concomitantly, eligible subjects were randomized to atorvastatin or placebo, which was so successful in reducing the incidence of the primary endpoint that it was stopped early, leaving the blood pressure-lowering arm of the trial with lower-than-expected statistical power. This was thought to justify a change in the primary outcome measure to total cardiovascular events and procedures for all pre-specified subgroup analyses, including that for the 5137 diabetics [65]. Although the study protocol recommended a target of <130/80 mm Hg for diabetics, their blood pressure was reduced, at 1 year, to 143/81 and 148/84 mm Hg, in the amlodipine and atenolol groups, respectively, and to 137/76 and 136/75 mm Hg at the end of the

study. During follow-up, the Kaplan-Meier curves for total cardiovascular events and procedures in diabetics were super-imposable for the first 3 years, but diverged thereafter, resulting in an overall significant advantage for the amlodipine-treated group (P = 0.0261). This difference was presumably driven by putatively significant differences (P < 0.05, uncorrected for multiple comparisons) in fatal and non-fatal stroke, chronic stable angina, nonfatal stroke, peripheral arterial disease, and other revascularization procedures, all favoring amlodipine. The original primary outcome measure was not significant (P = 0.46), although the trend favored amlodipine. Overall, these results in diabetics paralleled those seen in the entire ASCOT study cohort, and have been criticized by those who believe that secondary outcomes can be properly evaluated only if the primary outcome is significant.

The ACCOMPLISH trial enrolled 11,505 high-risk hypertensive subjects (including 6946 with diabetes), and randomized them to initial therapy with benazepril and either amlodipine or hydrochlorothiazide [66]. The primary outcome measure was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for angina, resuscitated cardiac arrest, or coronary revascularization. The protocol recommended a target blood pressure of <130/80 mm Hg for all diabetics, but the average office blood pressures were 132/73 and 133/74 mm Hg in the amlodipine- and hydrochlorothiazide-treated groups during follow-up. Despite its early termination due to superiority of amlodipine over hydrochlorothiazide, diabetics randomized to the former therapy enjoyed a significant 23% reduction in the primary endpoint (P = 0.003), with significantly lower rates of coronary events (revascularization and the composite of myocardial infarction, unstable angina pectoris, or sudden cardiac death). In addition, the *post-hoc* renal endpoint (increase in serum creatinine by >50% and above the reference range) was significantly reduced in incidence by 47% (95% CI: 36–55%, P < 0.001) in diabetics, and even more in non-diabetics (62%). These data have caused some guideline committees to favor a calcium antagonist over hydrochlorothiazide as second-line antihypertensive therapy for diabetics, but most ALLHAT investigators believe that chlorthalidone would have produced different results, if it had been used instead of the much shorter-acting and less potent hydrochlorothiazide.

Beta-Blockers

As discussed above, most authorities currently recommend a beta-blocker for diabetics only if there is a compelling indication (e.g., post-MI, heart failure with diminished left ventricular function), because of their propensity to mask hypoglycemic signs and symptoms, potential hyperglycemia, and reduction of exercise tolerance (which may promote weight gain). Before concerns about atenolol were raised [39, 40, 65], the United Kingdom Prospective Diabetes Study 39 randomized 1158 newly diagnosed type 2 diabetics with hypertension to twice-daily captopril or once-daily atenolol, with a second randomization (discussed below) to different target office blood pressure levels. During 9 years of follow-up, significantly more subjects abandoned atenolol than captopril, but there were no significant differences

across treatment arms for any of the several pre-specified endpoints (although they all favored atenolol) [67].

Diuretics

Diuretics have long been used to lower blood pressure in diabetics; for many such patients, attainment of blood pressure goals is difficult or impossible without a diuretic. These agents decrease the intravascular volume that is common in many type 2 diabetics, prevent heart failure, and counter the hyperkalemic effects of renin-angiotensin system inhibitors. Their adverse effects sometimes include erectile dysfunction, hypokalemia, and an increased risk of worsening glycemic control.

There is nonetheless a solid base of clinical trial evidence supporting the use of diuretics for hypertensive diabetics. In the Systolic Hypertension in the Elderly Program (SHEP) trial, chlorthalidone-based therapy was significantly better than placebo in reducing major cardiovascular disease events, with the same 34% relative risk reduction, but a twofold higher absolute risk reduction [68]. A meta-analysis from the Individual Data Analysis of Antihypertensive Drug Interventions project that included the Hypertension Detection and Follow-up Program, European Working Party on Hypertension in the Elderly, Swedish Trial of Older Patients with Hypertension, and SHEP showed a significant reduction in stroke (36%) and major cardiovascular events (20%) with an initial diuretic, compared to control intervention [69]. Lastly, and perhaps most importantly, as briefly mentioned above, the ALLHAT trial enrolled more diabetics than any other trial, and concluded that the diuretic they chose, chlorthalidone, was superior to all other classes of initial antihypertensive drugs for preventing one or more forms of cardiovascular disease among all hypertensives, as well as diabetics [56]. This conclusion, based largely on the inclusion of heart failure as an independent endpoint, rather than part of a composite (as originally planned), was originally quite controversial. Since then, the controversy has shifted to how large the differences are between chlorthalidone and the much more popular hydrochlorothiazide. Using very selective criteria that included data from only 9 trials, investigators from Connecticut concluded that chlorthalidone was clearly superior to hydrochlorothiazide in preventing cardiovascular events [70]; other investigators did not find a significant difference in outcomes between the two drugs in two other network meta-analyses that included data from 5 and 83 clinical trials [71, 72], although outcomes data (particularly in preventing heart failure) are far more plentiful with chlorthalidone [73].

Other Drug Classes

Most authorities agree that an alpha-1 adrenergic antagonist was inferior to low-dose chlorthalidone in preventing heart failure and combined cardiovascular disease events in ALLHAT diabetics [74]. There are many possible explanations for this disparity, including the use of seated (rather than standing) blood pressures, but it

reinforces the importance of hard endpoints in clinical decision-making. Many previous studies had shown putatively beneficial effects of alpha-1 blockers on blood pressure, glucose and lipid metabolism, which were also seen in ALLHAT, but eventually found to be less important for preventing cardiovascular disease outcomes. Centrally-acting alpha-2 agonists are sometimes needed to control blood pressure, and have few adverse metabolic effects, but sedation, dry mouth, and other common adverse effects make them less popular for routine therapy of hypertension. Aldosterone antagonists are also occasionally useful, but hyperkalemia and worsened renal impairment are common adverse effects.

Blood Pressure Treatment Targets for All Diabetics?

Controversy still exists regarding the effects of a lower-than-usual blood pressure target for all diabetics. This had been a basic tenet in the diabetes and hypertension communities for many years, but was challenged by the ACCORD trial [37], rejected by JNC 8 [75], and then indirectly validated in SPRINT [76] (which included no diabetics), and eventually reinstated by the ACC/AHA 2017 US Hypertension Guideline [3].

Evidence supporting a lower-than-usual blood pressure target for diabetics came from at least 3 clinical trials: the United Kingdom Prospective Diabetes Study, the Hypertension Optimal Treatment Study, and a small multiple-intervention trial in Denmark. Back in 1985, 1148 newly-diagnosed type 2 diabetics in the United Kingdom were randomized to a "lower blood pressure target" (≤150/85 mm Hg) or "less tight control" (≤180/100 mm Hg), and followed for 8.4 years [77]. The group randomized to the lower target achieved a mean blood pressure of 144/84 mm Hg, compared to 154/87 mm Hg for the other group, and suffered significantly fewer diabetes-related endpoints (the primary outcome measure, by 24%), deaths (32%), strokes (44%), and microvascular endpoints (37%). Formal cost-effectiveness analyses, based on then-current British healthcare costs, indicated that lowering blood pressure to the lower target saved both discounted disease-free life-years **and** money (£1049 per endpoint-free year of life saved) [78]. Note that the incremental blood pressure reduction between the two randomized groups seen in UKPDS (10/5 mm Hg) was **exactly** that recommended a year earlier (for diabetics compared to non-diabetics) by the 1997 US hypertension guidelines committee, which was also supported by a pharmacoeconomic analysis showing overall cost-savings for the lower target [79]. The second trial that showed a significant benefit of a lower-than-usual blood pressure target for diabetics randomized 1501 diabetics (among the enrolled total of 18,790 subjects) to diastolic blood pressures of ≤80, ≤85, or ≤90 mm Hg [80]. Over a median of 3.8 years of follow-up, diabetics randomized to the lowest diastolic BP had a significant, 51% lower risk of major cardiovascular events, compared to those randomized to ≤90 mm Hg. The results of this trial were therefore used to support lowering the diastolic blood pressure target for diabetics to <80 mm

Hg in many national and international guidelines written between 1998 and 2012. This target was seemingly supported by a small trial of 180 type 2 diabetics in Denmark, which showed a significant 55% reduction in the risk of cardiovascular complications in those who received "intensive therapy," which included a lower-than-usual blood pressure target [81]. Extended follow-up for another 5.5 years demonstrated a significant 45% reduction in overall mortality in the "intensive therapy" group [82].

The largest and most direct test of the lower blood pressure target for diabetics was the ACCORD trial, which enrolled 10,251 subjects, and randomized them to a systolic blood pressure of <140 or <120 mm Hg [37]. Although some argue that the <120 mm Hg is too low, the average achieved systolic blood pressure in this group was 119 mm Hg, proving that it was possible to meet such a low target. However, the overall cardiovascular event rates were not significantly different (P = 0.20), although the 12% relative risk reduction favored the lower target; only the secondary endpoint of fatal or nonfatal stroke was reduced significantly (by 41%, P = 0.01). By design, the Systolic blood Pressure INtervention Trial excluded diabetic subjects (because ACCORD-BP already answered the question of whether a lower-than-usual BP goal was beneficial in this population), but the overwhelmingly positive effects of the systolic target of <120 mm Hg were robust to many subgroup analyses [76]. Rather than simply addressing the question of whether the lower-than-usual target was appropriate for diabetics, the ACC/AHA 2017 US Hypertension Guideline simply recommended a target of <130/80 mm Hg for all subjects with a blood pressure higher than that [3].

Despite the controversy, there does seem to be some support for a lower-than-usual blood pressure treatment target for diabetics with nephropathy, based on *post-hoc* analyses of both IDNT and RENAAL. This makes perfect sense from the precepts of preventive medicine, as the recommended treatments are nearly always more intensive (and usually more beneficial) for high-risk, compared to low-risk, groups. This principle is supported by analyses of stroke prevention with antihypertensive drugs, previously-recommended targets for LDL-cholesterol reduction across the cardiovascular risk continuum, and former post-exposure prophylaxis for needlesticks that might transmit the human immunodeficiency virus. So several very recent guidelines have recommended a lower-than-usual blood pressure for diabetics [4] (and non-diabetics [51] if the albumin/creatinine ratio is >30 mg/gm). While one might argue that this recommendation is not completely or unanimously evidence-based, it fits with the more intensive treatment of predictors of outcomes that is common in other disease states.

To summarize, the optimal treatment of hypertension in diabetics is still controversial, but probably includes lifestyle modifications whenever feasible, one inhibitor (but **not** two inhibitors) of the renin-angiotensin system, and sufficient other antihypertensive medications to keep the blood pressure at a level inversely proportional to the absolute risk of cardiovascular and renal disease in the individual patient, based on assessment of other all risk factors, including albuminuria [83].

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Chapter 12
Obesity and Metabolic Syndrome

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The number of patients with diabetes and chronic kidney disease (CKD) has been increasing globally, in line with the rising prevalence of diabetes, driven largely by obesity. Obesity has become a significant concern in the US and many other resource-rich countries [1, 2]. In 2017–2018, the age-adjusted obesity prevalence among U.S. adults was 42.4% [3]. By 2030, it is estimated that about 50% of all adults in the US will be classified as having obesity [4].

Obesity promotes incident CKD and progression to end stage kidney disease (ESKD), reducing in the quality of life and life expectancy. Excessive adipose tissue also negatively impacts the lipid metabolism, blood pressure and glucose control, leading to cardiovascular disease (CVD). It is important that healthcare providers understand the mechanisms of kidney disease development and progression in the setting of obesity and metabolic syndrome.

The Role of Visceral Adiposity

Under normal conditions, adipose tissue is localized in two major areas; about 80% in the subcutaneous tissue, and approximately 20% surrounding the internal organs [i.e. visceral adipose tissue (VAT)] [5]. VAT is also more vascular, exhibit increased sympathetic innervation, have more β3-adrenergic receptors and higher metabolic activity [5]. Abnormally high accrual of visceral adipose tissue is known as visceral obesity, which is associated impaired glucose and lipid metabolism, insulin resistance and CVD [6–8].

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Renal Alterations in Obesity

Obesity, specifically visceral adiposity, is a major cause of hypertension, accounting for 65% to 75% of the risk for human primary hypertension [9]. An almost linear relationship exists between blood pressure and obesity in all population including whites, blacks, Hispanics and Asians. In addition, weight loss is shown to reduce blood pressure in both normotensive and hypertensive individuals who are obese. Increasing duration of obesity is also shown to exacerbate the obesity-induced blood pressure increase [10].

In addition to high blood pressure, obesity is associated with multiple hemodynamic alterations. Excessive adiposity increases blood and extracellular fluid volumes [10] as well as heart rate, cardiac output and venous return predisposing the heart to left ventricular hypertrophy [11].

In the kidney vasculature, excessive weight gain initially causes renal vasodilation, increased renal blood flow and glomerular filtration rate (GFR). Renal vasodilation in obesity is regulated by multiple factors, including renal compression, hyperglycemia, high protein intake, and increased blood pressure combined with impaired renal autoregulation [9]. Increased perirenal and renal sinus fat in obesity leads to compression of the thin loop of Henle and vasa recta of the medulla. This compression leads to reduced tubular flow rate and increased sodium absorption in the nephron. Subsequently, sodium delivery to macula densa decreases, resulting in feedback-mediated dilation in the afferent arterioles, and increases in the renal blood flow and GFR [10].

In addition to kidney compression, activation of the renin–angiotensin–aldosterone system (RAAS), renal mineralocorticoid receptor (MR) activation, and sympathetic nervous system activation also lead to excessive sodium reabsorption by the kidneys in the setting of obesity. [Fig. 12.1]. The resultant increased renal sodium reabsorption leads to compensatory renal vasodilation which, along with increased blood pressure, causes increased glomerular hydrostatic pressure and glomerular hyperfiltration, which may further exacerbate renal injury [10]. Sustained obesity over time with progressive renal injury aggravates hypertension and increases cardiovascular risk.

In addition, obesity-related glomerulopathy (ORG), a form of secondary focal segmental glomerulosclerosis (FSGS), is recognized as a distinct entity that occurs in the setting of obesity. ORG is characterized by glomerulomegaly, proteinuria, progressive glomerulosclerosis, and decline in kidney function [12].

Increased Sympathetic Nervous System Activity

Obesity could also lead to elevated blood pressure and renal injury through sympathetic nervous system (SNS) activation. Multiple mechanisms has been shown to activate SNS in obesity: (1) through impairing baroreceptor reflexes; (2) activating

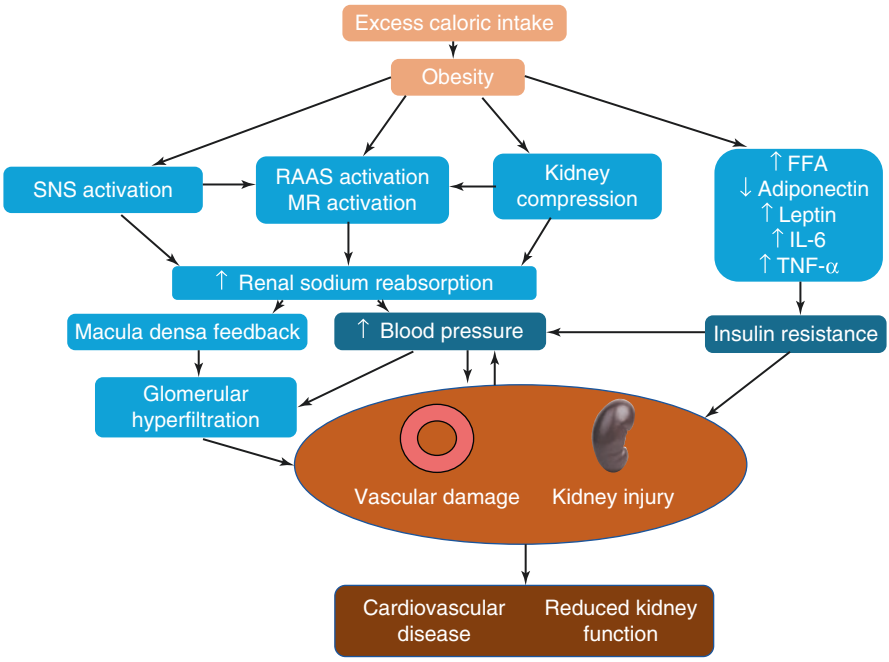

Fig. 12.1 The interplay between obesity, hypertension, kidney injury and cardiovascular disease. *SNS* sympathetic nervous system, *RAAS* renin–angiotensin–aldosterone system, *MR* mineralocorticoid receptor, *FFA* free fatty acid, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α

chemoreceptors in carotid bodies (especially in patients with obstructive sleep apnea and hypoxemia); (3) activating the central nervous system proopiomelanocortin (POMC) pathway through the central actions of leptin secreted by growing adipocytes [10].

The Role of Adipose Tissue and Kidney Disease

Three types of adipocytes are found in humans; white adipose tissue (WAT), which constitutes the largest energy reservoir, brown adipose tissues (BAT), which is responsible for thermogenesis, and beige adipose tissue, that can be induced from WAT by transdifferentiation or de novo in response to hypothermia or β-adrenergic stimuli [13]. Brown adipocytes contain large number of mitochondria and uncoupling protein 1 (UCP1), which uncouples ATP generation and dissipates energy in the form of heat [14].

Adipose tissue secretes various bioactive substances and coordinates numerous metabolic and cardiovascular functions through crosstalk between the adipose and non-adipose tissues [14]. These bioactive molecules secreted by the adipocytes (i.e.

adipokines) regulate the adipose tissue microenvironment through local paracrine effects, as well as the systemic metabolism through endocrine effects.

Adipose tissue exerts its effects on the kidney through the actions of an array of adipokines and metabolites such as leptin, adiponectin, angiotensin II, tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1) and transforming growth factor-beta (TGF-β) [15, 16]. The balance between these adipokines mediates the appetite, energy expenditure and glucose metabolism.

Adipocytes and macrophages play pivotal roles in the pathophysiology of the kidney damage in the setting of obesity. Excess caloric intake leads to expansion of WAT by either hypertrophy and/or hyperplasia of adipocytes along with development of insulin resistance and dysregulation of lipid metabolism [14]. Macrophage polarization shifts from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype promoting chronic inflammation. Combined with dysmetabolism of adipokines, these factors result in oxidative stress, inflammation and fibrotic transformation in the kidneys and lead to kidney damage.

Conversely, CKD is inherently associated with insulin resistance and inflammation. Insulin resistance of CKD is multifactorial in nature and is linked to various disturbances in CKD such as physical inactivity, chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anemia, adipokine imbalance due to reduced clearance of adipokines and hyperinsulinemia due to reduced insulin clearance [17, 18]. Although the skeletal muscle is the primary site for insulin resistance in CKD [19], adipose tissue also exhibits insensitivity to the actions of insulin, which exacerbates the metabolic derangements caused by obesity and aggravates the renal injury. Furthermore, CKD promotes beiging of adipose tissue, which favors energy loss and might also worsen the kidney injury [Fig. 12.2].

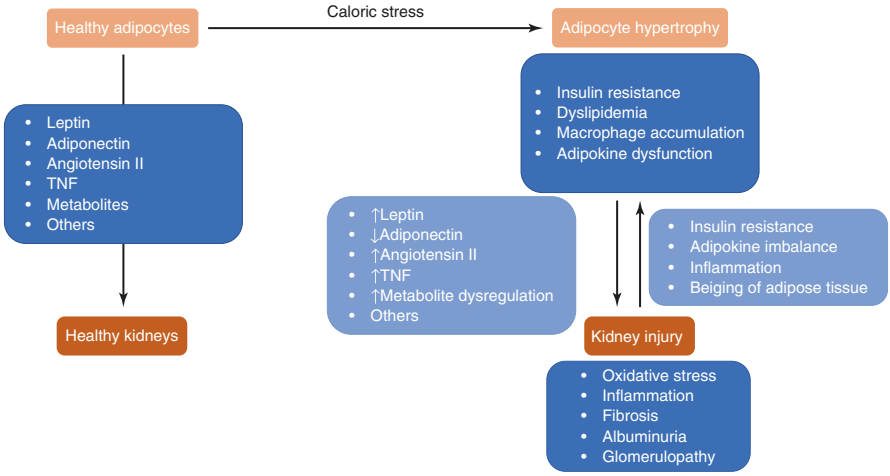

Fig. 12.2 The crosstalk between the adipose tissue and kidneys. *TNF* tumor necrosis factor

Metabolic Syndrome

Metabolic syndrome seems to evolve not as a linear sequence of events but as a matrix of interconnected pathways that result in multiple abnormalities in various organs. The pathogenesis of metabolic syndrome in the setting of abdominal obesity is characterized by several crucial alterations in metabolism; (1) elevated circulating free fatty acids (FFA), (2) increased intracellular lipid accumulation and insulin resistance in the adipose tissue, hepatocytes, skeletal myocytes and pancreatic β cells, (3) reduced functional activity of two insulin-sensitizing adipokines; leptin and adiponectin, and (4) enhanced macrophage infiltration in the adipose tissue with release of proinflammatory cytokines [20].

These phenomena originating in the adipose tissue and eventually affecting multiple tissues generate the clinical picture recognized as metabolic syndrome. Although there are multiple definitions for metabolic syndrome, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is the most widely used criteria [21, 22]. The presence of any three of the following five traits is defined as metabolic syndrome: (1) abdominal obesity, defined as a waist circumference ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches) in women; (2) serum triglycerides ≥150 mg/dL (1.7 mmol/L) or pharmacologic treatment for elevated triglycerides; (3) serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women or pharmacologic treatment for low HDL cholesterol; (4) blood pressure ≥ 130/85 mmHg or pharmacologic treatment for high blood pressure; (5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or pharmacologic treatment for elevated blood glucose [22].

Epidemiological data suggest that metabolic syndrome is an independent risk factor for incident CKD [23–25]. A stepwise increase in the hazard ratio of CKD was also observed with a greater number of metabolic syndrome components [23]. In a recent study, changes in the metabolic syndrome status altered the 10-year risk of CKD development, suggesting that lifestyle modifications may decrease the prevalence of CKD [24]. While it is not clearly established which component(s) lead to increased risk for incident CKD, it is likely that multiple mechanisms are in play predisposing individuals with MS to subsequent kidney disease. Although not studied in detail, MS could also potentially increase the risk for progression of prevalent CKD. Overall, prevention and treatment of MS is likely to be beneficial in patients with or at risk for kidney disease.

Quantification of Adipose Tissue in Chronic Kidney Disease

Monitoring body composition and fat content accurately is very important and could be challenging in patients with kidney disease due to inherent abnormalities in their metabolism. Hence, it is important to know the anthropometric measures and body composition assessment tools that are used to measure adiposity in

CKD. BMI is a simple, cheap and widely recognized standard measure to assess adiposity. The standard adult weight status categories defined by the World Health Organization (WHO) (<18.5 kg/m^2: underweight, 18.5–24.9 kg/m^2: normal weight, 25.0–29.9 kg/m^2: overweight, and ≥ 30 kg/m^2: obese), are also valid in the CKD population [26]. However, BMI is not an ideal marker of obesity for several reasons as it cannot differentiate between increased adiposity and muscularity. Also, BMI is limited in identifying visceral adiposity, the compartment associated with insulin resistance and atherogenic abnormalities [27]. Waist-to-hip ratio, waist-to-height ratio, waist circumference, and the conicity index are also used to estimate abdominal fat depots. Waist-to-hip ratio is associated with cardiovascular events and mortality and is less influenced by muscle and bone mass than BMI. Waist circumference is also a simple but reliable market of visceral fat and is correlated with cardiovascular disease risk factors. However, the efficacy of the latter two parameters is limited in peritoneal dialysis patients [5]. Maximum abdominal circumference (MAC), triceps (TSF) and subscapular skinfolds (SSF), and arm circumference are alternative methods to assess subcutaneous adipose tissue (SAT), but these measurements require enough experience and are influenced by fluid status, sex and age. Dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis, computed tomography and magnetic resonance imaging are more precise and reliable methods to estimate body composition in dialysis patients. DEXA is a direct method that is considered the gold standard for assessing body composition in patients with CKD; however, it is not readily available and can be influenced by a number of CKD related factors such as hydration status. In patients on maintenance hemodialysis (MHD), multi-frequency bioelectrical impedance (MF-BIA) is recommended as the preferred method to assess body composition [26]. Abdominal magnetic resonance imaging (MRI) and computerized tomography (CT) may also provide accurate assessment of the SAT and VAT however, they are not feasible in clinical practice due to cost and long exploration time.

Treatment

Treatment of metabolic syndrome is focused on weight management and the treatment of cardiovascular risk factors if they persist after lifestyle modifications [28–30]. Treating obesity with lifestyle modifications or medication slows the progression of kidney disease and reduces albuminuria [31].

Lifestyle Modifications

Diet with or without exercise is shown to be effective in reducing weight, proteinuria and blood pressure [32–36]. However, no specific dietary pattern or popular diet has been observed to be superior to other diets in promoting weight loss in the

general population or in patients with CKD [37, 38]. Individualized diets based on patients' comorbidities and preferences is required to achieve weight loss with the help of a registered dietitian nutritionist.

Exercise reduces BMI, systolic and diastolic blood pressure, and improves quality of life in patients with kidney disease [31]. A meta-analysis showed that exercise was associated with a slight increase in eGFR in non-dialysis CKD patients but this was limited to studies with a duration of less than 3 months [39]. Diet and exercise can also improve metabolic profile in overweight or obese stage 3–4 CKD patients [40].

Drug Therapy

Several medications are approved for weight loss along with diet and exercise. Table 12.1 summarizes the weight loss medications that can be considered for patients with kidney disease. Several other medications are either contraindicated in kidney disease (phentermine-topiramate) or discontinued from the market due to significant complications (lorcaserin, sibutramine).

Table 12.1 Weight loss medications for patients with kidney disease

	Dosing	Mechanism of action	Side effects	Notes
Orlistat	120 mg TID with meals	Inhibits gastric and pancreatic lipase; fat malabsorption	Flatulence, fecal incontinence, oily rectal leakage	Does not require renal dose adjustment
Bupropion-naltrexone ER	8 mg/90 mg daily increase to 32 mg/360 mg daily	Anorexiant; bupropion (dopamine/norepinephrine reuptake), naltrexone (opioid antagonist)	GI symptoms, headache, dizziness, hepatotoxicity, dry mouth, elevated BP and HR, palpitations	Increased creatinine
GLP-1 receptor agonist	0.6 mg SC daily and weekly increase to 3 mg SC daily	Stimulates insulin secretion, inhibit glucagon, regulate appetite and calorie intake	GI symptoms, decreased appetite, dizziness, abdominal pain, increased HR, hypoglycemia, increased lipase	Use caution when initiation or escalating dose in patients with kidney disease: Postmarketing data points to renal impairment

Data source: US Food and Drug Administration [41]
TID three times daily, *ER* extended release, *GI* gastrointestinal, *BP* blood pressure, *HR* heart rate, *GABA* gamma aminobutyric acid, *GLP-1* Glucagon-like peptide-1, *SC* Subcutaneous

Bariatric Surgery

Treatment with lifestyle modifications and medications does not always yield satisfactory results and certain patients may benefit from bariatric surgery. Medicare requirements for bariatric surgery are BMI $\geq$ 35 kg/m^2, the presence of at least one obesity-related comorbidity and failed medical treatment of obesity [42]. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy are the two procedures that are used most frequently [43]. The main mechanisms in promoting weight loss is reduced hunger. Studies comparing the outcomes in patients who undergo bariatric surgery with non-surgically treated patients show that bariatric surgery is associated with a slower eGFR decline and a lower risk of kidney failure [43–45].

Management Obesity in Patients with ESKD

The benefit of weight loss remains controversial in patients with kidney failure. Data from observational studies indicate higher BMI is protective in patients on maintenance hemodialysis [46, 47]. However, abdominal adiposity, which is a better measure to assess obesity in this population, is associated with higher risk of death in ESKD [48, 49]. Kidney transplantation, which is associated with improved survival in ESKD, is usually not offered to patients with severe obesity due to risk of graft loss and delayed graft function. However, most patients with kidney failure have trouble in losing weight with lifestyle modifications or medical treatment. Weight loss in patients on peritoneal dialysis is particularly more challenging due to increased appetite, glucose load from the dialysate and fluid overload [50]. Bariatric surgery should be considered in patients with ESKD, who are candidates for kidney transplantation, given the large benefits of kidney transplantation [51]. However, it is important to note the risks associated with bariatric surgery, some of which are; micronutrient deficiencies, hyperoxaluria and increased risk of nephrolithiasis. Thus, careful evaluation is warranted in selecting patients for bariatric surgery.

Conclusion

The pathogenetic pathways of obesity, hypertension and other elements of the metabolic syndrome are intertwined, all contributing to the renal injury implicated in metabolic syndrome. Prevention, accurate assessment and effective treatment of obesity, metabolic syndrome, and diabetes are crucial to prevent the development and progression of kidney damage and importantly, to reduce cardiovascular mortality in this population. More effective strategies targeting the distinct pathways involved in the interplay between metabolic syndrome and kidney disease are required to reduce the cardiorenal, metabolic and other obesity-associated diseases.

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Chapter 13
Anemia and Diabetes

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Diabetes is the leading cause of chronic kidney disease (CKD) and is associated with excessive cardiovascular morbidity and mortality [1, 2, 3]. Anemia is common among those with diabetes and CKD and greatly contributes to patient outcomes [4, 5]. Observational studies indicate that low Hb levels in such patients may increase risk for progression of kidney disease and cardiovascular morbidity and mortality [6]. Controlled clinical trials of anemia treatment with erythropoietin stimulating agents (ESAs) demonstrated improved quality of life (QOL) but have not demonstrated improved outcomes [7–11]. In some trials, ESA treatment for high Hb levels is associated with worse outcomes such as increased thrombosis risk [7–12]. Consequently, the U.S. Food and Drug Administration (FDA) and the National Kidney Foundation (NKF) have modified their recommendations regarding anemia treatment for CKD patients [13, 14]. The objectives of this review are to (1) update clinicians on the prevalence, causes, and clinical consequences of anemia; (2) discuss the benefits and risks of treatment; and (3) provide insight into anemia management based on clinical trial evidence in patients with diabetes and kidney disease who are not on dialysis.

Definition and Prevalence of Anemia in CKD

The NKF defines anemia in CKD as an Hb level < 13.5 g/dl in men and 12.0 g/dl in women [15]. This definition is based on the fact that these levels are outside the 95% CIs of the mean for normal men and women. Anemia is common in diabetic patients with CKD [6]. It is estimated that one in five patients with diabetes and stage 3 CKD have anemia, and its severity worsens with more advanced stages of CKD and in those with proteinuria [8, 16, 17]. As kidney disease progresses, anemia increases in

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prevalence, affecting nearly all patients with stage 5 CKD [18, 19]. For example, in a 5-year prospective observational study conducted in a diabetes clinic in Australia, anemia was found in early kidney disease, and declining Hb levels were more common among those with higher levels of albuminuria [20]. In a cross-sectional study involving 808 adults with type 2 diabetes and kidney disease conducted in Peninsular, Malaysia, showed that anemia among patient with type 2 diabetes and CKD in primary care setting was more common and the majority goes unrecognized. Inadequate treatment of anemia was also very prevalent [21]. Therefore, screening of anemia should be incorporated into the routine assessment of diabetic complications. The distribution of Hb in patients with diabetes and CKD is similar to that in those without diabetes, but on average, Hb levels are lower. For these reasons, it is recommended that clinicians measure serum creatinine and urine albumin and creatinine to estimate glomerular filtration rate (GFR) and identify and quantitate albumin excretion rate in patients with diabetes and anemia patients.

A common complication of chronic kidney disease and diabetes is that, anemia can influence glycated hemoglobin A1c levels. In diabetic patient anemia course earlier and with higher severity over the course of CKD stages. Hung-Chun Chen et al. showed that in diabetic ckd stages 3–4, higher hemoglobin A1c is associated with higher risk of poor clinical outcomes in patient with hemoglobin greater than 10 g/dl [22].

Causes of Anemia

Anemia in diabetic patients with CKD may result from one or more mechanisms. Vitamin deficiencies such as folate and B12 are relatively uncommon, and clinical practice guidelines do not recommend routine measurement of these serum levels. (See below.) The major causes of anemia in CKD patients are iron and erythropoietin deficiencies and hyperresponsiveness to the actions of erythropoietin.

(a) Iron deficiency.
(b) Erythropoietin deficiency and hypo responsiveness.
(c) Nephrotic syndrome.
(d) ACE inhibitors and angiotensin receptor antagonists.

Iron Deficiency

Iron deficiency in the general population is a common cause of anemia and is prevalent in patients with diabetes and CKD. In these same patients, dietary deficiency, low intestinal absorption, and gastrointestinal bleeding may result in absolute iron-deficiency anemia. Recent analyses of the National Health and Nutrition Examination Survey IV suggest that up to 50% of patients with CKD stages 2–5 have absolute or relative (functional) iron deficiency [23]. In CKD, both absolute and relative iron deficiency are common. Absolute iron deficiency is defined as a depletion of tissue iron stores evidenced by a serum ferritin level < 100 ng/ml or a transferrin saturation

of <20%. Functional iron deficiency anemia is adequate tissue iron defined as a serum ferritin level ≥ 100 ng/ml and a reduction in iron saturation. The latter is more common and is strongly associated with upregulation of inflammatory cytokines and impaired tissue responsiveness to erythropoietin, which can inhibit iron transport from tissue stores to erythroblasts [24]. Increased levels of inflammatory cytokines such as interleukin-6 enhance production and secretion of hepcidin, a hepatic protein that inhibits intestinal iron absorption and impairs iron transport from the reticuloendothelial system to bone marrow. In addition, erythropoietin, which normally enhances iron transport from macrophages to the blood stream, is impaired, thereby exacerbating relative iron deficiency [25].

As CKD patients have lower intestinal iron absorption, and require greater iron turnover to maintain the ESA-driven red cell mass than do healthy individuals, in these patients, intravenous iron reduces ESA dose requirements and increases the likelihood of maintaining levels of hemoglobin within the desired range. Oral iron is inferior to intravenous iron in advance ckd patients. The availability of various iron preparations and new developments in delivering iron should enable adequate provision of iron to patients with CKD. Moreover, iron therapy, and in particular IV iron therapy, was found to improve the response to ESA treatment and reduce ESA requirements in CKD patients [26].

Erythropoietin Deficiency and Hypo Responsiveness

Both deficiency and hypo responsiveness to erythropoietin contribute to anemia in diabetic patients with CKD [19, 27]. The cause of erythropoietin deficiency in these patients is thought to be reduced renal mass with consequent depletion of the hormone. Lower erythropoietin levels have been reported to predict poor survival in diabetic patients. In a study conducted by Yoshiharu Tsubakihara et all showed that low EPO levels but not hemoglobin levels were associated with the faster decline in GFR, especially in diabetic population with iron deficiency [28]. Hypo responsiveness is defined clinically as a requirement for high doses of erythropoietin in order to raise blood Hb level in the absence of iron deficiency. It is believed to represent impaired antiapoptotic action of erythropoietin on proerythroblasts. Possible causes of this erythropoietin hypo responsiveness include systemic inflammation and microvascular damage in the bone marrow [17, 27]. However, some studies suggest that other factors (i.e., autonomic failure) may play a role in impaired erythropoietin production or secretion by failing kidneys [29].

Nephrotic Syndrome

Nephrotic syndrome characterized by edema, hypoalbuminemia, dyslipidemia, and urine protein-to-creatinine ratio ≥ 3 is not uncommon in patients with diabetic nephropathy and can occur even in early stages of CKD (e.g., stages 1–2) [29, 30]. The mechanism of anemia in nephrotic syndrome is complex and involves both

inflammatory-mediated mechanisms as discussed above as well as absolute iron deficiency. Iron excretion increases in early stages of kidney disease in patients with diabetes and albuminuria and is exacerbated by development of nephrotic-range proteinuria. In nephrotic syndrome, many nonalbumin proteins are excreted in the urine, including transferrin and erythropoietin. Significant losses of transferrin and erythropoietin can occur in nephrotic syndrome, leading to both iron- and erythropoietin-deficiency–caused anemia in patients with diabetes [31]. Evidence for increased transferrin catabolism in nephrotic syndrome may contribute to iron deficiency–caused anemia [32]. Decreased erythropoietin production, secretion, and hyperresponsiveness can contribute to anemia in nephrotic patients. (See above.)

ACE Inhibitors and Angiotensin Receptor Antagonists

Both of these drug classes may cause a reversible decrease in Hb concentration in patients with diabetes and CKD [33]. The mechanisms by which ACE inhibitors and angiotensin receptor blockers lower Hb include a direct blockade of the proerythropoietic effects of angiotensin II on red cell precursors, degradation of physiological inhibitors of hematopoiesis, and suppression of IGF-I. Long-term administration of losartan in 50- to 100-mg doses once daily in patients with diabetes and albuminuria is expected to lower Hb by ∼1 g/dl. Importantly, this effect does not diminish the renoprotective effect of losartan. It should be recognized that these classes of agents may induce or worsen symptomatic anemia in nephropathy patients [34].

Consequences of Anemia

(a) Quality of life.
(b) Progression of kidney disease.
(c) Cardiovascular disease.

Quality of Life

Anemia is an important cause of physical and mental impairments in diabetic CKD patients including malaise, fatigue, weakness, dyspnea, impaired cognition, and other symptoms. Clinical trials indicate that improving anemia improves cognitive function, sexual function, general well-being, and exercise capacity and reduces the need for blood transfusions [7, 9, 10, 11, 35] There is renewed evidence of anemia in diabetes contributing to retinopathy, neuropathy, diabetic foot ulcer, hypertension, progression of kidney disease, and cardiovascular events [17].

Progression of Kidney Disease

In general, kidney disease in diabetes is progressive, and it has been hypothesized that anemia may contribute to progression of kidney disease [8, 20, 36, 37]. Possible mechanisms include renal ischemia caused by reduced oxygen delivery due to low Hb and underlying heart failure. For example, anemia may worsen renal medullary hypoxia, leading to renal interstitial injury and fibrosis [38, 39]. Whole animal and in vitro studies indicate that renal hypoxia upregulates hypoxia-inducible factor-1α, a transcriptional regulator of the erythropoietin gene as well as heme oxygenase, nitric oxide synthases, extracellular matrix, and apoptosis genes. It is upregulated by renal hypoxia and induces collagen gene expression in renal fibroblasts, thereby increasing interstitial fibrosis. Anemia may also increase renal sympathetic nerve activity, resulting in increased glomerular pressure and proteinuria (which in turn may accelerate progression of kidney disease), and contribute to worsening kidney function by exacerbating underlying heart failure—a common complication in patients with diabetes and kidney disease, [37].

Early animal model studies in renal ablation, hypertension, and diabetes demonstrated that treatment of anemia worsened systemic and glomerular hypertension and renal structural and functional damage, suggesting that anemia may actually be renoprotective [40, 41]. Recently, Nakamura et al. [42] demonstrated that administration of an erythropoietin-stimulating agent to patients with anemia and CKD decreased urine fatty acid–binding protein—a molecule known to be associated with increased risk for kidney disease progression—suggesting that ESA may have a renoprotective effect independent of Hb level. However, in clinical trials, erythropoietin has not yet been proven to slow kidney disease progression in patients with diabetes and nephropathy. (See below.)

Cardiovascular Disease

Observational studies indicate that death is five times more likely than progression to end-stage kidney disease in patients with CKD [43]. Moreover, cardiovascular disease is the most common cause of death in patients with diabetes and CKD; and anemia appears to be a risk multiplier for all-cause mortality among those same patients. Anemia prevalence is up to ten-fold higher among diabetic patients with CKD and heart failure and is a modifiable risk factor among diabetic patients [44, 45]. Low Hb concentration is an independent risk factor for left-ventricular hypertrophy, heart failure, and cardiovascular mortality [45–52]. Heart failure is common in diabetic patients with nephropathy and may result in reduced renal blood flow, thereby contributing to further reduction in GFR and erythropoietin production. Also, anemia may aggravate tissue hypoxia, and subsequently heart failure, resulting in further renal sodium retention, volume expansion, increased venous return, and increased venomotor. For these reasons, treatment of anemia in patients with diabetes and CKD is a proposed strategy to reduce excessive cardiovascular morbidity and mortality. (See below.)

Clinical Trials of Erythropoietin-Stimulating Agents

It is important to note that none of the published trials examining the safety and efficacy of ESA for anemia treatment included a placebo control group. With one exception [53], all study subjects (with varying Hb levels) were treated with an ESA.

Kidney Outcomes

Several small trials in patients with CKD, including those with diabetes, demonstrated a beneficial effect on kidney disease progression. Kuriyama et al. [53] studied 106 patients with stage 3–4 CKD with or without anemia. Those with anemia were randomized to ESA treatment or no treatment. The time to a doubling of serum creatinine from baseline was the study's primary end point. They found that time to doubling of serum creatinine was significantly longer in the treated group than in the nontreated group and similar to that in the nonanemic control subjects [53]. Gouva et al. [54] randomized 88 anemic stage 3–5 CKD patients to early versus late treatment with erythropoietin-α to test the hypothesis that this intervention would slow the rate of progression to end-stage renal disease (ESRD). They found that early correction of anemia was associated with improved renal and patient survival compared with delayed treatment of anemia. Rossert et al. performed a randomized controlled trial involving 390 patients with stage 3–4 CKD and anemia to test the hypothesis that treatment of anemia with an ESA to reach a higher Hb level would slow decline in kidney function. Subjects were targeted to one of two Hb levels (13–15 or 11–12 g/dl) and followed for 12 months. Although the decline in GFR was numerically less in the high-Hb group, this difference was not statistically significant. Still, those randomized to the high group showed improvement in QOL and vitality [55]. However, the two largest trials to date to examine the effect of ESA on progression of kidney disease (as a secondary outcome) did not show any renal benefit of raising Hb to a higher level. (See below.)

Cardiovascular Outcomes

Roger et al. [10] conducted a prospective, randomized, open-label trial in 155 anemic CKD patients (stage 3–4), testing the hypothesis that ESA treatment could prevent development or progression of left-ventricular hypertrophy. Study subjects were randomized to receive subcutaneous dosing with erythropoietin-α to achieve and maintain Hb in the range of 9–10 or 11–13 g/dl and followed for 2 years with repeated measures of left-ventricular structure and function. They found no difference in the primary outcome of left-ventricular wall thickness; however, those assigned to the higher Hb arm of the study experienced improvement in QOL. Levin

et al. [9] conducted a randomized clinical trial to test the hypothesis that prevention or correction of anemia, by immediate versus delayed treatment with erythropoietin-α in patients with CKD, would delay or prevent left-ventricular hypertrophy. The primary outcome was the change in left-ventricular mass index. They randomized 176 CKD patients who had experienced a decrease of 1 g/dl Hb in the prior year and a baseline Hb level of 11–13.5 g/dl to treatment with epoetin-α to maintain Hb in the range of 12–14 g/dl or to maintain a target Hb range of 9–10.5 g/dl; the subjects were followed for 24 months with repeated measures of left-ventricular structure and function. Despite significant difference in Hb level between groups, they found no significant difference in left-ventricular mass index. Those assigned to higher Hb experienced improvement in QOL (Table 13.1).

Ritz et al. randomized 172 anemic patients with type 1 or type 2 diabetes and stage 1–3 CKD to treatment with epoetin-α and a target Hb level of either 13–15 or 10.5–11.5 g/dl and followed them for 19 months. The primary outcome was the change in left-ventricular mass index, and secondary outcomes included kidney function and QOL. There were no significant differences in left-ventricular mass index in those randomized to the higher target; however, QOL measures were significantly better in the higher Hb arm. There were no differences in kidney function decline and no significant differences in adverse events [56].

Cardiovascular Events

Singh et al. [12] tested the hypothesis that a higher Hb level would reduce risk for the composite cardiovascular outcome of stroke, myocardial infarction, heart failure, and all-cause cardiovascular mortality among patients with various causes of CKD including diabetes (~46%). In this trial, the Correction of Hb and Outcomes in Renal Insufficiency (CHOIR) trial, 1432 patients with anemia and stage 3–4 CKD were randomized to an Hb target of 11.5 or 13–13.5 g/dl and followed for an average of 16 months [12]. During the trial, Hb levels were significantly higher in those randomized to the higher Hb arm. The composite event rate was higher in those assigned to the higher Hb arm; however, there was no difference in the rate of development of ESRD. Also, in contrast to the results of other studies, there was no improvement in QOL in those randomized to the higher target. The authors concluded that use of a target Hb level of 13.5 g/dl (compared with 11.3 g/dl) was associated with increased risk and no incremental improvement in QOL. Post hoc analysis demonstrated that a higher fraction of patients in the higher Hb arm had prior coronary events, hypertension, and dropout prior to an event or completion of the study. In the Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE), Drueke et al. [7] randomized 603 patients with stage 3–4 CKD, from various causes including diabetes (~25%), to early versus late treatment with epoetin-α to test the hypothesis that a higher Hb level would reduce risk for cardiovascular morbidity and mortality. Subjects were randomized to an Hb target range of 11–11.5 or 13–15 g/dl and followed for an average of 36 months.

Table 13.1 Randomized controlled cardiovascular outcome trials of anemia treatment with erythropoietin- stimulating agents in patients with chronic kidney disease

	Study population		Study type	Ckd stages	Target hg	Study period in months	outcome		
Roger et al.	155	24–33	Open label	3–5	9–10/12–13	24	ΔLVMI	No benefit	Improved
Levin et al.	172	35–41	Open label	2–5	9–10.5/12–14	22.6	LVMI	No benefit	Improved
Singh et al.	1432	48	Open label	4–5	11–11.5/13–13.5	16	Death or cardiovascular event	Worse in high Hb arm	No difference
Druecke et al.	603	25	Open label	4–5	11–11.5/13–15	36	Death or cardiovascular event	No benefit	Improved
Ritz et al.	176	100	Open label	1–3	13–15/10.5–11.5	18	LVH	No benefit	Improved
Pfiffer et al.	4000	100	Double blind and placebo controlled	3–4	13.0/<11.0	24–48	Death or cardiovascular event	No benefit	Increased risk of stroke

HCT hematocrit, *HD* hemodialysis, *LVH* left ventricular hypertrophy, *LVMI* left ventricular mass index

They found no significant differences in the primary composite outcome, but there was a trend toward a higher event rate in the higher Hb arm. In addition, multiple QOL measures were significantly improved in those randomized to the higher Hb arm. In contrast to the CHOIR study, the time to ESRD, a secondary outcome, was shorter in the higher Hb arm. Post hoc analysis demonstrated that the study was underpowered to detect a difference in the primary outcome variable as a result of the lower-than-expected overall event rate in both arms of the study.

The increased risk for adverse outcomes during ESA treatment of anemia in clinical trials of patients with CKD is not completely understood. One possibility is that higher Hb increases risk for thrombosis. Another possibility is that those who experience adverse cardiovascular events have higher comorbidity, are relatively resistant to erythropoietin, and require higher doses of ESA to achieve higher Hb and that the higher doses of ESA are vasculotoxic [57]. The Trial of Reduction of End points with Aranesp Therapy (TREAT) is a large-scale, randomized, double-blind, and placebo-controlled study including 4000 anemic patients with type 2 diabetes and CKD [58, 59]. The primary outcome is a composite of all-cause mortality and cardiovascular morbidity. This trial is unique in many respects, including the double-blind, placebo-controlled design; the population of exclusively anemic patients with type 2 diabetes and CKD; and a large sample size. In this trial Pfiffer et al., assigned half of the patients in the treatment arm to receive darbepoetin alfa and to achieve higher Hb levels of around 13 g/dl and half of the patients were assigned to placebo arm with rescue darbepoetin alfa when hemoglobin dropped below 9.0 g/dl. Patients were followed for total of 29 months. The use of darbepoetin in patient with higher arm of hemoglobin did not reduce the risk of primary composite outcome of all-cause mortality and cardiovascular morbidity and was associated with increased risk of stroke.

Further studies are needed to determine whether higher doses versus resistance to action of ESA cause harm in anemic patients with CKD.

In summary, two clear messages emerge from the anemia treatment trials. (1) Treating patients to achieve a higher compared with a lower Hb target typically improves QOL. (2) Treatment to reach a higher Hb level does not reduce risk for cardiovascular events and may cause harm.

Clinical Practice Guidelines for Evaluation of Anemia

The NKF clinical practice guidelines for diagnosis and management of anemia in patients with CKD and KDIGO Clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: recommend a routine history and physical examination, a complete blood count, a reticulocyte count, evaluation of serum iron and total iron binding capacity and serum ferritin level, and a fecal test for occult blood for evaluation of anemia [15, 60]. Additional tests to evaluate anemia should be guided by this initial evaluation (e.g., serum folic acid, vitamin B12 level, Coombs test, etc.). Despite the high prevalence of anemia in the

CKD population, treatment with erythropoietin or iron often is not used in the predialysis period. For example, nearly 70% of patients initiated on dialysis are anemic by the NKF definition but are not treated with erythropoietin, and > 50% of these patients have severe anemia (hematocrit <30%).

Recommendations for Treatment of Anemia

(a) KDIGO and NKF clinical practice guidelines.
(b) Food and Drug Administration.

KDIGO and NKF Clinical Practice Guidelines

Both the KDIGO and NKF currently recommends that when treating anemia in CKD with an ESA, the Hb target range should be 11–12 g/dl and should not exceed 13 g/dl [60]. A hemoglobin target range of 10–11 seems reasonable for renal anemia. This is also compatible with current recommendation by ESA producers and the food and drug administration (FDA). This target range avoids the upper and lower risk levels for hemoglobin and probably ensures a positive ESA effect on quality of life. It is much more cost efficient than the target range of 11–12 recommended by the kidney Disease outcome quality initiative (KDOQI) in 2007 [61, 62, 63, 64]. In addition, the NKF recommends that treatment should be individualized, taking into account patient characteristics including symptoms, Hb level, and evaluation for other causes of anemia. (See above.) If the initial evaluation indicates absolute iron deficiency as the cause, treatment with supplemental iron and a search for the cause of iron loss should be undertaken. If absolute iron deficiency is not present and causes other than kidney disease are excluded, then treatment with an ESA should be administered at a dose sufficient to increase Hb within the target range of 10–12 g/dl. Importantly, ESA-treated patients should, in general, receive iron to ensure that adequate stores are available for erythropoietic response [60]. The NKF notes that with few exceptions, anemia treatment trials in CKD patients demonstrated that treatment with an ESA to achieve Hb values in the range of 11–13 g/dl is associated with improved QOL few exceptions, anemia treatment trials in CKD patients demonstrated that treatment with an ESA to achieve Hb values in the range of 11–13 g/dl is associated with improved QOL.

Food and Drug Administration

In early 2007, the Food and Drug Administration (FDA) promulgated new recommendations for use of ESA in patients with CKD, advising them that ESA can increase risk for heart attack, stroke, blood clots, heart failure, and death when given

to maintain higher Hb [65]. Drugs affected by their recommendation included epoetin-α and darbepoetin. The FDA advised practitioners to use the lowest dose of an ESA needed to avoid blood transfusion, targeting blood Hb in the range of 10–12 g/dl, and to withhold the dose of ESA when Hb level exceeds 12 g/dl. Manufacturers of ESA accordingly added black box warnings noting these recommendations [66].

In summary, the NKF and FDA recommendations are in conflict. Whereas there is agreement that ESAs are valuable for treating anemia, they differ with regard to the level of Hb at which to initiate ESA and the upper limit of the Hb target. The NKF supports the safety of ESA use and recognizes the importance of individualizing anemia treatment. Further studies on the safety of ESA use in the diabetes population, as well as efforts to better understand the explanation for the association of higher Hb with worse cardiovascular outcomes reported in clinical trials, are needed.

Anemia Management

The first step in the management of anemia is evaluating the underlying cause. (See above on diagnosis and evaluation) (Table 13.2).

Iron Replacement

If absolute iron deficiency is present, the patient should be put on oral or intravenous iron therapy. Several oral iron preparations are available for treatment

Table 13.2 Clinical Algorithm for treatment of Anemia

Anemia work up and treatment		CKD stage 2 → CKD stage 3	→CKD stage 4 → CKD stage5
Blood work		Check CBC, absolute retic. Count, serum iron, TIBC and ferritin, fecal occult blood test, additional test folate and Vit b12,	
Diagnosis of anemia		If Hg <11 g/dl in females	
		Hg <13 g/dl in males	
Monitoring	Anemic	Annually	Every 6 months
	Not anemic	Every 3 months	Every month
Iron therapy; if ferritin <100 & transferrin sat. <20%		Start P.O. Iron trial for 3 months, if fail then start I.V. Iron	Start I.V. Iron
Iron monitoring		Every 6 months on P.O. Iron	Every 3 months on I.V. Iron
ESA therapy		If iron sat. >30% & ferritin >500	Initiate ESA therapy if Hg < 10.0
		but Hg ≤10.0	
ESA monitoring		Check hg every month to maintain levels between 10–12 g/dl	

including ferrous gluconate, fumarate, and sulfate. Doses of 300–325 mg of one of these agents three times daily can increase the Hb level significantly in such patients. Notably, significant gastrointestinal side effects may lead to poor adherence and compliance with oral iron. An alternative is to administer intravenous iron on a periodic basis. Several studies indicate that these preparations are effective and safe in predialysis populations [12, 67, 68, 69]. The most common schedules for IV iron was a dose of 100–200 mg every 1–2 weeks for the older iron formulations i.e. iron sucrose and iron gluconate or 500–1000 mg 1–2 times for the newer iron preparations ferric carboxymaltose and ferrumoxytol [69, 70]. Dahdah et al. [67] administered intravenous iron dextran to anemic, iron-deficient (serum ferritin <100 ng/ml or transferrin saturation < 20%) patients with an estimated GFR <50 ml/min and not on dialysis in doses of either 200 mg/week for 5 weeks or 500 mg/week for 2 weeks. Significant increases in Hb occurred within 2 weeks; all patients tolerated infusions without serious adverse reactions. Intravenous iron preparations including ferric sodium gluconate, iron sucrose, and iron dextran are available and can be administered safely. Among these agents, iron dextran has been associated with the highest incidence of adverse reactions, although the incidence of such reactions is low with all three preparations [68, 69, 70, 71]. Although some studies indicate that intravenous iron is in general more efficacious than oral iron for achieving increases in Hb in patients with CKD, oral iron is also effective [68]. Moreover, no definite advantages have been shown with intravenous versus oral iron in patients with CKD not on dialysis [72]. Table 13.3.

Table 13.3 Different Iron formulations available

Types of IV Iron	Brand Name	Available in USA	Test Dose Needed	Maximum Single Dose	Side Effects (Anaphylactic Reaction)
HMW- iron dextran	Dexferrum	Y	Y	20 mg/kg	33%
LMW- iron dextran	Cosmofer INFeD	Y	Y	20 mg/kg	3.3%
Ferric gluconate	Ferrlecit	Y	N	125–250 mg	0.9%
Iron sucrose	Venofer	Y	N	200–300 mg	0.6%
Ferric Carboxymalt OSE	Ferrinject Injectafer	N	N	15 mg/kg max 750–1000 mg	–
Iron Isomaltoside	Monofer	N	N	20 mg/kg Max 1000 mg	–
Ferumoxytol	FerraHeme	Y	N	510 mg	–

ESA Therapy

Different Erythropoiesis stimulating agents are used to treat anemia in CKD. Several agents are available including short acting Epogen alpha or beta as well as longer acting agents including darbepoetin alfa and metho oxy polyethylene glycol-epoetin beta, CERA Marcera [72, 73, 74, 75].

An initial dose of 10,000 units epoetin-α once weekly or 0.75 μg/kg darbepoetin-α every other week subcutaneously are effective for increasing Hb concentration by 1–2 g/dl over 4–8-week periods [35]. Darbepoetin can be administered subcutaneously every other week at outset and then administered once monthly to maintain Hb target. Ling et al. [76, 77] demonstrated efficacy of maintaining Hb in the range of 10–12 g/dl (total dose of 88 μg) after extending the dosing interval from every other week to once every 4 weeks. Provenzano et al. [78] found that an increased dosing interval from weekly to once monthly using epoetin-α in doses up to 40,000 units maintained Hb in a similar range.

Extended dosing of short- and long-acting ESA, including the hematopoietic and adverse effects, has recently been reviewed [79]. Currently, the only ESA approved by the FDA for extended interval dosing is darbepoetin. In clinical practice, darbepoetin is often administered every other week initially, until the Hb target is achieved, before extending dosing to every 4 weeks. Extended dosing may require an increase in dose monthly using epoetin-α in doses up to 40,000 units maintained Hb in a similar range [35, 79].

Once monthly subcutaneous CERA Mercera maintains stable hemoglobin controlled in patients with CKD. Analysis demonstrated that CERA was as effective as epoetin in maintaining hemoglobin and was well tolerated [80, 81, 82, 83] (Table 13.4).

Table 13.4 Dosing schedule for different ESA agents

	Available in USA	Half life	Dosing
First generation ESA			
Epotein alfa (Epogen)	Y	Short	3/week
Epotein alfa (Procrit)	Y	Short	3/week
Epotein alfa (Eprex)	N	Short	3/week
Epoetin Beta (neo recormon)	N	Short	3/week
Second generation ESA			
Darbopoetin (Aransep)	Y	Long	Once a week or once in 2 weeks
Third generation ESA			
Continuous erythropoietin receptor activator	Y	Longer	Every 2 weeks or once a month
Methoxy Polyethyleneglycole			
Epoetin Beta (Mircera)			
Epoetin alfa Epbx- Retacrit	Y	Longer	Every 2 weeks or once a month

Monitoring Response to Treatment

Patients should be evaluated for improvement in symptoms including fatigue, vitality, physical functioning, and cognitive function. Initially, Hb level should be measured every other week to monitor the hematopoietic response and monthly thereafter. In general, if an Hb level deviates from the target range (see above), the dose of the ESA should be adjusted either upward or downward by 25%. In most patients, increases or decreases in ESA dose should not be made more frequently than monthly. Also, for safety reasons, if Hb is rising at a rate of >1 g/dl within a 4-week period, the dose should be held, as more rapid increases may be associated with increased risk for adverse events such as hypertension.

Functional iron deficiency should be suspected in any patient not responding to ESA treatment, and patient compliance with iron therapy should be investigated. Routine measurement of iron stores including serum iron, iron binding capacity, and ferritin should be monitored monthly for 3 months then quarterly once Hb target is achieved [72, 84].

Adverse Side Effects of Therapy

In clinical trials, up to 25% of patients experience an increase in blood pressure or develop overt hypertension (blood pressure > 140/90 mmHg) [9, 35, 55, 85–87]. Thus, ESA should not be used to treat anemia in patients with uncontrolled blood pressure. Moreover, increases in blood pressure should be looked for in any anemic CKD patient treated with an ESA, and dose adjustments in ESA, iron, or antihypertension medications should be undertaken as needed. Common side effects include local pain or tissue reaction to subcutaneous injection and development of flu-like symptoms within hours or days of administration of an ESA.

A rare but serious form of pure red cell aplasia can occur during ESA treatment, including in those treated with epoetin and darbepoetin [88, 89]. The anemia is sudden in onset and can occur as early as 2 months after initiation of treatment. As noted above, ESA may increase risk for death and cardiovascular events and thrombotic events. The risk for thrombotic events includes MI, CVA and vascular access thrombosis. The adverse CV effects are seen in those who had higher targeted Hgb level levels >12 g/dl in some clinical trials. in clinical trials. Pfifer et al.; Therefore, it is prudent to modify the dose of ESA to reduce the likelihood of excursions of Hb exceeding 13 g/dl as recommended by the NKF [60]. Adverse effects of iron use are described above and include gastrointestinal side effects with oral preparations and anaphylactic reactions with intravenous preparations.

Economic Burden of Anemia

In CKD patients, untreated anemia of CKD leads to higher costs, higher health care resource utilization, and lower quality of life compared with initiating anemia treatment. Relative to aiming for lower hemoglobin targets with ESAs, higher targets conferred modest HRQoL improvements and were associated with higher health care resource utilization [90, 91].

Areas of Uncertainty

Analysis of available evidence from clinical trials clearly indicates that there is enough uncertainty regarding the risk-to-benefit ratio of treatment of anemic CKD patients with ESA to warrant additional major randomized clinical trials [92]. Because nearly 50% of new cases of ESRO in the U.S. are attributed to diabetes, further studies are needed to help guide management of anemia. Areas of uncertainty that remain include establishment of the optimal individual Hb level—the level at which patient QOL is maximized and morbidity and mortality risks are minimized. The optimal dose of a given ESA, the frequency of dosing, and the indication and target Hb range remain controversial. For example, should ESA dosing begin at an Hb level of 10, 11, or 12 g/dl? Another area of uncertainty concerns the diagnosis and management of erythropoietin hypo responsiveness, for which there is no widely accepted, standardized definition. This confounds the analysis of clinical trials in which higher doses of ESA and higher Hb occur in those randomized to higher Hb targets. Additional studies are needed to understand the nature and extent of hypo responsiveness to erythropoietin in patients with CKD—an area of high priority for future research. However, it is not established whether the benefits of improved QOL measures outweigh the risks of cardiovascular morbidity and the economic costs related to treatment to achieve a higher Hb level. Another area of uncertainty related to hypo responsiveness is the role of iron use in treating anemia. New research that provides a better understanding of the role of inflammation in iron metabolism, utilization, and the response to ESA treatment is another important research priority.

Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitor (HIF-PHI): A New Beginning?

HIF-PHI enzymes are small peptides that inhibit proline hydroxylation of HIF-**α** [93].Their mechanism of action relies on the natural mechanism by which the body responds to low oxygen levels and works by reversibly inhibiting the HIF-PH

enzymes, thus mimicking a coordinated natural erythropoietic response through genes transcribing the proteins involved in iron absorption, mobilization and transport as well as stimulation of red blood cell progenitors. [94] (Fig. 13.1).

While there are several HFI-PHIs in development (Table 13.5); at the time of this chapters writing, one is scheduled for launch in the United States, Roxadustat™. Currently available in China for anemia of chronic kidney patients both on and not on dialysis and in Japan for dialysis dependent patients, Roxadustat™ has been shown to be safe & effective. Phase 3 global trials have shown, in addition to efficacy; that Roxadustat™ lowers iron requirements, decreases hepcidin levels, lowers LDL cholesterol levels, reduces transfusion requirements and appears efficacious in inflamed patient [95, 96, 97, 98]. Additionally; it was shown to lower Major Adverse Cardiovascular Events (MACE) & MACE+ (MACE in addition to unstable angina

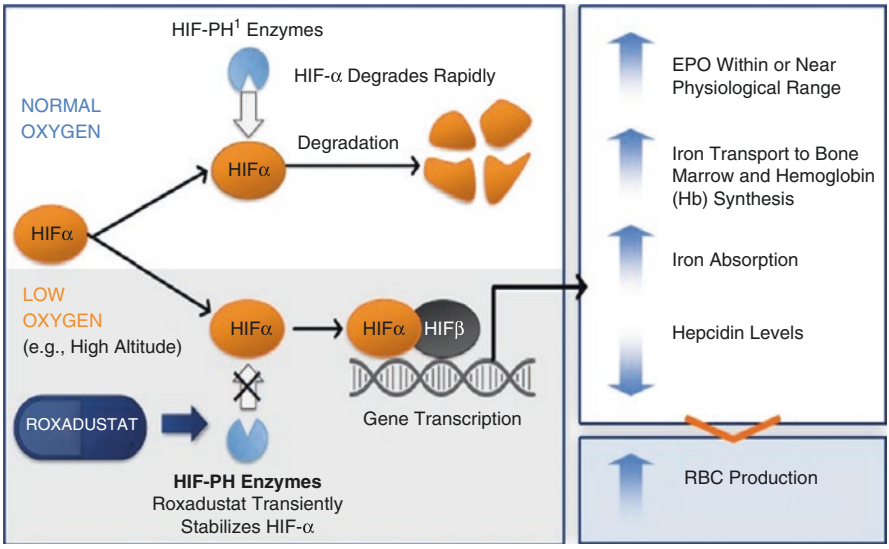

Fig. 13.1 Stylized Mechanism of action for HIF alpha and beta subunits under normal and low oxygen environments as well as site of action of Roxadustat mimicking low oxygen environment

Table 13.5 HIF-PHIs in Advance Clinical Development. (Ref. [93])

Compound	Effective daily oral doses	Dosing schedule	Noninferiority compared with ESA	Licensing
Daprodustat	4–25 mg	QD	NDD-CKD DD-CKD	Japan
Desidustat	100–200 mg	QOD	–	–
Enarodustat	2–8 mg	QD	NDD-CKD DD-CKD	–
Molidustat	25–150 mg	QD	NDD-CKD	–
Roxadustat	0.7–2.5 mg/kg	TIW	DD-CKD	China Japan (DD-CKD)
Vadadustat	150–600 mg	QD (TIW)	NDD-CKD DD-CKD	Japan

& congestive heart failure requiring hospitalization) events in incident dialysis patients as well lowering MACE+ events in prevalent dialysis patients.

While it is too early to draw any conclusions from these data, HIF-PHI stimulation of a physiologic erythropoietic response vs. our current standard of care of delivering a pharmacologic ruEPO dose opens exciting prospects of readdressing appropriate target hemoglobin, cardiovascular safety, patient quality of life to name a few.

Summary

Anemia is common and contributes to both poor QOL and increased risk for adverse outcomes including death. Treatment of anemia improves QOL; however, thus far, evidence is lacking for a benefit of anemia treatment on progression of kidney disease and cardiovascular outcomes. The NKF recommends that physicians consider treating anemia in patients with diabetes and kidney disease when Hb is <11 g/dl in patients. Further, they recommend a Hb target of 11–12 g/dl, not to exceed 13 g/dl, when using an ESA as part of the therapeutic regimen for managing anemia. Currently available ESA combined with iron supplementation can be used safely and effectively to achieve this goal. However, available clinical trial evidence leaves sufficient uncertainty regarding the optimal Hb target and ESA dose for a given individual. For this reason, the NKF recommends individualizing treatment of anemia with ESA. Additional randomized clinical trials are needed to more precisely define these parameters for an individual patient. Future studies are also needed to elaborate the mechanisms of anemia in patients with diabetes and CKD including the role of iron metabolism, inflammation, and resistance.

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Chapter 14
Cardiovascular Disease and Diabetic Kidney Disease

Keith C. Ferdinand, Samar A. Nasser, and Ayan Ali

Cardiovascular disease (CVD) is the leading cause of death worldwide and is often associated with diabetes, diabetic kidney disease (DKD), and other forms of chronic kidney disease (CKD) [1]. Moreover, in patients with diabetes, the most prominent cause of mortality is CVD, usually associated with coexisting conditions including hypertension and dyslipidemia that further contribute to increased morbidity and mortality [2, 3]. Additionally, DKD greatly amplifies the risk, complications, and death from CVD and is the most common cause of end-stage renal disease (ESRD) worldwide [4]. Specifically, patients with DKD are more likely to suffer adverse CVD outcomes than to develop ESRD [5]. As documented by the United States Renal Data System (USRDS) and the adult National Health and Nutrition Examination Survey (NHANES), the prevalence of CVD in patients with CKD is as high as 63%, compared to only 5.8% for non-CKD patients [6]. Nevertheless, despite intensive treatment of major risk factors, DKD rates may remain high [5]. Intensive glycemic control per se does not reduce CVD risk and only has a modest effect on DKD in established type 2 diabetes [5]. However, numerous studies have revealed that controlling individual CVD risk factors is efficacious in the prevention and slowing of CVD in patients with diabetes [2]. In consideration of the above, diabetes, CKD, DKD, and CVD are interrelated and often coexist, causing public

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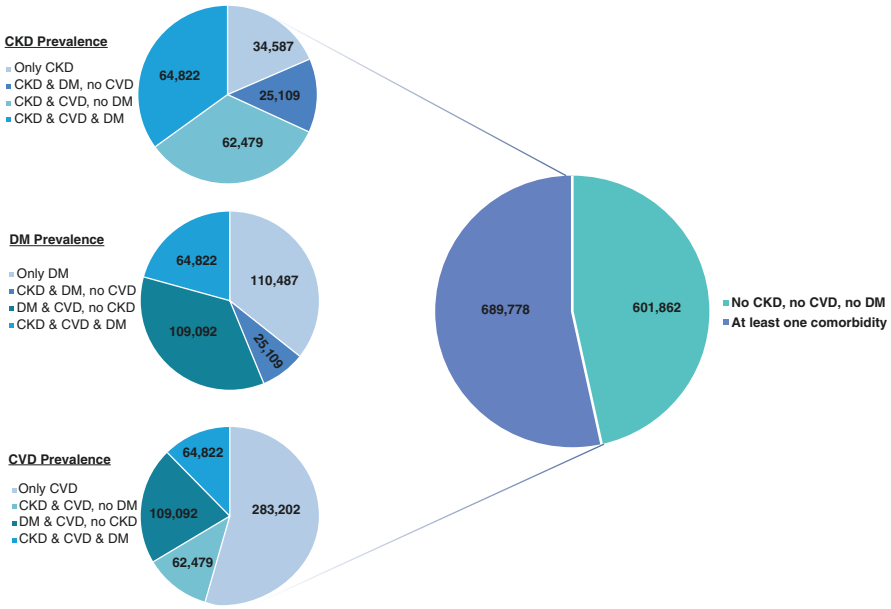

Fig. 14.1 Prevalence of comorbid conditions in Medicare patients. Point prevalence distribution for Medicare patients with chronic kidney disease (CKD), cardiovascular disease (CVD), and/or diabetes mellitus (DM). Date source: Special analyses, Medicare 5% sample (age 65 and older) in the United States [19]

health burdens with significant physiologic and economic ramifications (Fig. 14.1). Overall, this chapter will focus on CKD and CVD, specifically as related to new developments in epidemiology and therapy and peer-reviewed literature emphasizing CVD outcome trials.

Cardiovascular Disease in Patients with Diabetes

Recently, the Centers for Disease Control and Prevention estimated that 34.2 million Americans have been diagnosed with diabetes, along with another 88 million individuals diagnosed with prediabetes [7]. Patients with diabetes often have other comorbidities, such as obesity, hypertension, hypercholesterolemia, and physical inactivity, contributing to a heightened risk of CVD and its complications [7]. This makes the prevention of CVD onset an important priority to mitigate disease morbidity and mortality [7]. Atherosclerotic cardiovascular disease (ASCVD) encompassing coronary artery disease (CAD), cerebrovascular disease, atrial fibrillation, and peripheral arterial disease, is the leading cause of morbidity and mortality in people with diabetes [2]. Moreover, ASCVD potential is increased in the presence of uncontrolled risk factors such as hyperglycemia, hypertension, and dyslipidemia [2]. According to the 2020 Heart Disease and Stroke Statistics, diabetes also increases

the risk of heart failure (HF) and adversely affects outcomes among patients with HF [8]. Therefore, the overall morbidity and mortality in persons with diabetes result in an estimated $37.3 billion in cardiovascular-related spending per year [2].

Observational studies have shown that before the initiation of CVD risk reduction strategies, there was a three- to fourfold higher all-cause and CVD mortality in participants with type 2 diabetes compared with those without type 2 diabetes [9]. Therefore, there is an urgent need to focus on aggressive cardiovascular (CV) risk reduction in patients with diabetes, especially those with established CAD. Many evidence-based practice guidelines recognize the prevention of CV events as a critical management priority. According to the American Diabetes Association Standards of Care – 2020, severe hypoglycemia is a potent marker of high absolute risk of CV events and mortality [2]. Therefore, preventing hypoglycemia is essential in patients in whom adequate targets cannot be safely and reasonably achieved [2].

Heart Failure and Type 2 Diabetes

Approximately 40 years prior to this review, the landmark Framingham Heart Study demonstrated that diabetes independently increases the risk of HF up to twofold in men and fivefold in women, compared to age-matched controls [10]. The increased incidence of HF in patients with diabetes persists presently, even after adjusting for other risk factors such as age, hypertension, hypercholesterolemia, and CAD [8]. The coexistence of diabetes and HF imparts structural and functional changes that characterize diabetic cardiomyopathy. This may lead to multiple pharmacologic interventions that may reduce the risk of HF in the context of type 2 diabetes. Kenney et al. described successful pathways that could alter the prognosis and risk of HF beyond what is currently achieved using existing antihyperglycemic and HF therapeutics [11].

In patients that have maximally blocked renin-angiotensin system (RAS), the addition of neprilysin inhibitors may be used to attenuate the effect of diabetes and slow worsening renal function in patients with chronic HF [12]. A double-blind randomized controlled trial was conducted using the addition of neprilysin inhibition to assess their effect on kidney disease in diabetic patients [12]. This study found that in patients using high doses of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), the addition of neprilysin inhibition slowed the rate of decline in the estimated glomerular filtration rate (GFR) [12].

Cardiovascular Disease in Chronic Kidney Disease

Defined as abnormalities in kidney structure and/or function that are present for 3 months or greater, the widely used criteria for CKD are a GFR <60 mL/min per 1.73 m^2 or a urinary albumin-creatinine ratio ≥ 30 mg/g [13]. Patients who meet

these criteria are at an increased risk of overall premature mortality [13]. The natural progression of CKD over time is to ESRD, which is an indicator for renal replacement therapy, premature CVD, and mortality [14]. Overall, the implications of CKD include increased morbidity, mortality, and reduction in the quality of life of patients at the individual level, with high costs attributed to treatment at the societal level [15]. Therefore, patients with severely decreased GFR are at high risk for adverse outcomes, including CVD events, kidney failure, and death [15]. On the other hand, when the GFR declines below approximately 60–75 ml/min/1.73 m^2, the probability of developing CVD increases linearly [16]. Thus, as the GFR declines, there is an increased prevalence of CVD risk factors ranging from albuminuria, anemia, inflammation, to endothelial dysfunction that worsen atherosclerosis and CKD [17].

Cardiovascular Disease and Diabetic Kidney Disease

Type 1 diabetes and type 2 diabetes have multiple vascular consequences [18]. Specifically, DKD is strongly associated with CVD and is directly linked to the development of DKD [2, 18]. In fact, ASCVD is the most important cause of death in patients with diabetes [18]. Approximately 40% of patients with type 2 diabetes subsequently meet criteria of DKD [19]. While there are acute manifestations and complications of diabetes, such as hyperglycemia, hypoglycemia, and diabetic ketoacidosis, these conditions are often important causes of morbidity early in the disease course [18]. However, as patients with diabetes often have decades living with the diagnosis, microvascular and macrovascular complications drive the excess in morbidity and mortality [18].

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial tested the hypothesis that finerenone slows CKD progression and reduces cardiovascular morbidity and mortality among patients with advanced CKD and type 2 diabetes [20]. Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist with optimized renin-angiotensin system blockade. An international, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, FIDELIO-DKD randomized 5674 with 45.9% patients having CVD at baseline [21]. Out of the 2605 patients with a history of CVD, 17.7% of patients taking finerenone developed a CV outcome, compared with 20.2% of patients in the placebo group (HR, 0.85; 95% CI, 0.71–1.01). Out of the 3069 patients without a history of CVD, 8.9% of patients taking finerenone developed a CV event, compared with 10.2% of patients in the placebo group (HR, 0.86; 95 CI%, 0.68–1.08). Overall, finerenone significantly slowed time to CKD progression by 18% and reduced CV events, compared to placebo [21, 22].

The USRDS reported that the prevalence of CKD was greater in older patients, Blacks, and those with type 2 diabetes, hypertension, or CVD [19]. Given the high mortality of CVD in patients with diabetes and kidney disease, Wang and colleagues compared CV characteristics and outcomes between patients with DKD and

non-diabetic kidney disease [23]. Overall, results demonstrated that patients with DKD had more severe CVD along with poorer renal and CV prognoses than those with non-diabetic kidney disease [23].

The key to slowing progression of DKD is by first and foremost controlling blood pressure (BP), then glucose, and, to a lesser extent, lipids. Clear guideline evidence supports the role for RAS blockade in all those with 300 mg or more albuminuria in slowing progression. More recently the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i), regardless of blood sugar control, also slows progression of DKD [2, 24]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial of 11,140 patients demonstrated that intensive glucose control significantly reduced the risk of ESRD by 65%, microalbuminuria by 9%, and macroalbuminuria by 30% [25]. In a 5.4-year follow-up of ADVANCE trial participants, the findings echoed the results from the original study: intensive glucose control was associated with a long-term reduction in ESRD, without evidence of any increased risk of CVD events or death [26]. These benefits were greater in those with preserved kidney function and well-controlled BP [26].

Sodium-Glucose Cotransporter-2 Inhibitors

As noted, DKD is associated with an increased risk of CVD, and both conditions include common risk factors such as hypertension and poor glycemic control [2, 27]. Intuitively, optimal current management requires intensive glucose and BP control. While the protective role of treating dyslipidemia has been delineated for reducing CVD, the relationship and results for kidney disease are unclear [28]. Yet the advent of novel glucose-lowering medications, including SGLT2i, glucagon-like peptide 1 (GLP-1) agonists, and, to a lesser extent, dipeptidyl peptidase (DPP-4) inhibitors, has resulted in impressive CV and renal outcomes in patients with diabetes and those without diabetes [27, 29]. These medications have been shown to work independently of glucose concentrations, demonstrating that the pathophysiology may be multifaceted. They provide new strategies for kidney and CV protection and reduce both microvascular and macrovascular outcomes in patients [27].

Recent data from diabetes-related CV outcome trials and renal specific trials have provided novel insights on SGLT2i in slowing the progression of DKD, as well as reducing adverse CVD outcomes, including HF. This is critical, as DKD contributes to the increase in morbidity and mortality of CVD and its complications.

Accordingly, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) randomized trial assessed the effects of canagliflozin primarily on renal outcomes in 4401 patients with type 2 diabetes and albuminuria-related CKD [30, 31]. The CREDENCE trial compared canagliflozin versus placebo in those with type 2 diabetes and a baseline estimated GFR (eGFR) of 30–90 mL/min per 1.73 m^2 and a urine albumin-to-creatinine ratio >300–5000 mg/g [31]. Participants received a stable dose of either an ACEi or ARB. The

kidney-specific composite was reduced by 30% in those treated with canagliflozin (HR, 0.70; 95% CI, 0.59–0.82; $P < 0.001$) [31]. Notably, canagliflozin treatment was also associated with a lower risk for several CV-related outcomes [30, 31].

A recent secondary analysis of the CREDENCE trial revealed that kidney and cardiac protection was also preserved in patients that had an eGFR between 30 and 45 mL/min/1.73 m^2 [30]. These data demonstrated that SGLT2i safely prevent renal and CVD events in patients with diabetes, substantial albuminuria, and an eGFR at commencement of treatment between 30 and 90 mL/min/1.73 m^2 [30]. Importantly, the results of these analyses are consistent across eGFR categories and support the expansion of SGLT2i treatment initiation for patients with decreased eGFRs and the continuation of medical treatment until the initiation of dialysis or transplantation [30].

The Dapagliflozin and Prevention of Adverse outcomes in Heart Failure (DAPA-HF) revealed the efficacy of SGLT2i in reducing the primary outcomes of worsening HF, defined as a hospitalization or urgent visit necessitating intravenous therapy and/or death due to CVD [32]. Over 18 months, the primary outcomes occurred in 16.3% (386 of 2373) of patients in the dapagliflozin group and 21.2% (502 of 2371) of patients in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P < 0.001) [32]. Specifically, worsening HF occurred in 10.0% of patients in the dapagliflozin group, compared to 13.7% in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83), while death from CV causes occurred in 9.6% in the dapagliflozin group and 11.5% in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98) [32]. This trial showed that in patients with HF, dapagliflozin lowered their risk of worsening HF or death due to CVD, irrespective of a diagnosis of diabetes [32]. The frequency of adverse events was not statistically different between treatment groups [32].

Recently, the DAPA-CKD trial demonstrated a reduction in the risk of kidney failure, death from cardiovascular causes, or hospitalization for heart failure, and prolonged survival, in people with chronic kidney disease, with or without type 2 diabetes, independent of the presence of concomitant cardiovascular disease [33]. Overall, the combined cardiorenal benefits of SGLT2 inhibitors in patients with chronic kidney disease, with and without T2D, are significant with or without a history of cardiovascular disease.

During a median follow-up of 2.4 years, in patients (n = 4304) with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. The hazard ratio for the primary end point was 0.61 (95% CI, 0.51–0.72; $P = 0.00000028$), and dapagliflozin achieved all three secondary end points, including a 31% risk reduction in all-cause mortality (HR, 0.69; 95% CI, 0.53–0.88; $P = 0.0035$) [34].

Overall, the addition of SGLT2i demonstrates CVD benefits and, as per Kidney Disease Improving Global Outcomes, is recommended for use in patients with established CVD or indicators of high risk [29]. Furthermore, the CVD benefits of SGLT2i are not dependent on glycemic control, and initiation can be considered in people with type 2 diabetes and CVD, independent of their current hemoglobin A1c (A1c) or A1c goal [29].

According to the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58), dapagliflozin reduced the rate of CV death or hospitalization for HF in patients with type 2 diabetes or those who have a high risk of ASCVD [35]. In a large population of 17,160 participants with type 2 diabetes and overall preserved renal function, dapagliflozin was associated with reduced progression of kidney disease and lower rates of clinically relevant renal events than placebo. The primary composite renal outcome developed in 370 (4.3%) vs. 480 (5.6%) in the dapagliflozin and placebo arms, corresponding to event rates per 1000 patient-years of 10.8 and 14.1 [HR, 0.76 (0.67, 0.87); $p < 0.001$] [35]. The beneficial effect of dapagliflozin on renal endpoints was consistently demonstrated in those with established ASCVD [35]. A recent meta-analysis of SGLT2i trials, including the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME), CANagliflozin cardioVascular Assessment Study (CANVAS), and DECLARE-TIMI 58, summarized their outcomes regarding the composite of worsening of renal function, ESRD, or renal death [36] (Fig. 14.2).

In order to determine the benefits in patients with and without diabetes, the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) randomized 3730 patients with class II–IV heart failure and left ventricular ejection fraction (LVEF) ≤40% to 10 mg empagliflozin daily or placebo in addition to recommended therapy. Of these patients, 50% had diabetes, 34% had prediabetes, and 16% had normoglycemia. Empagliflozin demonstrated a reduced risk of CV death or hospitalization for heart failure in patients with and without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; $P < 0.001$). Furthermore, the annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (−0.55 vs. –2.28 ml per minute per 1.73 m^2 of body-surface area per year, $P < 0.001$), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Overall, empagliflozin demonstrated a significant improvement in renal and cardiovascular outcomes in patients with heart failure and LVEF ≤40% regardless of HbA1c [37].

As previously mentioned, hypertension is a potent risk factor for CVD, especially in patients with type 2 diabetes. Ferdinand and colleagues recently evaluated 150 African Americans, a high-risk population, with type 2 diabetes and hypertension who were randomized to once daily empagliflozin or placebo to investigate effects on BP and overall CV mortality [38]. After 24 weeks of treatment, patients treated with empagliflozin exhibited a significantly greater hemoglobin A1c decrease compared with patients treated with placebo [38]. Additionally, patients also experienced significantly greater weight loss and a decrease in 24-hour ambulatory systolic BP [38]. Thus, empagliflozin effectively reduced hemoglobin A1c, body weight, and BP in African Americans with type 2 diabetes.

The clinical benefits of novel anti-diabetic medication in CVD and kidney protection have been established (Table 14.1). Newer studies have revealed that GLP-1 agonists have a role in the treatment of diabetes and decrease overall ASCVD events and have substantial benefits in CV and kidney outcomes [29]. In contrast to the

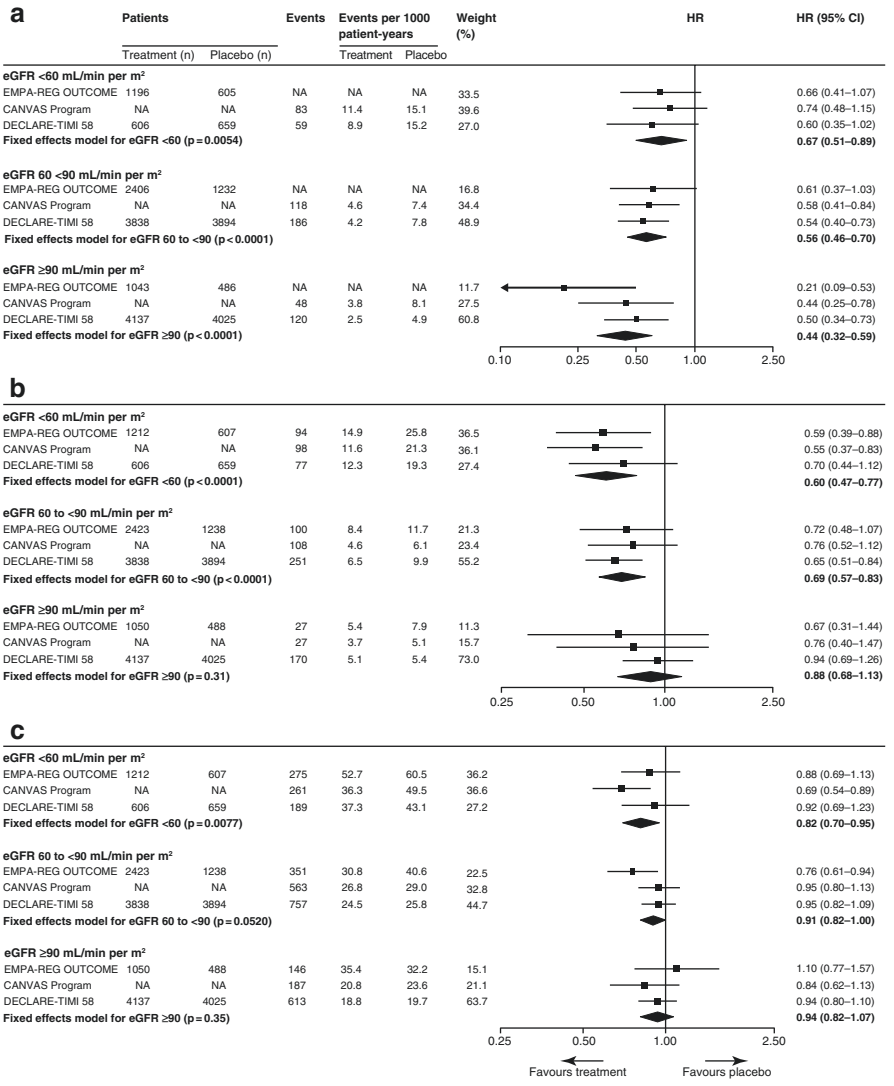

Fig. 14.2 Meta-analysis of sodium-glucose cotransporter-2 inhibition trials on the composite of worsening of renal function, ESRD, or renal death (**a**), hospitalization for heart failure (**b**), and major adverse cardiovascular events stratified by the eGFR levels (**c**) https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32590-X/fulltext

benefits of GLP-1 agonists and SGLT2i, DPP-4 inhibitors have not shown to decrease major ASCVD events [29]. In fact, the Food and Drug Administration has revealed that DPP-4 inhibitors, particularly saxagliptin, may increase risk of HF [39]. Although there are multiple CV outcome trials among patients with diabetes and CKD (Table 14.2), this review focused upon the most recent data on SGLT2i or GLP-1 agonists.

Table 14.1 General concepts of cardiovascular and kidney effects of newer anti-diabetic agents

	Cardiovascular effects		Kidney effects	
Drug	Major atherosclerotic cardiovascular events	Heart failure	Albuminuria or albuminuria-containing composite outcome	GFR loss
SGLT2 inhibitors	↓/–	↓↓	↓↓	↓↓
GLP-1 receptor agonists	↓/–	–	↓	↓/–
DPP-4 inhibitors	–	–/↑	↓	–

Summary of the benefits and harms of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, by class, as observed in large, placebo-controlled clinical outcomes trials. ↓ = significant reduction in risk, with HR estimate >0.7 and 95% confidence interval not overlapping 1; ↓↓ = significant reduction risk, with HR estimate ≤0.7 and 95% confidence interval not overlapping 1; ↔ = no change; ↑ = increase; – = no significant effect. Adapted from Ref. [29]

Table 14.2 CV outcome trials among patients with diabetes and DM and CKD, 2013–2020

Trial acronym	Trial name	Year published
EXAMINE study	Examination of cardiovascular outcomes with Alogliptin versus standard of care	2013
SAVOR-TIMI 53	Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus–thrombolysis in myocardial infarction	2013
EMPA-REG OUTCOME	[Empagliflozin] cardiovascular outcome event trial in type 2 diabetes mellitus patients	2015
ELIXA	Evaluation of Lixisenatide in acute coronary syndrome	2015
TECOS	Trial evaluating cardiovascular outcomes with Sitagliptin	2015
LEADER	Liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results	2016
SUSTAIN-6	Trial to evaluate cardiovascular and other long-term outcomes with Semaglutide in subjects with type 2 diabetes	2016
IRIS	Insulin resistance intervention after stroke	2016
FREEDOM-CVO	A study to evaluate cardiovascular outcomes in patients with type 2 diabetes treated with ITCA 650	2016
CANVAS	Canagliflozin cardiovascular assessment study	2017
DEVOTE	A trial comparing cardiovascular Safety of insulin Degludec versus insulin glargine in patients with type 2 diabetes at high risk of cardiovascular events	2017
ACE	Acarbose cardiovascular evaluation	2017
EXSCEL	Exenatide study of cardiovascular event lowering	2017
CARMELINA	Cardiovascular and renal microvascular outcome study with Linagliptin in patients with type 2 diabetes mellitus	2017
PIONEER 6	A trial investigating the cardiovascular Safety of Oral Semaglutide in subjects with type 2 diabetes	2018
HARMONY outcomes	Effect of Albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in subjects with type 2 diabetes mellitus	2018

(continued)

Table 14.2 (continued)

Trial acronym	Trial name	Year published
REWIND	Researching cardiovascular events with a weekly incretin in diabetes	2018
VERTIS CV	Cardiovascular outcomes following Ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease	2019
Dapa-HF	Dapagliflozin in patients with heart failure and reduced ejection fraction	2019
CAROLINA	Cardiovascular outcome study of Linagliptin versus glimepiride in patients with type 2 diabetes	2019
DECLARE-TIMI 58	Multicenter trial to evaluate the effect of Dapagliflozin on the incidence of cardiovascular events	2019
CREDENCE	Evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic kidney disease (DKD)	2019
EMPEROR-preserved	Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction	2020
EMPEROR-reduced	Empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction	2020
DAPA-CKD	A study to evaluate the effect of Dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease	2020

The ADA Standards of Care gave a Level of Evidence: A recommendation, based on large well-designed clinical trials or well-done meta-analyses, for the use of SGLT2i in patients with type 2 diabetes and DKD with an eGFR ≥30 mL/min/1.73 m^2 and urinary albumin >30 mg/g creatinine, particularly in those with urinary albumin >300 mg/g creatinine, to reduce risk of chronic kidney disease (CKD) progression, cardiovascular events, or both [2] (Fig. 14.3). However, in patients with CKD who are at an increased of CVD event, the use of GLP-1 agonists received a Level of Evidence: C, based on supportive evidence from poorly controlled or uncontrolled studies, for the reduced risk of progression of albuminuria, cardiovascular events, or both [2]. These agents – SGLT2i, GLP-1 agonists, and DPP-4 inhibitors – do have adverse effects and may be restricted for usage below certain GFR thresholds and must be cautiously administered [29].

Conclusion

Research into CVD treatment and its complications is critical in reducing disease burden. The prevention of CVD onset can mitigate overall morbidity and mortality from its complications, including diabetes, CKD, and DKD. There is also a clear economic impact of these conditions, resulting in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes alone. Fortunately, trials such as ADVANCE, CREDENCE, DAPA-CKD and DAPA-HF, DECLARE-TIMI 58, EMPEROR-Reduced, and FIDELIO-DKD have delineated the relationship

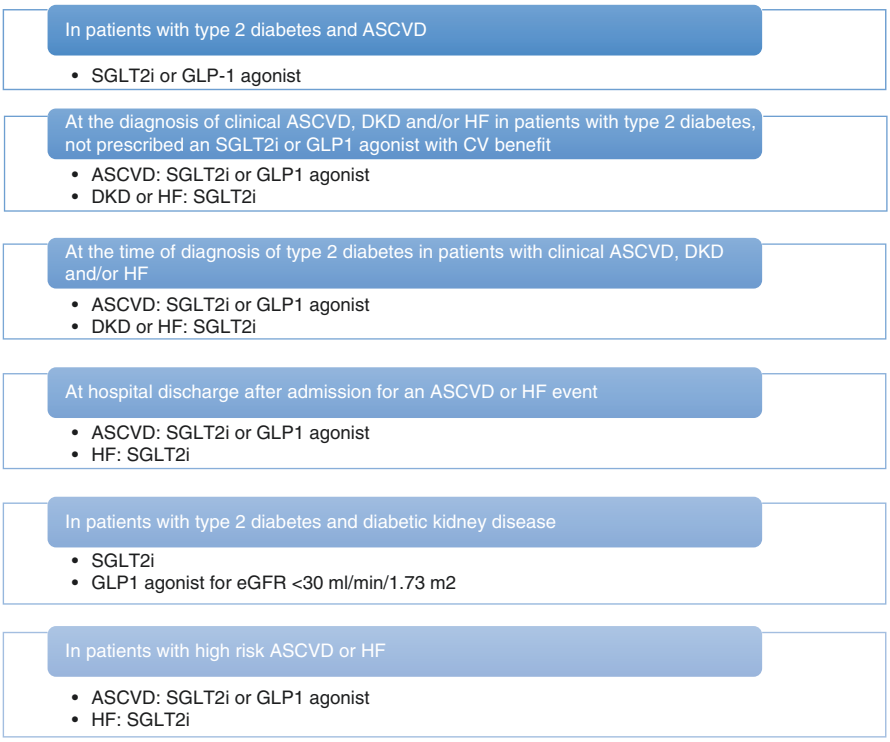

Fig. 14.3 Initiation of SGLT2i or GLP-1 agonist with demonstrated cardiovascular or renal benefit in patients with type 2 diabetes. (*ASCVD* atherosclerotic cardiovascular disease, *SGLT2i* sodium-glucose cotransporter-2 inhibitor, *GLP1 glucagon-like peptide 1*, *DKD* diabetic kidney disease, *HF* heart failure, *eGFR* estimated glomerular filtration rate. Adapted from Ref. [40])

of CVD, CKD, and DKD and offer insight on therapies, particularly SGLT2i, GLP-1 agonists, and, to a lesser extent, DPP-4 inhibitors. Opportunities to initiate SGLT2i or GLP-1 agonists in patients with type 2 diabetes warrant increased vigilance and surveillance for hypoglycemia, especially if on insulin, sulfonylurea, or glinide therapy. It is important to use clinical judgment when initiating SGLT2i in patients who will be starting ACE inhibitor or ARB therapy when renal function is impaired (Fig. 14.3). Understanding and revealing the relationship of these diseases is important to continue generating best-practice therapies and guidelines for patients.

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Chapter 15
Dyslipidemia and Diabetes

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Introduction

Diabetic nephropathy is a severe kidney-related complication of type 1 diabetes and type 2 diabetes, which develops in approximately 30% of patients with type 1 diabetes mellitus (T1D) and approximately 40% of patients with type 2 diabetes mellitus (T2D) [1–3]. Nearly half of all chronic and end-stage kidney disease can be ascribed to diabetic kidney disease (DKD), and it is thought to be the leading cause of chronic kidney disease (CKD) worldwide [4]. The course of diabetic kidney disease comprises glomerular hyperfiltration, progressive albuminuria, declining glomerular filtration rate (GFR), and, finally, end-stage renal disease (ESRD). Metabolic alterations related to the presence of diabetes result in the development of glomerular hypertrophy, glomerulosclerosis, and tubulointerstitial inflammation and fibrosis [1]. DKD is associated with lipid disturbances. The dysregulation of lipid metabolism in CKD could lead to dyslipidemia; however, when CKD is accompanied by diabetes mellitus, dyslipidemia could be further aggravated as a result of hyperglycemia and insulin resistance [5–7]. Growing evidence indicates that kidney lipid metabolism may play a direct role in the progression of DKD [8, 9]. As early as in 1936, Kimmelstiel and Wilson described for the first time lipid accumulation in DKD [10]. After that, numerous studies have confirmed the correlation between lipid deposition and kidney injury [8, 9, 11, 12]. Qualitative and quantitative alterations of lipoprotein profile probably contribute to the increased risk of atherosclerotic events [13]. This enhanced risk is associated with the presence of increased

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concentrations of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) cholesterol, small dense and oxidized LDL particles, and lipoprotein(a) [13]. Patients with diabetic nephropathy have very high cardiovascular risk, comparable to that of patients with coronary heart disease [14, 15]. Despite novel therapies, large residual risk of diabetic kidney disease onset and progression is still reported worldwide.

DKD: Definition and Diagnosis

Diabetic kidney disease (DKD), also known as diabetic nephropathy (DN), is not only the most common complication of diabetes mellitus but also the leading cause of end-stage renal disease, requiring dialysis or transplantation [16–18]. The prevalence of DKD is constantly increasing due to high prevalence of diabetes mellitus and obesity and in spite of novel management strategies of diabetes [19]. DKD is characterized by a progressive elevation in albuminuria and a consequent diminishing of the glomerular filtration rate [20]. It is defined as diabetes mellitus with persistently high urinary albumin-to-creatinine ratio $\geq$ 30 mg/g and/or an impaired glomerular filtration rate (GFR) (<60 mL/min/1.73 m^2), or both [16, 21]. Its diagnosis is made on the basis of the measurement of estimated glomerular filtration rate (eGFR) (calculated from the serum creatinine concentration) and albuminuria (urinary albumin-to-creatinine ratio performed on a spot sample, preferably in the morning) as well as the analysis of clinical features, including diabetes duration and the presence of diabetic retinopathy [1–3, 22, 23]. Microalbuminuria alone seems not to be the optimal identification tool of patients with type 2 diabetes at higher risk of renal impairment [24]. The confirmation of decreased eGFR or albuminuria requires two abnormal results of tests at least 3 months apart [1]. Some patients present atypical features of DKD, such as abrupt onset of low eGFR or rapidly lowering eGFR, rapid rise in albuminuria or the development of nephrotic or nephritic syndrome, refractory hypertension, signs or symptoms of another systemic disease, and > 30% eGFR decline within 2–3 months of initiation of a renin–angiotensin system inhibitor [1] [25]. It has been suggested that genetic predisposition (race/ethnicity, family history) as well as inadequate metabolic control (including hyperglycemia and dyslipidemia) are key players in the DKD. Among other DKD risk factors, there are the following: age and sex (susceptibility factors), hyperglycemia and acute kidney injury (AKI) (initiation factors), as well as hypertension, dietary factors, and obesity (progression factors) [1]. The screening process toward DKD should be carried out annually in patients with type 1 diabetes mellitus (DM1) (starting from fifth year after the diagnosis) and in those with type 2 diabetes mellitus (DM2) (starting at the time of diagnosis) [1]. Diabetic retinopathy development in patients with albuminuria is strongly suggestive of DKD.

Numerous alterations in the structure of many kidney compartments are observed in the course of DKD development [1]. Its progress is usually preceded by significant structural changes within the kidney, such as glomerular basement membrane (GBM)

thickening resulting from excessive deposition of extracellular matrix (ECM) that becomes apparent within 1.5–2 years of DM1 diagnosis, capillary and tubular basement membrane thickening, loss of endothelial fenestrations, mesangial matrix expansion, glomerular sclerosis, and podocyte loss with effacement of foot processes [26–29]. Other changes include mesangial volume expansion (which becomes detectable within 5–7 years after DM1 diagnosis), renal hypertrophy, glomerular hypertrophy, interstitial fibrosis, as well as the enlargement of glomerular capillaries [26–30]. As the diabetes progresses, segmental mesangiolysis develops and it is thought to be related with Kimmelstiel–Wilson nodules and microaneurysm development [31, 32]. The presence of exudative lesions resulting from subendothelial deposits of plasma proteins can lead to luminal compromise, such as hyaline arteriolosclerosis. Lower eGFR and albuminuria and disproportionate reduction in afferent arteriole resistance and rise in efferent arteriole resistance lead to the development of intraglomerular hypertension [33]. In more advanced stages of diabetes, the coalesce of interstitial changes and glomerulopathy into segmental and global sclerosis is observed [1].

There are two types of diabetic nephropathy that in some aspects differ from each other [34]. For example, in patients with type 2 diabetic nephropathy, structural heterogeneity is higher compared to patients with type 1 diabetic nephropathy [34]. Clinical data indicate that type 1 diabetic nephropathy is characterized by glomerular hypertrophy, higher glomerular basement membrane width, diffuse mesangial sclerosis, podocyte damage, microaneurysm, hyalinosis, hyaline arteriolosclerosis, and also tubulointerstitial fibrosis and tubular atrophy and dedifferentiation [35]. In these patients, GFR, albuminuria, and hypertension were shown to be strongly correlated with mesangial expansion and less strongly related to glomerular basement membrane width [1]. The presence of tubulointerstitial fibrosis and atrophy is reported even in patients with diabetic nephropathy and minimal or mild glomerular lesions [36]. In patients with type 2 diabetic nephropathy, early diabetic glomerulopathy is observed, and it was found to be more advanced in those with microalbuminuria and proteinuria. These lesions are, however, milder than those found in type 1 diabetic patients. Morphometric results obtained with the use of electron microscopy showed heterogeneity of renal structure in type 2 diabetic patients. According to studies, diabetic kidney disease develops in 40% of patients with diabetes, sometimes even in those with well-controlled glucose levels.

DKD, in some patients, does not strictly follow the standard pattern of glomerular hyperfiltration progressing to persistent albuminuria and resulting in hypertension and GFR reduction. The United Kingdom Prospective Diabetes Study (UKPDS) of DKD course in patients with DM2 revealed that they progressed approximately 2% per year from normo- to microalbuminuria and from micro- to macroalbuminuria [24, 37]. In this study, 40% of participants developed albuminuria, and 30% developed eGFR <60 ml/min per 1.73 m^2 or doubling of the blood creatinine level at a median of 15 years after diagnosis [24, 37]. Authors underlined that 60% of patients who developed kidney functional impairment did not have preceding albuminuria and 40% never had albuminuria during the study [24]. This observation indicates that albuminuria development is a dynamic state, not a linearly progressive process.

Lipid Disturbances in Diabetes, CKD, and DKD

Both diabetes and renal disease are associated with variations in serum lipids levels and their metabolism. The presence of dyslipidemia has been demonstrated to be associated with Diabetic nephropathy (DN) progression and also enhanced cardiovascular risk [38, 39]. Hypertriglyceridemia, higher VLDL cholesterol, diminished high-density lipoprotein (HDL) cholesterol, average levels of LDL cholesterol, but higher content of small dense LDL cholesterol are observed in both diabetes and CKD. However, according to studies, lipid metabolism is different in diabetes and CKD [40]. Altered profile of plasma lipoprotein in patients with type 2 diabetes (T2D) involving increased triglycerides, and small dense low-density lipoprotein (LDL) particles, and decreased high-density lipoprotein (HDL) cholesterol is called diabetic dyslipidemia [41]. The deficiency of insulin was shown to rise levels of non-esterified or free fatty acids (NEFA) released from adipocytes due to the activity of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) [42]. The action of the first enzyme involves the hydrolysis of triglycerides to diacylglycerol that is further used by HSL as a primary substrate. In the next step of triglyceride conversion, monoglycerol lipase participates in the formation of NEFA and glycerol within adipocytes. In healthy state, large percentage of released NEFA molecules is cleared by the liver where they are recycled in the form of newly secreted triglycerides; however, in diabetes, such clearance is frequently impaired due to lower activity of insulin-sensitive lipoprotein lipase (LPL) [43]. Therefore, it seems that diabetes-related hypertriglyceridemia is associated not only with enhanced triglyceride formation but also with defective plasma triglyceride removal and higher de novo synthesis [44]. In type 2 diabetes, higher production of TG-rich lipoproteins seems to be the predominant alteration. Hepatic VLDL synthesis is triggered by the elevated flux of free fatty acids. Enhanced hepatic lipase activity translates into the generation of smaller, denser LDL particles and a reduction in HDL2 subspecies [45].

Cholesteryl ester transfer protein (CETP), which mediates the exchange of cholesteryl ester from HDL to VLDL or LDL in exchange for triglycerides, diminishing serum HDL concentrations, and TG, has been found to play an important role in dyslipidemia development [46]. Its activity was found to be regulated by apoC-I (physiological inhibitor of CETP); however, in patients with diabetes, the ability of apoC-I to limit CETP activity seems to be compromised due to the glycation of this inhibitor [47]. VLDL reception of cholesteryl ester from HDL and subsequent transfer of TG to HDL result in the increased generation of cholesterol-rich VLDL remnant particles and cholesterol-depleted HDL particles. Further, TG-rich HDL can undergo hydrolysis by LPL or hepatic TG lipase (HTGL) to become lipid-poor HDL that is filtered by the glomeruli and degraded in renal tubular cells [48]. The results of studies have indicated that variation in CETP levels correlates with lipid metabolism and insulin resistance in patients with type 2 diabetes and also with the susceptibility to atherosclerosis and CVD [49, 50].

The result of epidemiologic study assessing the effect of albuminuria/renal function on dyslipidemia in diabetic patients indicated that levels of VLDL-C did not differ at different stages of nephropathy, while subjects with higher serum creatinine had elevated concentrations of intermediate-density lipoprotein cholesterol and lower level of HDL-C [51]. In that study, no differences in LDL levels were found between diabetic and non-diabetic patients.

Also, in the course of chronic kidney disease, profound lipid disorders can be observed. Irrespective of the underlying cause of renal disease, patients suffering from chronic kidney disease were found to develop severe quantitative and qualitative lipoprotein metabolism abnormalities that were associated with alterations in apolipoproteins, lipolytic enzymes, lipid transfer proteins, as well as lipoprotein receptors observed even at the earlier stages of the disease [13]. These alterations are mostly associated with the dysregulation of high-density lipoprotein (HDL) and triglyceride-rich lipoprotein metabolism [52]. Renal function worsening is accompanied by the rise in triglyceride and the decrease in high-density lipoprotein (HDL) cholesterol levels; the concentration of low-density lipoprotein (LDL) cholesterol either remains at the same levels or becomes slightly diminished. At the same time more atherogenic small dense LDL particles are progressively accumulated [13]. A compromised renal function promotes the decrease in lipoprotein and hepatic TG lipase activity and the VLDL receptor abundance [53]. Moreover, it lowers ApoC-II to ApoC-III ratio as well as ApoA-I and lecithin-cholesterol acyltransferase (LCAT) activities. These modifications translate into lower VLDL clearance as well as disturbed HDL synthesis and maturation, which results in uremic dyslipidemia involving elevated levels of TG, IDL-C, and small dense LDL-C and reduced concentrations of HDL-C [53]. In patients with stage 4/5 CKD, reduced levels of apolipoprotein A-containing lipoproteins as well as higher concentrations of triglyceride-rich apolipoprotein B-containing lipoproteins are observed [13]. The impairment of HDL maturation due to the downregulation of lecithin-cholesterol acyltransferase (LCAT) (primarily) and increased plasma cholesteryl ester transfer protein (CETP) (to a lesser extent) and its altered composition are characteristic for CKD. Hampered HDL maturation results in disturbed reverse cholesterol transport [54]. Diminished synthesis of HDL in CKD is also associated with decreased hepatic synthesis and increased catabolism resulting in lower ApoA-I concentrations as well as with reduced lecithin-cholesterol acyltransferase activity and binding capacity with adenosine triphosphate-binding cassette transporter 1 [5, 52, 55]. Hepatic lipase deficiency and increased CETP activity result in triglyceride enrichment of HDL in CKD [52]. Recent publications suggest that in CKD patients, HDL loses its beneficial properties and becomes dysfunctional. At that time, it may exert pro-atherogenic effects.

In CKD patients with nephrotic syndrome, both an increased production and a decreased catabolism of LDL cholesterol result in increased total cholesterol and LDL cholesterol levels as well as an increase in small dense LDL particles [56]. Both proteinuria and hypoalbuminemia can separately contribute to impaired lipoprotein catabolism in these patients [57].

The downregulation of hepatic lipase, lipoprotein lipase (LPL), and very-low-density lipoprotein receptor together with upregulated hepatic acyl-CoA cholesterol acyltransferase (ACAT) stimulates the occurrence of CKD-related hypertriglyceridemia. Reduced endothelial expression of LPL and its decreased activity observed in patients with CKD can result in delayed catabolism of ApoB-containing triglyceride-rich lipoproteins [52]. Also reduced expression and activity of hepatic lipase, which hydrolyzes TG and phospholipid in chylomicron remnants and HDL, have been observed in CKD patients [52, 58]. Decreased disposal of TG-rich proteins appears to be dominant in CKD [40]. Also disturbed HDL metabolism contributes to alterations in triglyceride-rich lipoprotein metabolism [52].

The removal of VLDL and chylomicron remnants is weakened due to the inhibition of lipoprotein lipase, which results in enhanced levels of intermediate-density lipoproteins (IDL) [59]. In animal models, the presence of CKD is associated with the downregulation of LDL receptor-related protein and VLDL-C receptor messenger RNA [60]. The effects of the aforementioned lipid disturbances include the accumulation of atherogenic chylomicrons and VLDL-C remnants. In CKD, not only CPT1, the rate-limiting enzyme in fatty acid metabolism, but also other enzymes participating in fatty acid metabolism are affected [4].

According to observational studies, both incipient diabetic nephropathy and overt diabetic nephropathy are associated with numerous lipid abnormalities [61, 62]. Hyperglycemia and hyperlipidemia are responsible for the initiation of DKD. These two metabolic disturbances usually affect each other. Dyslipidemia, or rather dyslipoproteinemia, defined as disorders of lipid levels, abnormalities in lipoprotein structure, as well as abnormal lipoprotein composition or density, is observed in the course of DKD; however, it is also a factor contributing to the development and progression of DKD [4, 63]. Insulin resistance in DKD has been found to enhance fatty acid lipolysis and release from adipose tissue into the circulation following the activation of hormone-sensitive lipase (in healthy state, it is inhibited by insulin) [16]. This results in enhanced synthesis of very-low-density lipoproteins (VLDLs) and their more pronounced secretion from the liver. In the presence of cholesteryl ester transfer protein, increased levels of VLDL may stimulate the transfer of TG into LDL or HDL. Subsequent hydrolysis of TG-rich LDL by hepatic lipase or lipoprotein lipase may result in the formation of small dense LDL particles. Moreover, TG-rich HDL particles may undergo additional hydrolysis, which results in the dissociation of ApoA-I from the HDL particle and decreased levels of functional HDL. In turn, elevated levels of LDL in DKD have been revealed to predict the development of microalbuminuria in type 1 diabetes (T1D) [16]. Serum level of apoB100 has been reported to be elevated in DN which shows the increment in the amount of VLDL and LDL particles [64]. Apart from enhanced fatty acid uptake, also greater renal lipid synthesis and decreased fatty acid oxidation might be vital causes of renal lipid accumulation in DKD [4]. According to in vitro studies, high glucose levels amplify SREBP-1 expression leading to greater triglyceride accumulation. Sterol regulatory element-binding proteins (SREBPs) are transcription factors involved in the regulation of cholesterol biosynthesis and uptake and fatty acid biosynthesis. Studies on animal models demonstrated that the treatment

with insulin prevented both increased renal expression of SREBP-1 and the accumulation of triglycerides [65, 66]. Lipid accumulation has been suggested to contribute to kidney disease development or progression. The traditional lipotoxicity theory states that the accumulation of fatty acid metabolites (e.g., diacyl-glycerols and ceramides) in non-adipose organs results in toxicity and cell death [67]. However, other theory suggests that lipid overload is associated with the accumulation of nontoxic esterified lipids in lipid droplets and this form is not detrimental [68].

The results of some studies suggest that different types of dyslipidemia are associated with different stages of diabetic nephropathy. Tseng et al. [69] found that in Taiwanese patients with T2D, ApoB levels increased in the microalbuminuria stage, while the rise in lipoprotein(a) levels was observed in the macroalbuminuria stage. Only the levels of triglycerides were shown to increase gradually from normoalbuminuria to microalbuminuria and macroalbuminuria [69]. In turn, in the Kidney Early Evaluation Program (KEEP) study of diabetic patients with CKD stages 3 to 5, only higher HDL-C level and overall glycemic control were connected with diminished odds of microalbuminuria [70]. Mechanisms of dyslipidemia-induced renal impairment and the aggravation of DN still need to be further investigated.

Dyslipidemia itself facilitates the development of glomerulosclerosis in diabetic state, while the combination of dyslipidemia and diabetes has been shown to be associated with the progression of DN. Many processes have been suggested to be involved in the development and progression of DKD since kidney cell populations are diverse and this organ covers various physiological functions [71].

Dyslipidemia is a common feature in most DKD patients [16]. Moorhead et al. formulated for the first time "lipid nephrotoxicity hypothesis" to describe the impact of dyslipidemia on reduced kidney function [72]. In diabetic conditions, dyslipidemia was shown to cause podocyte apoptosis, to boost macrophage infiltration, as well as to promote excessive extracellular matrix production in the glomeruli, contributing to the development of DKD. Moreover, the accumulation of lipids in the kidney can directly induce kidney injury through the increased uptake via lipoprotein receptors/transporters, augmented lipogenesis, or diminished efflux and consumption (oxidation). The results of studies confirmed increased cholesterol absorption and low cholesterol efflux in the kidney in various models of T1D and T2D [36]. Studies on animal models provide evidence that hypercholesterolemia amplifies albuminuria in diabetic rats [73]. This study for the first time revealed the role of macrophage infiltration into the glomeruli in the progression of DN [73]. Moreover, lipid-lowering therapy was found to improve glomerulosclerosis in the Zucker rat, a model of diabetes complicated with dyslipidemia [74]. Hyperglycemia is inherently connected with insulin resistance. The results of animal studies indicated that insulin resistance facilitated the development of hyperlipidemia and contributed to renal disease pathogenesis in diabetic animals [75]. Surplus amounts of carbohydrates can be converted via lipogenesis into free fatty acids and TG as a result of the activation of acetyl-CoA carboxylase (ACC), FA synthase (FAS), or stearoyl-CoA desaturase-1 [16]. Tubular epithelial lipid accumulation and

diminished FA oxidation (FAO) are characteristic features observed in DKD [10]. Chronic hyperglycemia was shown to activate pathological processes exerting impact on mesangial cells, glomerular endothelial cells, podocytes, as well as cells of the tubular and collecting ducts leading ultimately to structural and functional changes in diabetic kidneys [76]. Hyperglycemic conditions are associated with the loss of systemic endothelial glycocalyx followed by structural immaturity of endothelial cells and podocytes and subsequent compromised glomerular capillary permeability [77]. Also, triglyceride-rich lipoprotein can stimulate monocytes and disrupt cellular glycocalyx increasing the permeability of the glomerulus [78]. The disruption of the endothelial cell glycocalyx has been shown to be the other mechanism of receptors for TG-rich lipoproteins (TGRLs)-induced glomerulosclerosis [57]. The glycocalyx, a layer built of glycoproteins, proteoglycans, and glycosaminoglycans located at the interface between the lumen and endothelial surface, functions as a barrier between a cell and its surrounding maintaining endothelial function and regulating glomerular permeability [79]. Nieuwdorp et al. [80] observed considerably lower volume of glycocalyx in patients with type 1 diabetes compared to age-matched control individuals and in those with microalbuminuria compared to subjects without it. This finding implies that the disruption of the glycocalyx may lead to modifications in glomerular permeability and subsequent albuminuria.

Triglyceride-rich lipoprotein was shown to induce the activation of the transforming growth factor-beta (TGF-β) pathway and subsequent enhancement of reactive oxygen species (ROS) production, finally resulting in glomerular damage and albuminuria [81]. Moreover, the activation of TGF-β stimulates matrix deposition in the tubulointerstitium and mesangium [82]. The progression of renal injury in DN was also shown to be potentially associated with the stimulation of pro-inflammatory and pro-fibrotic cytokine production, the modulation of mesangial cell proliferation, cell apoptosis, and vasoconstriction [83, 84]. The results of studies have demonstrated that mesangial cells and glomerular epithelial cells (podocytes) express receptors for TG-rich lipoproteins (TGRLs) which, through the secretion of pro-inflammatory cytokines (e.g., TNF-α, transforming growth factor (TGF)-β, and interleukin (IL)-6), activate inflammatory pathways [56, 85]. The stimulation of these pathways enhances the formation of reactive oxygen species (ROS) and leads to subsequent excessive ECM production [56, 85]. Due to the fact that ROS itself heighten TGF-β-mediated signalling, a vicious circle of excessive ROS and ECM production could be observed [86]. The binding of ox-LDL to scavenger receptors in mesangial cells and podocytes enhances the production of not only ECM but also chemokines, including monocyte chemoattractant protein (MCP)-1 [87, 88]. MCP-1 has been shown to stimulate the migration of monocytes toward the glomeruli and consequent macrophage infiltration [89]. Following the uptake of ox-LDL, macrophages become foam cells, and inflammatory pathways are activated again.

Diabetic nephropathy is characterized by disproportionate deposition of extracellular matrix proteins in the mesangium and basement membrane of the glomerulus as well as in the renal tubulointerstitium [90]. The results of studies confirmed that changes in podocyte structure and function were associated with

increase in albuminuria in DKD [91]. The excessive accumulation of ECM proteins (collagen IV and fibronectin) in mesangial cells contributes to renal fibrosis and subsequent glomerulosclerosis [90, 92]. Several mechanisms have been demonstrated to be involved in hyperglycemia-induced tissue damage, including the activation of renin–angiotensin–aldosterone system (RAAS) and protein kinase C (PKC), the hexosamine pathway flux, and advanced glycation end product (AGE)-dependent pathways. Also, NADPH oxidase (NOX) was shown to interfere with regulatory processes controlling homeostasis and to promote several detrimental cellular signalling events [20]. Numerous studies confirmed that the occurrence of podocytopenia was an independent predictor of DKD progression [93–95].

Also lipid accumulation has been suggested to contribute to kidney disease development or progression. It has been suggested that sterol regulatory element-binding proteins (SREBPs) play a key role in renal lipid accumulation in diabetic nephropathy [96]. The study of animal model of streptozotocin-induced diabetic nephropathy confirmed significantly enhanced expression of SREBP-1 and FAS in kidneys; this upregulation translated into TG and cholesterol accumulation in the kidney. In SREBP-1a transgenic mice, higher concentrations of TG as well as greater expression of TGF-β1 and mesangial expansion, glomerulosclerosis, and proteinuria were observed, while the knockdown of SREBP-1 improved the diabetic kidney injury and protected from cell dysfunction [96]. In renal cell culture, high glucose levels were found to rise the expression of SREBP-1a and SREBP-1c mRNA, SREBP-1 protein, and FAS, as well as TG content confirming the role of hyperglycemia in the upregulation of SREBP-1 in a high glucose media. However, the results of Stadler et al. [4] demonstrated that lipid accumulation (in the form of lipid overload) in the presence of sustained fatty acid oxidation capacity did not inevitably cause kidney dysfunction. Whether diminished fatty acid oxidation is already present in early DKD is not known. On the one hand, kidney biopsy samples collected from patients with DKD displayed a strong decrease in fatty acid oxidation-related enzymes and transcriptional regulators; on the other hand, the studies of mouse models of DKD failed to observe the development of progressive kidney fibrosis or changes in PPARα and PGC1α levels [4].

In DKD patients, also the expression of CD36 has been demonstrated to be upregulated by hyperglycemia [97, 98]. Long-chain fatty acids, especially palmitate and stearate, were found to enter cells predominantly via FA translocase molecule – CD36, a transmembrane protein of the class B scavenger receptor family expressed in macrophages, podocytes, adipocytes, microvascular endothelial cells, platelets, and tubular cells [99]. The expression of CD36 correlated with elevated uptake of ox-LDL and with tubular epithelial apoptosis and was associated with tubular degeneration and progression of DKD [98]. Park et al. suggested that lipid droplet protein was involved in lipid accumulation in DKD kidneys [99]. Herman-Edelstein et al. [100] observed that lipid droplet accumulation localized within the podocyte foot in patients with DKD was associated with the downregulation of genes encoding proteins participating in cholesterol efflux (ABCA1, ABCG1, and APOE), an upregulation of LDL receptors, impaired FAO, and higher expression of angiopoietin-related protein 4. Moreover, it was implied that the decrease in podocyte numbers contributed to the progression of

DKD. It seems that both lipids and lipid-modulating proteins are vital determinants of podocyte biology and they underlie the pathogenesis of glomerular diseases in DKD.

Quantitative changes of lipoproteins are accompanied by qualitative alterations resulting in the higher level of pro-atherogenic lipoproteins, e.g., oxidized LDL (ox-LDL) in diabetes [101]. In diabetes mellitus, modifications of LDL, including glycation and oxidation, are more accelerated. Enhanced reactive oxygen generation has been demonstrated to be involved in the development of DKD. Lipid peroxidation, a process in which a potent hydroxyl radical is required to form lipid radicals (LOO•), was suggested to be a potentially important contributor of tubule epithelial damage. The series of chain reactions results in the accumulation of reactive lipid-end products (LOOH), such as 4-hydroxynonenal and isoprostanes. These molecules are used as biomarkers in human diabetes; however, their role in renal physiology and pathology remains unknown. Oxidized lipoproteins hamper nitric oxide-mediated vasodilation, modify mesangial cell proliferation, and rise the expression of monocyte chemoattractants contributing to glomerular injury [102, 103]. Due to reduced levels of HDL in CKD, the reversal of the aforementioned adverse effects is compromised precipitating further kidney injury.

Some studies indicated that the development of DN is associated with LDL molecule glycation resulting in the formation of advanced glycation end products (AGEs). AGEs together with their receptors (RAGE) are believed to play a vital role in the pathogenesis of diabetic vascular complications, endothelial dysfunction, and atherosclerosis [104]. Following the recognition of AGE particle (e.g., glycated LDL), inflammatory and fibrotic responses become induced [105].

The presence of insulin resistance can also be associated with the accumulation of toxic lipids including lysophosphatidylcholine, ceramides, and free cholesterol in the tissues. Lipid nephrotoxicity is mediated by several factors, such as sterol regulatory element binding protein (SREBP)-1 and Toll-like receptor (TLR) 4 [106, 107]. SREBP-1 expression has been shown to be upregulated in streptozotocin (STZ)-induced diabetic rats; however, the progression of DN was repressed in SREBP-1-deficient mice [108]. The inhibition of diabetic nephropathy was also found in TLR4-deficient mice fed with a high-fat diet [106, 107]. It has been demonstrated that lipotoxicity and lipid accumulation result in podocyte injury (disturbing normal functionality of glomerular filtration barrier) and apoptosis in DKD patients.

Management of CKD

The identification and management of risk factors for diabetic nephropathy followed by timely diagnosis and quick management of the disease are of utmost importance [37, 101, 109, 110]. The treatment of lipid metabolism alterations in CKD and DKD patients has the potential to prevent the progression of renal disease and to reduce risk of cardiovascular disease.

The importance of lipid profile control has been shown in many studies. The large Atherosclerosis Risk in Communities (ARIC) study confirmed that hypertriglyceridemia and a low HDL-C level are risk factors for the worsening of glomerular filtration rate in individuals with T2D [111]. Also the results of the Early Treatment Diabetic Retinopathy Study (ETDRS) indicated that major modifiable risk factors such as dyslipidemia, hyperglycemia, and hypertension were predictive of renal replacement therapy (RRT).

The results of the Action in Diabetes and Vascular Disease (ADVANCE) study in T2D revealed the relationship between low concentrations of HDL cholesterol and considerably augmented risk of microalbuminuria and macroalbuminuria [112]. In this study, patients in the lowest third of HDL levels had a 17% higher risk of microvascular disease (adjusted hazard ratio (AHR), 1.17 [95% CI 1.06–1.28]; p = 0.001) after adjustment for potential confounders compared with patients in the highest third, which translated into a 19% higher risk of renal events (1.19 [1.08–1.32], p = 0.0005). In turn, the Diabetes Control and Complications Trial (DCCT) found that altered lipid profiles were observed in those participants with type 1 diabetes mellitus (T1D) who progressed to diabetic nephropathy [113]. The Finnish Diabetic Nephropathy Study (FinnDiane) demonstrated a significant correlation between high levels of triglycerides and progressive albuminuria, while increased total cholesterol concentrations were associated with the progression to renal failure in patients with T1D. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study demonstrated the relationship between lower LDL-C and TG levels and diminished risk for progression from moderate albuminuria to severe albuminuria or ESRD [114]. Moreover, in patients with type 2 diabetes mellitus, low levels of total cholesterol (TC) and triglicerides (TG) are linked with the regression from moderate albuminuria to normoalbuminuria in T2D [115].

Dyslipidemia, as it has been presented above, exerts impact on the progression of diabetic nephropathy; therefore, it seems that treatment with lipid-lowering agents may prove beneficial in terms of renal outcomes as well as CVD risk in patients with T2D [116]. Interventional studies with the use of statins provided evidence for the role of dyslipidemia in increasing the risk of diabetic nephropathy by indicating that the reduction in LDL-C levels delayed the progression of the disease.

The results of studies carried out on animal models of diabetes demonstrated that the administration of statins reduced lipid peroxidation and the accumulation of advanced glycation end products, enhanced antioxidant enzyme levels, and reversed podocyte injury [117–119]. A meta-analysis of 13 prospective controlled trials examining the effects of antilipemic agents on renal function, proteinuria, or albuminuria in diabetic and non-diabetic patients with renal disease revealed beneficial effects of dyslipidemia control with a statin on renal outcomes in terms of improved glomerular filtration rate (GFR) and proteinuria [119]. Also the use of atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS) was associated with lower renal function deterioration in T2D, especially in patients with albuminuria [120]. However, according to the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline, statin therapy is not appropriated for diabetic

patients undergoing dialysis [25]. Apart from statins, also fibrates may have an advantageous impact on renal function in diabetic patients. The Diabetes Atherosclerosis Intervention Study (DAIS) found that fenofibrate therapy lowered the risk of developing microalbuminuria [97]. The results of multinational, randomized controlled FIELD indicated that fenofibrate was associated with slower albuminuria progression ($p = 0.002$) and also with significant 24% reduction in nonfatal myocardial infarction and 21% decrease in coronary revascularization [121].

Also the control of glycemia is of high importance in diabetic patients as it enables the reduction of risk of microvascular and macrovascular complications in diabetic patients. Numerous studies have indicated that the treatment of uncontrolled glucose levels with the use of, for example, metformin directly translates into improved lipid levels (particularly triglycerides), suggesting the existence of crosstalk between hyperglycemia and dyslipidemia. However, some studies found that several other glucose-lowering agents did not exert a favorable effect on the lipid profile. The United Kingdom Prospective Diabetes Study of patients with newly diagnosed T2D demonstrated that intensive blood glucose control (HbA1c of 7.0% versus 7.9%) reduced the risk of microvascular disease (relative risk reduction, 25%) and microalbuminuria (relative risk reduction: 33%) as well as cardiovascular events (relative risk reduction, 16%; $p = 0.052$) over a median follow-up of 10 years [122].

Guidelines

Most recent guidelines of the American Diabetes Association (ADA) recommend the measurement of urinary albumin at least annually in patients with T1D duration ≥5 years and in all patients with T2D (from the date of diagnosis) [123]. In turn, urinary albumin excretion (UAE) should be assessed by measuring the urinary albumin/creatinine ratio in a spot urine sample. Due to the fact that UAE varies over time, two or more urine specimens collected from patients without febrile infections, within a period of 3–6 months, should show elevated albumin excretion in order to make a diagnosis of nephropathy [123].

According to current ABCD-Renal Association Clinical Practice Guidelines for management of lipids in adults with diabetes mellitus and nephropathy and/or chronic kidney disease [124], the examination of full lipid profile (TC, LDL cholesterol, HDL cholesterol, TGs) should be a common practice in DN-DM CKD (Grade 1A) performed at least annually (Grade 1C). The control of lipid profile should be also performed on commencement or change of modality of renal replacement therapy (dialysis or kidney transplantation) (Grade 1D). In patients with end-stage renal disease (ESRD), measurement of the lipid profile should be performed annually to assess compliance and need for continuing therapy (Grade 2D). All patients with DN-DM CKD who have undergone renal transplantation should have lipid status evaluated once the immediate postoperative period has passed (typically 3 months post-transplantation) (Grade 2C) and then annually. The

main goal of the introduction of lipid-lowering therapy in adult patients with DN-DM CKD should be the reduction of cardiovascular event risk (Grade 2A). According to these guidelines, in patients with stage 1–2 DN-DM CKD, lipid-lowering therapy with statins should be initiated in those with type 1 diabetes and persistent microalbuminuria aged >30 years, patients with type 2 diabetes with progressing early CKD (loss of GFR >5 ml/min/year) irrespective of albuminuria status, patients with type 2 diabetes aged >40 years irrespective of cholesterol levels, and finally all patients with type 2 diabetes and persistent microalbuminuria or macroalbuminuria. They also recommend the introduction of lipid-lowering therapy with statins in all patients with stage 3–5 DN-DM CKD (Grade 1B). However, such therapy should be prescribed with caution in women of child-bearing potential. Moreover, lipid-lowering therapy should be discontinued during pregnancy and lactation (Grade 1B). In DN-DM CKD patients not requiring renal replacement therapy, the initiation of statin therapy with either atorvastatin 20 mg or simvastatin 20–40 mg is recommended (Grade 1D). The management of dyslipidemia should be similar in patients with reduced GFR ± persistent albuminuria, irrespective of whether the individual has type 1 or type 2 diabetes (Grade 1B). Recommended statin therapy goal in patients with type 1 diabetes with persistent albuminuria and/or reduced eGFR [60–90] should be as follows: TC reduction to 4.0 mmol/l, LDL cholesterol to 2 mmol/l, and non-HDL cholesterol to 2.5 mmol/l (Grade 1D). Higher intensity statin use (atorvastatin 40–80 mg) can be considered for those with persistent albuminuria and/or reduced eGFR [30–60] at highest CVD risk (e.g., aged >40 years, poor glycemic control (HbA1c >75 mmol/mol) and those with additional CVD risk factors, such as smoking, hypertension, dyslipidemia, and proliferative retinopathy) who do not attain aforementioned lipid targets on lower statin doses (Grade 1D). Atorvastatin at the dose of 80 mg is recommended for all type 2 diabetes patients with stage 1–2 CKD with albuminuria, who have the highest risk of CVD (Grade 1A). Ongoing lipid-lowering therapy should be continued in patients with DN-DM CKD starting dialysis (Grade 2C). The decision on the initiation of lipid-lowering therapy in DN-DM CKD patients requiring either hemodialysis or peritoneal dialysis should be made on the basis of risk of future atherosclerotic vascular events, life expectancy on dialysis, and other comorbid diseases (Grade 2C). The start of lipid-lowering therapy is recommended in patients with DN-DM CKD who have undergone renal transplantation (Grade 1B); however, its choice should take into account concurrent immunosuppressive therapy (Grade 2D). All patients with DN-DM CKD who have undergone kidney-pancreas transplantation and also those who develop post-transplant diabetes mellitus are recommended to receive statin treatment (Grade 2D). The use of simvastatin in the dose of >40 mg/day in DN-DM CKD is not recommended due to the increased risk of muscular side effects (Grade 1A). In patients who do not tolerate higher statin doses, ezetimibe combination therapy should be considered as an alternative to high-intensity atorvastatin in DN-DM CKD at all stages (Grade 1B). The routine measurement of liver enzymes is recommended before statin initiation in DN-DM CKD and at 3 months after commencement and annually thereafter. In patients taking amlodipine or diltiazem, the maximum dose of simvastatin should not exceed

20 mg (Grade 1B). Fibrates in advanced DM CKD (3b–5) are not recommended – either as monotherapy or in combination with statins – outside specialist care (Grade 1A); however, fenofibrate therapy alone or alongside statins should only be used in DN-DM CKD 3a or earlier stages, mainly to decrease risks of progressive microvascular events in patients with statin intolerance or residual dyslipidemia despite statin therapy (Grade 2C).

Conclusions

The presence of DKD is associated with alterations in both systemic and intrarenal lipid metabolism. Numerous pathways have been suggested to be involved in the development and progression of DKD; however, the exact mechanisms are not fully understood. The advances in understanding and improving the clinical management of diabetes have not fully translated into better outcomes and the prevention of DKD or ESRD. Therefore, the Global Kidney Health Initiative has been established by the International Society of Nephrology in order to attract attention to kidney diseases and promote important strategic research with the aim of improving health outcomes for people with diabetes and DKD.

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Chapter 16
Bone Disease and Diabetes

Stefana Catalina Bilha and Adrian Covic

Introduction

According to the World Health Organization Global Health Estimates in 2019, diabetes mellitus is among the top ten global causes of disability-adjusted life years (DALYs) [1]. Although in the backseat of diabetes complications due to the more thundering cardiovascular or kidney diseases, diabetic osteopathy proves a great menace to the quality of life in both type 1 (T1D) and type 2 (T2D) diabetic patients via the great risk of hip fracture that it poses independent of classic risk factors, such as bone mineral density (BMD), body mass index (BMI), and falls [2–4].

The underlying mechanisms of diabetic osteopathy comprise physiopathological pathways common to both T1D and T2D, such as advanced glycation end products (AGEs) that alter collagen structure, inflammation, microvascular damage, and a negative calcium balance, but also distinct specific features (e.g., insulinopenia in T1D and hyperinsulinism, increased visceral adiposity, and the effect of oral anti-diabetic drugs in T2D) [4, 5]. Nonetheless, diabetic bone disease is characterized by low bone turnover, bone microarchitecture changes leading to altered bone quality, and low vitamin D levels, although BMD is variable. Despite fracture risk being unanimously high in T1D and T2D, identifying those subjects more prone to fractures is a major challenge in daily practice, as BMD and the current available algorithms for fracture prediction underestimate fracture risk in diabetic patients [4, 5].

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Truly little is known about the superposition of diabetic bone disease and chronic kidney disease mineral and bone disorder (CKD-MBD) – a unique, complex, and multifactorial association that is generally overlooked due to uncertainty with regard to optimal evaluation and therapeutic approach. This chapter focuses on bone disease in diabetes, with particular interest in diabetic kidney disease (DKD).

Epidemiology: Fracture Risk

Diabetes mellitus globally increases the risk for fractures (51% and 22% increase in T1D and T2D, respectively [6]), but T1D is more harmful for the bone when compared to T2D [6]. T1D patients are five times more likely to experience a hip fracture compared to T2D [7]. Compared to non-diabetic controls, the odds rise to sevenfold increase in hip fracture risk for T1D [7, 8]. As expected, BMD declines with age [9], but young T1D patients (18–50 years old) are also reported to have a 4.4-fold increased risk of hip fracture [10], while T1D women are more prone to fragility hip fractures compared to T1D men [10].

Hip fracture risk in T2D is also increased, although rather less than in T1D: although initially reported up to a threefold surge in T2D men, recent meta-analyses demonstrated a 30% higher risk of hip fracture in T2D compared to controls [6, 11]. In addition, T2D patients have an increased mortality rate following hip fracture with lower 1-year survival probabilities compared to non-diabetic patients [12]. Age, HbA1c, and postoperative complications are mortality predictors in T2D patients with a hip fracture [12].

Regarding fractures at sites other than the hip, the risk for upper arm – but not distal forearm – is similarly increased in both types of diabetes, mostly in men. Ankle fracture risk is also increased in diabetic women, with a more pronounced effect in T1D. Nevertheless, vertebral fractures are not associated with diabetes in a pooled analysis of cohort studies; the risk becomes apparent only when analyzing retrospective studies separately [6].

The presence of neuropathy, poor glycemic control (HbA1c $\geq$7.9%), and long disease duration ($\geq$26 years compared to <14 years) are risk factors for fragility fractures in T1D. In contrast, a higher creatinine clearance reduces fracture risk in T1D [13]. More so, an abnormal serum creatinine, rather than uncontrolled diabetes (HbA1c $\geq$7%), doubles the risk for osteoporosis in diabetic patients [14]. Microvascular complications, elevated HbA1c, and diabetes duration increase fracture risk in T2D, although not in all studies [2].

Bone Density in Diabetes

Femoral neck BMD, rather than lumbar spine bone density, is reduced in T1D patients compared to non-diabetic controls [9]. T1D women have lower BMD compared to their male counterparts [9]. Low bone mass occurs early in T1D and

remains rather stable afterward [5], irrespective of disease progression [15] and after adjustment for BMI [16].

BMD at the lumbar spine and femoral neck is generally reported to be higher in T2D compared to controls in large-scale studies and meta-analyses [8, 17], but data comparing T1D and T2D with regard to bone mass are less consistent: T1D patients, although younger, are 4.6 times more likely to have low BMD compared to T2D patients in some studies [7], while there are studies reporting similar BMD in both types of diabetes [18]. A high heterogeneity between studies regarding diabetes-related factors may explain the existing discrepancies. While male gender, young age, and increased BMI are associated with a higher BMD [17], a longer duration of diabetes (>5 years) seems to negatively impact bone mass [19] in T2D. Indeed, although BMD is increased in the early stages of T2D, the accelerated aging, microvascular disease, and muscle dysfunction in the later stages of disease evolution possibly lead to low BMD [4].

Despite variable BMD, both T1D and T2D are considered secondary causes of osteoporosis due the associated high risk of fracture. The underlying mechanisms are further discussed in this chapter (Fig. 16.1).

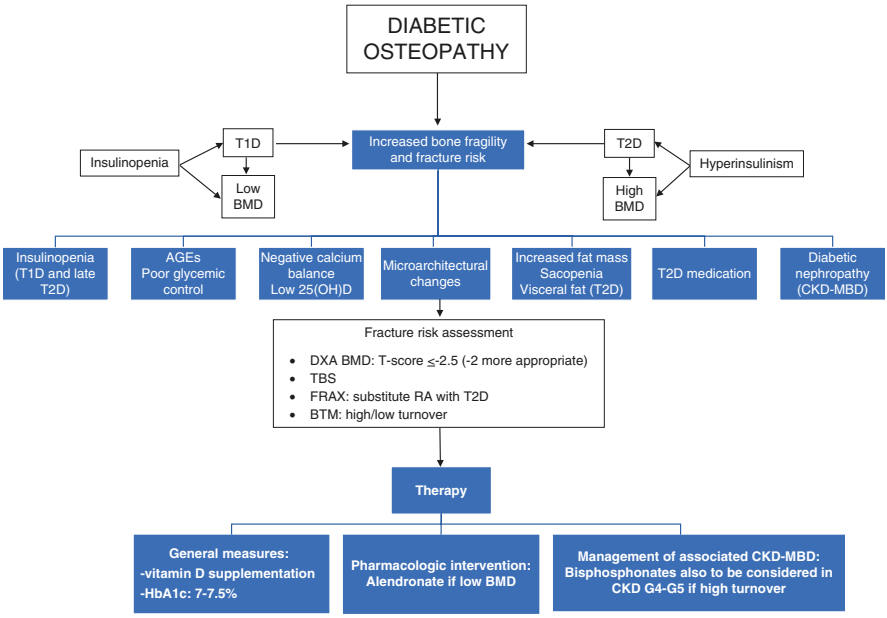

Fig. 16.1 Pathophysiology, fracture risk assessment, and treatment in diabetic osteopathy
AGEs advanced glycation end products, *BMD* bone mineral density, *BTM* bone turnover markers, *CKD-MBD* chronic kidney disease mineral and bone disorder, *DXA* dual-energy X-ray absorptiometry, *TBS* trabecular bone score, *RA* rheumatoid arthritis, *T1D* type 1 diabetes mellitus, *T2D* type 2 diabetes mellitus

Underlying Mechanisms of Bone Fragility

Insulin

Experimental data have demonstrated the osteoanabolic effects of insulin. Insulin receptors are expressed on pre-osteoblasts and mature osteoblasts, thus suggesting a critical involvement of insulin in osteoblastogenesis [20]. The homologue structure of insulin-like growth factor 1 (IGF1) may also account for some of the anabolic effects of insulin upon the bone [21]. Osteocalcin, an osteoblast-derived osteokine, was reported in experimental models to stimulate β-cell replication [22], pancreatic insulin production [23], and also muscle metabolism and energy expenditure [24], thus regulating glucose homeostasis via the "bone-pancreas loop." Osteocalcin-deficient mice exhibit significantly higher blood glucose and higher fat mass [23]. Also, hyperglycemia favors the adipogenic differentiation of muscle-derived stem cells [25]. A high-fat diet promotes bone-specific insulin resistance, which leads to low bone turnover with decreased osteocalcin activation and the consequent decreased insulin sensitivity in rodents [26].

The early and acute insulinopenia in T1D negatively impacts bone accrual and peak bone mass via low bone turnover [5], as clinical studies report low levels of circulating bone formation markers, such as osteocalcin and bone-specific alkaline phosphatase (BAP), in children and adolescents with T1D [27, 28]. This confirms the experimental data reporting decreased bone turnover in mouse models of insulinopenia [5].

On the contrary, hyperinsulinism in T2D is associated with increased BMD, independent of BMI and fat mass [4, 8, 17]. It is thought, therefore, that the hyperinsulinism secondary to insulin resistance counteracts, at least to some extent, the detrimental effects of prolonged hyperglycemia and increased visceral adiposity upon the bone [4].

If insulinopenia impairs bone mass accrual and hyperinsulinism favors an increased bone density, one would expect insulin treatment to restore bone metabolism and optimize bone mass. Although systemic insulin administration indeed restored bone turnover in a mouse model of osteopenia [29], the favorable bone effects of insulin administration in experimental models do not necessarily translate into clinical positive bone effects. Insulin substitution is generally associated with a high risk of fractures via the increased risk of falls due to occurring hypoglycemia [30].

In T1D, however, although low BMD is encountered in the early stages, bone density stabilizes afterward or even increases: BMD of long-standing T1D is similar to that expected for age and sex, with studies even reporting higher BMD at the lumbar spine in both females and males [15, 16]. T1D patients on lower insulin doses had a lower BMD compared to those treated with higher doses in a recent study [15].

In T2D, insulin administration is the last treatment option, being introduced when the disease and complications are already well established. T2D insulin users

have a greater BMD loss at the femoral neck [31] and a higher risk for foot and humerus fractures [32] – generally typical for an increased BMI [4]. An increased hip fracture risk was also reported in T2D women using insulin [33]. Exogenous insulin administration rather functions as a disease severity surrogate in T2D, thus explaining the detrimental bone effects registered in diabetes [32].

AGEs

The production of AGEs as a consequence of long-term hypoglycemia is responsible for the well-known complications of diabetes and may also contribute to increased skeletal fragility. Scarce data from animal models and limited bone tissue biopsies from diabetic patients show accumulation of AGEs in the bone [4, 34]. Collagen fibers are enzymatically cross-linked, thus improving collagen stiffness and bone strength. It is possible that non-enzymatic cross-linking of collagen by pentosidine, a well-recognized AGE, alters bone matrix properties and compromises bone strength [34]. Besides affecting the material properties of the bone, AGEs also exert biological effects upon the bone cells: AGEs promote osteoblast apoptosis via increased oxidative stress and suppress bone mineralization. AGEs also increase sclerostin expression, a strong bone formation inhibitor, and decrease osteoclast-mediated bone resorption and parathyroid hormone (PTH) secretion, thus contributing to the low bone turnover state seen in diabetes mellitus [34]. Low bone turnover further impairs the material properties of the bone, predisposing to fractures [35]. Increased circulating levels of pentosidine are associated with an increased fracture risk in both T1D [36] and T2D patients [37], independent of BMD. Thus, altered bone quality induced by AGE is responsible, at least in part, for the increased bone fragility in diabetic osteopathy.

Vitamin D and Calcium

Diabetes mellitus markedly impairs calcium homeostasis. Prolonged hyperglycemia leads to impaired PTH production and decreased calcitriol synthesis, promoting decreased calcium reabsorption and increased renal calcium wasting [38]. Vitamin D levels and PTH are also lower in DKD compared to non-diabetic CKD [39]. Experimental data also suggest FGF23 dysregulation under diabetic conditions that leads to hyperphosphaturia [38] – although not reported in all clinical studies [40]. Thus, the overall negative calcium balance and phosphate wasting contribute to impaired bone mineralization [38]. The diabetes-associated low bone turnover state may also lead to diminished phosphate uptake by the bone, explaining the higher serum phosphate – and the higher FGF23 as a consequence – in diabetic compared to non-diabetic CKD. Higher FGF23 levels are indeed associated with diabetes in CKD patients, suggesting an important role in the pathogenesis of diabetic

CKD-MBD [40, 41]. Diabetes is a significant predictor of serum FGF23 in CKD [41]. Other studies have found, on the contrary, lower FGF23 levels in early CKD, but not in the later stages, in diabetic compared to non-diabetic CKD; the authors speculated toward a certain degree of osteocyte dysfunction linked to low bone turnover, leading to lower FGF23 than expected [39]. Nevertheless, CKD-MBD occurs earlier in DKD compared to non-diabetic CKD [40], suggesting concurrent detrimental effects of both diabetes and kidney dysfunction upon bone turnover and bone quality.

Bone Microarchitecture

Bone microarchitecture is disturbed in both T1D and T2D, although there are some notable differences. Microarchitectural changes may contribute to bone fragility. High-resolution peripheral quantitative computed tomography (HR-pQCT) is a relatively novel imaging tool that allows the three-dimensional measurement of bone microarchitecture and volumetric BMD in vivo; it is a noninvasive modality to estimate bone strength, and it also provides fracture risk prediction [42]. HR-pQCT evaluation in T1D revealed altered microarchitecture at the level of the trabecular compartment (decreased trabecular bone volume and thickness at the tibia and radius), especially if microvascular complications were present. Trabecular bone score (TBS), a texture parameter that offers information regarding bone microarchitecture as a complementary approach to dual-energy X-ray absorptiometry, is also reduced in T1D compared to non-diabetic individuals. However, the highest fracture risk is reported to concern the hip, which is primarily composed of cortical bone. The contribution of the microarchitectural changes to fracture risk in T1D is yet to be clarified [5, 43].

Obesity is associated with a favorable cortical bone microarchitecture and increased volumetric BMD, as assessed by HR-pQCT [4]. Analogous to obesity, insulin resistance is also inversely related to cortical porosity and generally associated with an improved bone structure; however, adjusting for weight attenuates this association and reveals an inverse relationship between measures of insulin resistance (such as the homeostatic model of insulin resistance – HOMA-IR) and periosteal circumference at the radius and tibia in postmenopausal women, suggesting that insulin-resistant women actually have lower bone size that counteracts the positive effect of increased insulin resistance [44]. This was also confirmed in older men with T2D [45]. T2D perimenopausal women, despite higher areal BMD, also have lower bone strength indices for compression and bending [46]. T2D, similar to obesity, is associated with a lower bone strength per unit bodyweight, suggesting a maladaptive response of the skeleton to increased mechanical load that contributes to skeletal fragility [47]. TBS is also reduced in approximately two-thirds of T2D women, according to a recent study [48], and is lower compared to controls even after adjusting for BMI and despite higher BMD [49]. It is also significantly correlated with prevalent vertebral fractures, independent of BMD [50]. Nevertheless,

HR-pQCT imaging in T2D revealed increased cortical porosity and decreased cortical density, especially at the peripheral skeleton, despite an increase in volumetric BMD. Also, the apparent increase in areal BMD is probably confounded by bone size, thus explaining the paradox of increased fracture risk, despite higher bone density. Moreover, the disturbances in the cortical bone compartment may explain the higher fracture risk in skeletal sites rich in cortical bone, such as the hip or peripheral regions [4, 51]. One cannot preclude, however, that the altered bone microarchitecture is rather an epiphenomena of the negative effects of diabetes upon the bone, without a substantial contribution to the increased fragility [4]. The presence of increased cortical porosity, rather unexplained in the context of low bone turnover, is, nonetheless, noteworthy [52].

Sarcopenia

Lean mass appears to mediate insulin actions upon the bone mineral content in young adults [53]. Sarcopenia, defined as decreased muscle mass, strength, and performance, is more prevalent in the aging and diabetes population. Inflammation, oxidative stress, vitamin D deficit, increased muscle catabolism, and low insulin secretion are all associated with sarcopenia. Poor muscle function predisposes to falls, thus increasing the risk for lower limb fractures, well recognized in the diabetic patient [4, 54].

HbA1c

Poor glycemic control is suggested to negatively impact bone metabolism and contribute to low bone turnover and increased fragility [55]. HbA1c is negatively related to serum osteocalcin in both T1D [56] and T2D [57] and also to fragility fractures. One percent increase in HbA1c results in an odds ratio of 1.9 to 4.13 for fracture risk in T1D [15, 36], although not in all studies [5]. A linear increase in hip fracture incidence with increasing HbA1c was also reported in older T2D patients [58].

The relationship between HbA1c and BMD varies considerably among studies. HbA1c is generally not related to BMD in well-controlled T1D [18] but rather inversely associated with low BMD in long-standing uncontrolled T1D, according to the meta-analysis of Shah et al. [9]. Thus, the presence of AGE resulting in collagen glycation and the development of microvascular complications may compromise bone quality and explain the higher fracture risk [9]. HbA1c is positively, negatively, or not correlated with BMD in various studies [17]. The meta-analysis of Ma et al. [17] reports a positive association between HbA1c and BMD. Other meta-analyses have not found, however, any link between HbA1c and BMD [8].

Also, TBS does not vary with HbA1c levels in some T2D studies [48], while others report an inverse relationship between the two [59].

Differences between studies regarding disease evolution (early versus late), age, and the presence of complications may account for the heterogeneity of the results. The mechanisms regarding the impact of metabolic control of diabetes and bone are plentiful, intricate, and still awaiting further clarification.

Adiposity-Related Factors

BMI is a validated protective factor for bone health. It does not, however, distinguish between body compartments. Analysis of body composition may help to better describe the risks associated with diabetes, among which the bone health risk is highlighted in this chapter. Increases in fat mass, especially abdominal fat mass, accompanied by a low or impaired muscle mass and function are frequently reported in both T1D and T2D [4, 60, 61]. Fat mass may impact bone tissue via the dysregulation of adipokines – hormones and cytokines secreted from the adipose tissue that regulate energy metabolism, appetite, inflammation, insulin sensitivity, blood pressure, and also bone metabolism [62, 63]. Leptin has dual bone effects, inhibiting bone formation via the central nervous system while having positive direct effects upon the bone mass [63]. Adiponectin stimulates bone resorption via the RANK/RANKL pathway and is inversely related to BMD in most studies [63, 64]. Resistin is also produced by the adipose tissue to "resist" the actions of insulin and is elevated in diabetes. The few studies investigating the relationship between resistin and bone either found a negative impact [65, 66] or a neutral effect [67, 68].

Obese subjects display an increased bone marrow fat, which may increase skeletal fragility [4]. Fat tissue distribution is also an important factor to account for, as visceral adipose tissue is generally considered a risk factor for low bone mass due to the associated inflammatory status (interleukin-6 and tumor necrosis factor-α stimulate bone resorption via the upregulation of the RANK/RANKL pathway) [61, 63].

Therapy

Anti-Diabetic Medication Diabetes drugs impact bone metabolism and fracture risk in various manners, having both positive and negative outcomes, depending on the type of medication used. The bone effects of exogenous insulin administration were discussed above. The potential bone implications of the drugs used to treat T2D are detailed below.

Metformin the most commonly prescribed oral anti-diabetic drug, promotes osteoblastic differentiation of bone marrow progenitor cells in vitro and also mineralization of osteoblasts via the activation of the AMP-activated protein kinase (AMPK) in the bone [32]. It was also shown to prevent bone loss and preserve bone

quality in experimental studies. Clinical trials generally reported a positive end result, with preservation of bone mass and reduction in fracture risk [69, 70]. It does not appear to have a significant influence upon TBS decrease [71].

Thiazolidinediones improve insulin sensitivity via the activation of the nuclear hormone receptor peroxisome proliferator-activated receptor (PPAR)-γ in the adipocytes. PPAR-γ is also expressed in the bone, where its activation by thiazolidinediones favors osteoclastogenesis and the differentiation of mesenchymal stem cells toward the adipocytic lineage, also impairing the function of the osteoblasts. Clinical trials proved undoubtable negative effects, with an important impairment of bone density and increase in fracture risk associated with this class of medication, which also appears to be dose dependent [4, 32].

Truly little clinical data exists regarding **sulfonylureas**, despite their common use in diabetes for more than 50 years. Their mechanism of action remains unclear. Clinical trials demonstrated a rather favorable effect upon the bone, with a reduction in fracture risk [4, 32].

Incretin-Based Diabetic Therapies such as glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors enhance insulin secretion in response to meals and supposedly play an important role in bone homeostasis. Evidence from preclinical data suggests osteoanabolic insulin-independent effects of incretin hormones, although the underlying mechanisms of their action upon the bone and whether these effects are important in humans are yet to be clarified [4, 32]. In a recent meta-analysis [72], the use of exenatide was associated with an increased fracture risk (although patients on exenatide had higher HbA1c and experienced greater weight loss), while liraglutide treatment reduced the risk with 62%. Reported clinical data regarding the bone effects of DPP-4 inhibitors are very heterogenous, with studies reporting incident fractures as an adverse effect rather than an endpoint. As such, a meta-analysis [73] of randomized controlled trials reported a 40% decrease in fracture incidence associated with DPP-4 inhibitors.

Sodium-Glucose Co-Transporter Type 2 (SGLT2) Inhibitors are a new class of oral antidiabetic drugs that have raised concerns regarding their potential adverse effects upon bone metabolism due to their mechanism of action. SGLT2 inhibitors promote glycosuria and increase sodium concentrations in the proximal renal tubule, which in turn enhances phosphate reabsorption and increases serum phosphate. This may prompt increased PTH and FGF23 production, with deleterious effects on bone mass [74]. Dapagliflozin treatment was indeed associated with a small increase in serum phosphate but without any change in serum calcium and calciotropic hormones. Also, bone turnover markers, BMD, and fracture risk were all similar in patients using dapagliflozin compared to placebo [75, 76]. Notably, canagliflozin treatment is associated with BMD decline and a 35% increase in the relative risk of fracture, specifically for arm and vertebral fractures [77]. Also, T2D patients with moderate CKD on dapagliflozin experienced a significant dose-

dependent increase in fracture risk when compared to placebo, although fractures were mainly at the level of the foot, suggesting rather the negative effect of diabetic neuropathy or orthostatic hypotension, both predisposing to falls [78]. Larger studies with fracture outcomes are needed to draw a definite conclusion.

Pramlintide an injectable amylin analogue drug approved for both T1D and T2D as an adjunct to mealtime insulin treatment, reduces appetite, slows gastric emptying, inhibits glucagon secretion, and is also implicated in bone biology. Amylin is anabolic for the bone in rodents, while the effects in humans upon BMD and bone turnover are reported to be rather neutral [4, 32].

Other Medication Frequently Used in Diabetes Both T1D and T2D patients, and more so DKD patients, frequently use antihypertensive medication and lipid-lowering drugs, with potential implications upon skeletal health. Loop diuretics and angiotensin-converting enzyme inhibitors (ACEi) are associated with an increased fracture risk via orthostatic hypotension that increases the chance of falling or urinary loss of minerals [5]. On the other hand, statins are associated with a significant increase in BMD [79]. Although generally overlooked when investigating bone health, accumulating evidence pleads for also considering the potential bone implications of the above-mentioned drugs.

Diabetic Kidney Disease

While discussing the underlying mechanisms of bone fragility in diabetes mellitus, the development of diabetic kidney disease should also be accounted for, especially as CKD is a major cause of secondary osteoporosis, affecting bone turnover, mineralization, and volume. Diabetic kidney disease is one of the classic main microvascular complications of both T1D (30–40%) and T2D (10–20%) [80]. Accumulating evidence also describes the presence of microangiopathy in the bone marrow, with stem cell depletion related to increased oxidative stress and activation of apoptosis [81]. Diabetic nephropathy is also a cause of reduced 1 alpha hydroxylase activity, with low activation of vitamin D. Indeed, the albumin-to-creatinine ratio (ACR) negatively correlates with serum 25(OH)D [82]. The well-known positive association between serum 25(OH)D and bone mass and metabolism is also encountered in T1D patients with CKD stage 5 [83].

ACR is also correlated with elevated bone turnover markers (osteocalcin, C-terminal telopeptide of type 1 collagen (CTx), and N-terminal propeptide of type 1 procollagen (P1NP)) even in the early stages of diabetic kidney disease, raising the concern that bone metabolic abnormalities may occur earlier than the impaired bone structure associated with the decline of the eGFR [82].

The presence of diabetic nephropathy aggravates bone mineral metabolism disturbances in T2D. T2D patients with diabetic kidney disease have lower BMD and higher urinary calcium excretion compared to T2D subjects without kidney disease,

while both groups exhibit lower bone turnover compared to healthy controls [84]. DKD patients develop more severe changes in bone and mineral metabolism (higher serum levels of FGF23 and PTH for the same given eGFR range) in CKD stages 2–4 [40], while diabetes is negatively related to bone mass in stage 5 [83]. Actually, diabetes patients undergoing dialysis are more prone at developing adynamic bone disease compared to their non-diabetic counterparts, and the presence of diabetes is a negative independent predictor of serum PTH concentrations after adjusting for various covariates, such as demographics, BMI, blood pressure, eGFR, and serum calcium and 25(OH)D [40]. The generally higher serum FGF23 for the same given eGFR may explain the lower-than-expected for CKD calcitriol concentrations, thus contributing to the more severe bone phenotype in diabetic CKD [40].

Decreased renal function (eGFR <60 ml/min/1.73m^2) is associated with low TBS in T2D patients, although BMD does not differ significantly compared to patients with eGFR ≥60 ml/min/1.73m^2. TBS was also shown to predict fracture risk in non-diabetic CKD patients with eGFR <60 ml/min/1.73m^2; this underlines the importance of performing TBS together with the dual-energy X-ray absorptiometry (DXA) analysis in the bone evaluation of these patients [85]. The detrimental effect of AGEs adds to that of uremic toxins upon bone quality, compromising bone structure and contributing to the pathogenesis of uremic osteoporosis [86]. The deterioration of bone material properties due to AGEs is not a feature of CKD-MBD but rather a supplementary risk factor for bone fragility in the renal patient [86].

Assessment

Diagnosis of Osteoporosis The diagnosis of osteoporosis is made according to the assessment of areal BMD via DXA and is defined in postmenopausal women and men as ≤ − 2.5 standard deviations (SD) from the BMD of young adult women at the lumbar spine or hip. This definition also confirms the diagnosis of osteoporosis in patients with diabetes mellitus and in CKD patients stages 1–3, while the latest consensus of the European Renal Osteodystrophy (EUROD) workgroup in 2021 also pleads in favor of using the same definition in G4–G5D CKD [52, 87, 88]. The finding of a fragility fracture also establishes the diagnosis. Guidelines for the general population recommend BMD screening in women >65 years and in men >70 years; earlier screening in postmenopausal women or men >50 years is advisable if risk factors for low bone mass are present [89–91]. Considering diabetes and DKD patients at high risk for osteoporosis, BMD testing should be considered in postmenopausal women and men >50 years with diabetes mellitus. As already discussed above, accumulating evidence suggests that BMD underestimates fracture risk in the diabetes population and, therefore, a T-score of −2 at spine or hip would be more appropriate when considering therapeutic threshold [52] (Fig. 16.1). Very recently, a higher threshold was also discussed for DKD, but clinical trial data are still lacking [87].

Fracture Risk Aassessment While low BMD is a classic risk factor for fractures, its use in fracture risk evaluation in diabetes patients has proven suboptimal, especially as T2D patients generally have higher BMD but a higher risk for fragility fractures due to impaired skeletal strength. The FRAX tool has been intensively used lately to assess the 10-year probability of a major and hip fracture. When estimating fracture risk, FRAX considers a wide range of contributing factors, such as age, sex, BMI, previous fracture or family history of fragility fracture, smoking, alcohol intake, and rheumatoid arthritis, and also has the possibility to check (yes or no) for secondary osteoporosis – among which T1D is included, but not T2D or CKD. However, the presence of diabetes-specific risk factors, such as diabetes duration >5 years, medication, HbA1c >7%, and microvascular complications, impairs the ability of FRAX to completely capture fracture risk in patients with diabetes mellitus. As recently reviewed, substituting rheumatoid arthritis with T2D when employing FRAX may be clinically useful, despite limitations [52, 92] (Fig. 16.1). Interestingly, FRAX performance is similar in the CKD and general populations [87].

TBS In the general population, TBS predicts fracture risk independent of BMD and FRAX score. TBS has proven its usefulness in predicting fracture risk in the diabetic and renal populations and also in diabetic CKD patients [52, 85]. TBS provides new information independent of BMD and can be easily obtained via DXA. Therefore, although not yet validated, TBS may be a practical method of optimizing fracture risk assessment in diabetes mellitus patients and specifically in patients with DKD characterized by increased complexity and multifaceted bone fragility [85, 87].

Bone Turnover Markers As presented above, bone turnover markers change early in the course of diabetic kidney disease, with recent research pleading for the detection of bone metabolic markers together with BMD in this particular group of patients [82]. Bone markers that are not cleared by the kidney, such as bone alkaline phosphatase (BAP) or tartrate-resistant acid phosphatase 5b, are preferred [87]. However, bone alkaline phosphatase (BAP) does not appear to change significantly in T2D patients without kidney disease [4]. In non-renal diabetes subjects, osteocalcin is the most prominent marker and is rather reported to be decreased, suggesting low bone turnover. Osteocalcin may find its use in evaluating the potential therapeutic benefit of anti-resorptive drugs, as a low turnover state would better respond to anabolic treatment [4, 52].

Treatment

General Measures Lifestyle interventions recommended for the general population, such as weight-bearing exercise, adequate nutrition, avoidance of smoking, and limitation of alcohol intake, remain important for the diabetic population as well, DKD patients here included [52, 87]. Nutritional calcium intake (1000 mg/

day) and 800–1000 UI/daily vitamin D intake are appropriate. Glycemic control to prevent complications is essential, with a reasonable treatment goal between 7 and 7.5% for HbA1c in most patients in order to minimize the risks of hypoglycemia and consequent risk of falling [4, 52] (Fig. 16.1).

Special attention should be paid to DKD, where dedicated guidelines should be followed when managing CKD-MBD, although Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend vitamin D supplementation to achieve 25(OH) serum levels as for non-CKD patients (20–30 ng/ml) [52, 87, 88]. Vitamin D supplementation positively impacts BMD in diabetic patients with CKD stages 1–4 [93].

Pharmacological Intervention Truly little data is available regarding bone active therapy in diabetes mellitus, deriving from post hoc analyses in subgroups from randomized clinical trials and from observational studies. Pharmacological treatment should address the pathophysiology of the diabetic osteopathy, characterized by low bone turnover and altered bone quality. In this context, the effect of antiresorptive treatment in diabetes mellitus is unclear. Experimental data proving increased levels of AGEs in cortical and trabecular bone after high-dose antiresorptive treatment have raised the possibility of occurring bone tissue adverse effects [4]. However, alendronate has proven similar efficacy upon the BMD and fracture risk in both diabetic and non-diabetic individuals [94, 95]. Much the same, risedronate had similar effects upon spine BMD in diabetic and non-diabetic subjects in post hoc analysis of phase III trials [96]. Data regarding the administration of IV bisphosphonates or regarding the anti-fracture risk of denosumab in diabetic patients are not yet available [52]. In the context of increased cortical porosity accompanied by low bone turnover, the bone anabolic teriparatide would seem more appropriate. Teriparatide appears to have similar outcomes on vertebral and total hip BMD and upon the risk of non-vertebral fractures, irrespective of the presence of diabetes. More so, the positive impact of teriparatide upon femoral neck BMD was more pronounced in diabetic patients [97]. Abaloparatide may also become of interest, as it simulates bone formation with a less effect on bone resorption and with a less risk of hypercalcemia [52, 87]. Romosozumab, a human monoclonal antibody against sclerostin, appears promising in diabetic patients that generally have high sclerostin levels. Experimental data proved increased bone formation, trabecular and cortical bone mass, and bone strength in diabetic rats treated with sclerostin inhibitors [98]. Although associated with favorable effects in the general population and particularly interesting due to the uncoupling of bone remodeling in favor of bone formation, cardiovascular safety concerns have been raised [87].

The Therapeutic Arsenal Is Even more Limited in DKD Bisphosphonates generally have contraindications in severe renal impairment (CKD stages 4 and 5) due to renal safety concerns. Alternative dosing regimens (lower dose or frequency) have been proposed but not validated in CKD patients. Nonetheless, bisphospho-

nates are cleared by dialysis, and the latest consensus on CKD-MBD discusses the possibility of "off-label" use of bisphosphonates in classical dosing regimens even in G4–G5D CKD after assessing the individualized overall risk-benefit ratio and after properly informing the patient about risks, benefits, and treatment options [87]. Although not influenced by renal function, denosumab therapy also has its drawbacks in DKD due to the increased risk of severe hypocalcemia. However, the risk is highest in patients with increased bone turnover. Also, cessation of treatment is associated with a rapid offset of the effect, which translates into an increased risk of fractures; thus, denosumab therapy should be followed by anti-resorptive treatment [87]. Last but not least, DKD with adynamic bone disease may well benefit from anabolic treatment with teriparatide, but the optimal administration protocol still needs to be determined. Data regarding abaloparatide administration in CKD-MBD are lacking [87].

The above treatment options generally refer to diabetic postmenopausal women and men over 50 years of age, where alendronate seems the most reasonable option if BMD is decreased and the eGFR is above 30 ml/min/1.73 m^2 (Fig. 16.1). In diabetic G4–G5D CKD, balancing of risks is essential: if the bone turnover is appreciated as high, the risks of denosumab should be weighed against the risks of bisphosphonates and the risks of not treating at all. In T2D patients with increased BMD but with poor bone quality and strength and also in DKD patients with adynamic bone disease, turning toward teriparatide or new medication such as romosozumab is of interest.

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Chapter 17
Diabetic Retinopathy

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Diabetes mellitus is a pandemic that has been associated with a significant increase in incidence among all ages, genders, ethnic groups, and regions over the last decade. It is estimated that 366 million will have diabetes worldwide in 2030 [1]. Over 30% of diabetics have some form of diabetic retinopathy.

Diabetic retinopathy (DR) is the leading cause of preventable blindness among individuals of working age (20–65 years) and a major cause of vision loss in the elderly population. Visual loss occurs secondary to complications of DR such as vitreous hemorrhage, retinal detachment, diabetic macular edema, and macular ischemia.

In 2010, 285 million people had diabetes worldwide. Over one-third of diabetics had signs of DR, and a third of them had vision-threatening retinopathy, defined as severe non-proliferative DR, proliferative diabetic retinopathy, or diabetic macular edema (DME) [2]. The likelihood of developing retinopathy is strongly related to the duration of diabetes in patients with both type 1 and type 2 diabetes. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the overall 10-year incidence of retinopathy was 74%, and among those with retinopathy at baseline, 64% developed more severe retinopathy and17% progressed to develop proliferative diabetic retinopathy (PDR). After 25 years, the incidence of retinopathy in patients with type 1 diabetes was 97%. Among those with retinopathy at baseline, 42% progressed to develop proliferative diabetic retinopathy [3], and 17%

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developed clinically significant macular edema (CSME) [4]. Although the main purpose of this chapter is to summarize the clinical state-of-the-art approach to the diagnosis and management of diabetic eye disease, a brief discussion of the relationship of diabetic retinopathy to diabetic kidney disease (DKD) as well as the pathogenesis of diabetic retinopathy is in order.

Epidemiological evidence exists regarding the correlation of morphologic parameters of diabetic retinopathy and nephropathy, especially early in the disease. The severity of diabetic retinopathy has been proven to correlate with morphologic measures of kidney biopsies, such as glomerular mesangial fractional volume and glomerular basement membrane width in patients with type 1 diabetes [5, 6]. Glomerular and retinal vascular pathology also correlates with the clinical features of patients with type 2 diabetes mellitus and hypertension [7].

Pericytes provide structural integrity for the retinal capillary wall and have control over endothelial cell proliferation to maintain vascular stability. The role of the pericyte, therefore, is crucial for the survival of endothelial cells, particularly under stress conditions such as diabetes. Although the exact mechanism of pericyte loss and vascular "disintegration" in the diabetic retina is not known, the changes are blamed on the following cascades: (i) destructive biochemical abnormalities within the endothelial cells and pericytes secondarily leading to basement membrane abnormalities, (ii) occlusion of the vascular lumen by these degenerating cells and leukocytes and/or platelets, and (iii) additional capillary endothelial cell apoptosis secondary to products generated by other neuroretinal cells (such as ganglion cells or glia) [8].

In addition to the vasculopathy or, according to some, as a result of it, certain inflammatory changes take place in the neuroretina of diabetic patients and experimental animals and also in cultured retinal cells exposed to elevated concentrations of glucose [9]. The concept that localized neuroretinal inflammatory processes play a role in the development of diabetic retinopathy is relatively new, but the evidence that supports this hypothesis is gathering rapidly. Research in this field may offer novel targets to inhibit the ocular disease using selective pharmacologic inflammation mediator inhibitors in the early stages of diabetic retinopathy before it advances to the occlusion of retinal capillaries [10, 11].

There is accumulating evidence to suggest that a neuropathy involving retinal neurons (retinal neuropathy) may also be associated with the vasculopathy or may even precede it [12]. This suggests a complex interplay between the retinal vasculopathy, neuropathy, and inflammatory processes in the development and progression of diabetic retinopathy.

Multiple epidemiologic studies have shown that hyperglycemia, hypertension, dyslipidemia, and obesity are risk factors for development and progression of diabetic retinopathy and clinically significant macular edema that is best summarized in the declared Position Statement of the American Diabetes Association (ADA) [13]**.** The following sections discuss these risk factors in more detail.

Hyperglycemia

The most important risk factor for DR and DME is poor glycemic control. Elevated blood sugar levels and the associated glucotoxicity induce and enhance inflammation and progress microangiopathy that results in progressive DR. Two large randomized clinical trials, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), provided strong evidence that tighter glycemic control reduces the risk of development and progression of DR in both type 1 and 2 diabetes.

In the DCCT, 1441 patients with type 1 diabetes were randomly assigned to either conventional or intensive insulin treatment and followed for a period of 4 to 9 years. In this study, the 3-year risk of development and progression of retinopathy was reduced by 75% and 54% in the intensive insulin treatment group compared with the standard treatment group. Analysis of data from DCCT demonstrated that the risk of progression of retinopathy reduced by 35% to 40% for every 10% decrease in HbA_1C [14–18]. Later, patients from DCCT were enrolled in the observational 7-year follow-up phase of the study, which demonstrated that the risk reduction of retinopathy progression was maintained in those patients initially randomized for intensive therapy even after cessation of intensive HbA_1C control [19].

The UKPDS and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study confirmed the significant benefit of glycemic control on the development and progression of retinopathy in type 2 diabetics [20–22].

Hypertension

Hypertension is an important risk factor for DR. Resulting microvascular pathology such as nephropathy, retinopathy, and peripheral neuropathy and macrovascular mechanisms such as central and peripheral cardiovascular disease including stroke are typical complications that are causative for the increased morbidity and mortality in Diabetus Mellitus (DM).

In the UKPDS, tight blood pressure control (systolic blood pressure < 150 mm Hg) in patients with type 2 diabetes reduced the risk of progression of retinopathy by 34%. The UKPDS showed that benefits from tight blood pressure control were present in patients on both beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, with no statistically significant difference between the two [23]. However, some clinical trials suggest that ACE inhibitors may have additional beneficial effects on diabetic retinopathy, independent of their blood pressure lowering effect [24–25]. The ACCORD study did not demonstrate a significant advantage of intensive blood pressure control (systolic pressure < 120) over standard blood-pressure control (systolic pressure < 140) in controlling the progression of diabetic retinopathy [26].

Often these late proliferative DR stages are accompanied by permanent reduced visual acuity. The available ophthalmological treatment options are predominantly focused on later stages of the disease and do not address the early and potentially reversible microvascular changes leading to DR. New targeted therapies are urgently required to prevent or slow down the progression of DR.

Hyperlipidemia

The role of elevated cholesterol and triglyceride in the development and progression of DR has been confirmed in several studies. The DCCT showed that severity of retinopathy was associated with elevated triglycerides and inversely related to the level of high-density lipoprotein (HDL) cholesterol in type 1 diabetes [27]. ACCORD demonstrated that intensive treatment of dyslipidemia with fenofibrate and simvastatin reduced the rate of progression of diabetic retinopathy in type 2 diabetics [22]. Other studies reported that an elevated serum lipid level was independently associated with the development of diabetic macular edema [28, 29].

Pregnancy

Diabetic retinopathy may be accelerated during pregnancy because of hormonal or glycemic control changes. In DCCT's ancillary study, some patients had transient worsening of retinopathy during pregnancy, even to the proliferative level. However, at the end of the study, mean levels of retinopathy in subjects who had become pregnant were similar to those patients who had not become pregnant [30]. It is known that pregnancy induces a transient increase in the risk of retinopathy [30–32]; therefore, ophthalmic examination should be performed more frequently during pregnancy and the first year postpartum.

Kidney Disease

Multiple studies have demonstrated that proteinuria is associated with increased risk of sight-threatening or proliferative diabetic retinopathy in type 1 diabetics [3, 33]. Proliferative retinopathy has also shown to be an independent marker of long-term nephropathy in type 1 diabetes [34].

Other Risk Factors

Several studies suggest a role for other factors including anemia [35–37], sleep apnea [38], inflammatory markers, homocysteine [39], as well as genetic predisposition [40–44] in the development and progression of diabetic retinopathy. In addition, the association between microalbuminuria and the presence/severity of diabetic retinopathy has been reported in several studies [45, 46].

Classification of Diabetic Retinopathy

Diabetic retinopathy is classified into an early stage, non-proliferative diabetic retinopathy (NPDR), and a more advanced stage, proliferative diabetic retinopathy (PDR).

Non-proliferative Diabetic Retinopathy

Characteristic retinal findings in NPDR include microaneurysms (Fig. 17.1a); cotton wool spots, which represent nerve fiber layer infarcts (Fig. 17.1a); hard exudates and intraretinal hemorrhages (Fig. 17.1a, b, and d); dilation and beading of retinal veins (Fig 17.1c); intraretinal microvascular abnormalities (IRMA) (Fig. 17.1c); and areas of capillary non-perfusion (Fig 17.1d).

Non-proliferative retinopathy is further categorized into four levels of severity based on the presence and extent of retinal findings: mild, moderate, severe, and very severe. In the mild to moderate non-proliferative categories, there are relatively few intraretinal hemorrhages and microaneurysms. Hard exudates and cotton wool spots can also be seen. The severe non-proliferative retinopathy is clinically detected by evaluating the retina in the four mid-peripheral quadrants. Patients with any one of the following features are considered to have severe NPDR: (1) severe intraretinal hemorrhages and microaneurysms in all four quadrants, (2) venous beading in two or more quadrants, or (3) moderate IRMA in at least one quadrant. If any two of these features are present, the retinopathy level is considered to be very severe non-proliferative.

Diabetic Macular Edema

Excessive vascular permeability and loss of blood–retina barrier result in the leakage of fluid and plasma constituents into the retinal tissue. This is usually most prominent in the macular area of the retina leading to the development of macular

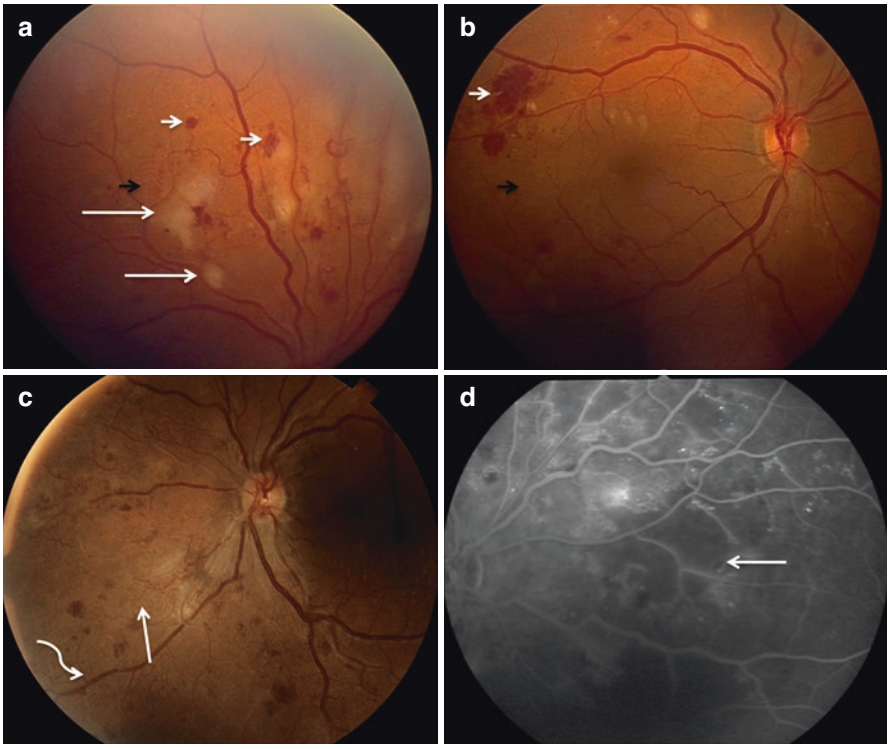

Fig. 17.1 Retinal changes seen in non-proliferative diabetic retinopathy. (**a** & **b**): Fundus photographs illustrating retinal "dot and blot" hemorrhages (small white arrows), retinal "cotton wool" spots (large white arrows), and clusters of microaneurysms (small black arrows). (**c**): Fundus photograph depicting intraretinal microangiopathy (straight arrow) and venous "beading" (curved arrow). (**d**): Intravenous fluorescein angiogram (IVFA) disclosing areas of peripheral retinal capillary non-perfusion (straight arrow). The scattered white spots are microaneurysms filled with the fluorescein dye; the microaneurysms are usually better seen on IVFA than on fundus examination or photography

edema (Fig. 17.2). DME may be associated with any stage of diabetic retinopathy. It can manifest as focal or diffuse macular thickening with or without exudates. Macular edema is the most frequent cause of visual impairment in patients with NPDR. In the Early Treatment Diabetic Retinopathy Study (ETDRS), the 3-year risk of moderate visual loss (a doubling of the initial visual angle or loss of 15 letters on a logarithmic visual acuity chart) secondary to macular edema was 32%. The ETDRS investigators classified macular edema by its severity. It was defined as clinically significant macular edema (CSME) if any of the following features were present: (1) thickening of the retina at or within 500 μm of the center of the macula; (2) hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; or (3) a zone of retinal thickening of one optic disk area or larger, any part of which is within one disk diameter of the center of the macula [47]. In addition to optimizing diabetic control, patients with CSME benefit

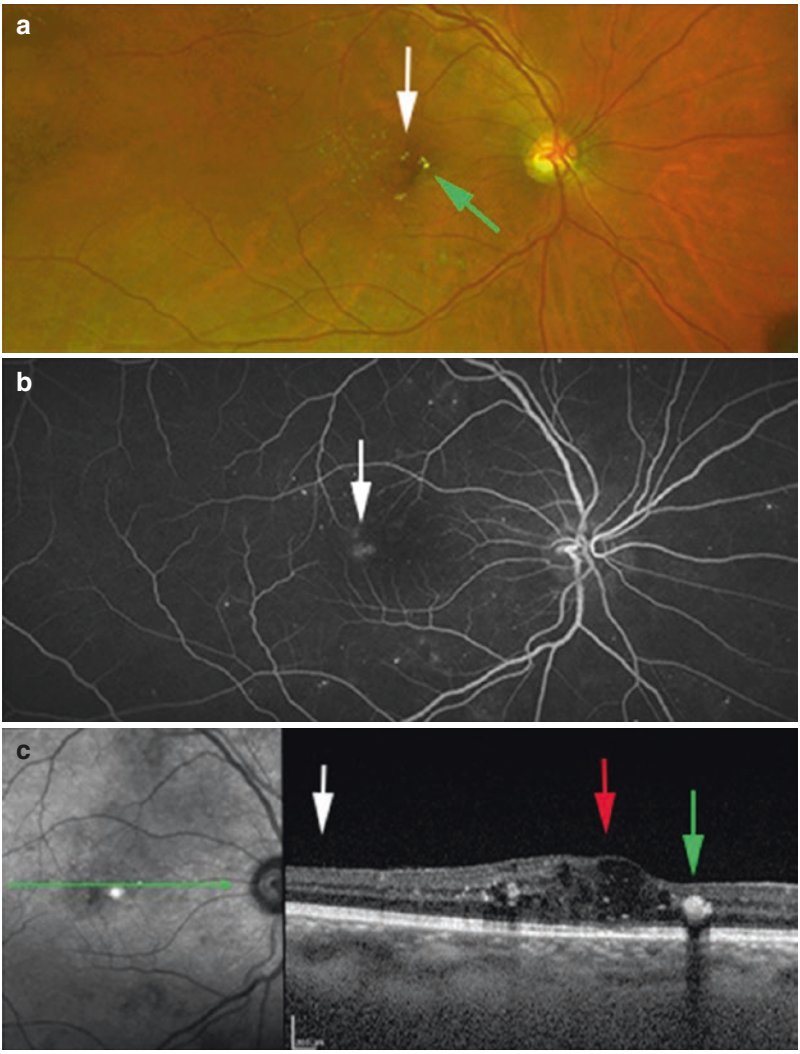

Fig. 17.2 Clinically significant macular edema associated with diabetic retinopathy. (**a**): Fundus photograph illustrating a ring of hard exudates (lipid deposits) that have escaped out of the retinal circulation surrounding an area of retinal swelling (vertical white arrow). Note that the process involves the center of the macula; the corresponding intravenous fluorescein angiogram (IVFA) (**b**) discloses a cluster of leaky microaneurysms (vertical white arrow) in the center of the hard exudate ring. (**c**): Optical coherence tomography (OCT) discloses swelling of the involved retina with disruption of the normal foveal contour and accumulation of cystic lacunae of intraretinal fluid (red arrow). Vertical white arrow in the same frame points to normal retina. Hard exudates are also seen within the retina (vertical green arrow) and correspond to the area also depicted with an angled green arrow in the fundus photograph in frame A

The hard exudates are composed of lipid and proteinaceous material, which leak from structurally impaired diabetic retinal vessels. The hard exudates are usually seen in the outer plexiform layer of the retina, and with OCT, these deposits are observed as hyperreflective foci with shadowing effect (vertical green arrow).

from ocular specific treatments such as laser photocoagulation or intravitreal injection of pharmacologic agents. This is discussed further in the treatment section. Ancillary tests such as fluorescein angiography (FA) (Figs 17.1d and 17.2b) and optical coherence tomography (OCT) (Fig 17.2c) complement the clinical exam and are extremely helpful for the detection of DME, guidance of treatment, and monitoring treatment response.

Proliferative Diabetic Retinopathy

Proliferative retinopathy is characterized by formation of new blood vessels and/or fibrous tissue induced by retinal ischemia. Patients can present with neovascularization on the optic disk (Fig. 17.3a), other parts of the retina (Fig. 17.3b), iris (Fig. 17.3c), and/or anterior chamber angle (Fig. 17.3d); preretinal and/or vitreous hemorrhages (Fig. 17.4a and b); vitreoretinal traction bands (Figs 17.4c and d); or tractional retinal detachment (Fig. 17.4c and d). PDR is considered high risk if neovascularization is accompanied by vitreous/preretinal hemorrhage or if it is located on the optic disk and occupies at least one-third of the disk area even in the absence of vitreous hemorrhage. Neovascular glaucoma, a potentially irreversible and blinding complication, can result from new vessel formation on the iris and anterior chamber angle structure (Figs 17.3c and d). Patients with high-risk PDR or neovascularization of iris/angle require prompt treatment with panretinal laser photocoagulation (PRP) and/or intravitreal injection of pharmacologic agents to reduce the chance of severe visual loss. This is discussed further in the treatment section.

Many of the above listed complications of DR can be depicted much better with the new wide-field imaging methodology commonly known as the Optomap ™. (Fig. 17.5 a, b). The Optomap™ ultra-wide-field retinal image is a unique laser technology that captures more than 80% (approximately 200 degrees) of the retinal surface in one panoramic image, while traditional imaging method usually shows 15–20% at one time. Note the difference between the conventional fundus photographs and wide-field views respectively in Figs. 17.4 and 17.5.

Screening for Diabetic Retinopathy

As diabetic retinopathy can progress with relatively few visual symptoms, the importance of regular eye screening and subsequent early intervention is essential for all diabetic patients. In patients with type 1 diabetes, screening eye examination can be delayed until 3–5 years after diagnosis of diabetes as prevalence of retinopathy during first 4 years after diagnosis is low and reported to be 1% [48, 49]. On the other hand, the time of onset of type 2 diabetes is often difficult to determine and may precede the diagnosis by number of years. Therefore, type 2 diabetics should be referred for eye exam at the time of diagnosis (Table 17.1).

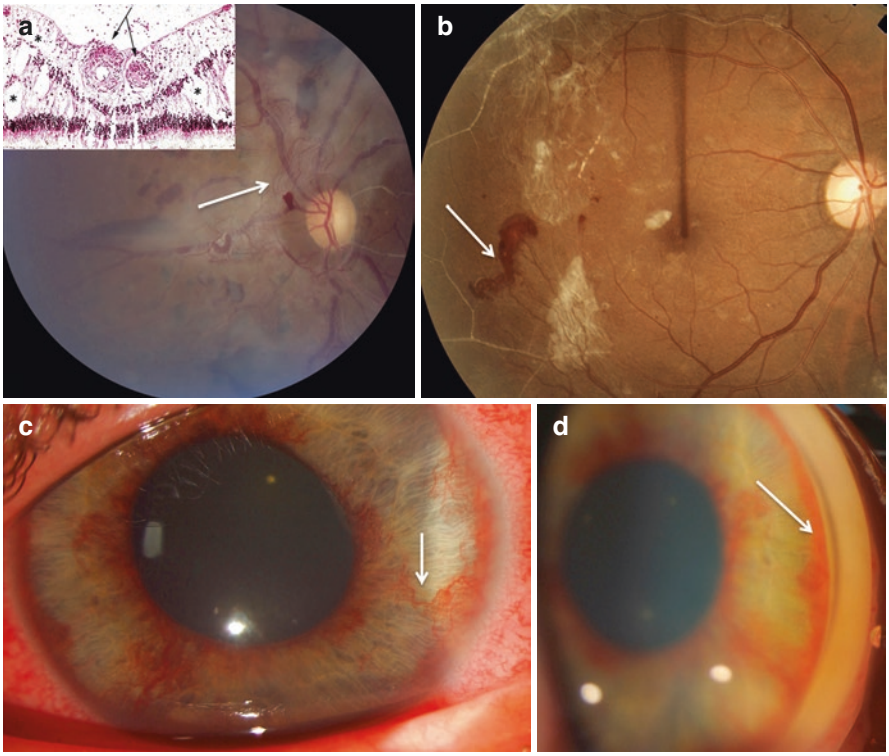

Fig. 17.3 Types of neovascularization seen in proliferative diabetic retinopathy (**a**): Fundus photograph illustrating neovascularization at the disk (NVD) (white arrow). Scattered hemorrhages and laser scars (black spots) are also seen. Insert: Histopathologic appearance of retinal neovascularization, forming vascular tufts (black arrows) in neuroretina. Note the substantial loss of retinal structural integrity secondary to fluid (*) leaking from newly formed abnormal vascular structures. Edema (*) is seen in all layers of the retina including the perivascular space surrounding the vascular tufts. The internal limiting membrane is thickened, is pulled inward, and is barely intact over the larger tuft. (**b**): Fundus photograph illustrating neovascularization affecting other parts of the retina (neovascularization elsewhere (NVE), white arrow). The scattered whitish tissue also represents NVEs that are primarily composed of fibrous rather than vascular tissue. (**c**): Slit-lamp photograph showing neovascularization of the iris (white arrow). (**d**): Photograph of the anterior chamber angle, depicting neovascularization (white arrow). The patient developed neovascular glaucoma, a serious complication of proliferative diabetic retinopathy that may lead to irreversible loss of vision in the involved eye.

Treatment of Diabetic Retinopathy

Management of patients with diabetic retinopathy entails adequate metabolic control of diabetes as well as other risk factors in addition to local ocular therapy.

Large, randomized trials have shown the benefits of systemic therapies for the prevention and treatment of diabetic retinopathy. The Diabetes Control and Complications Trial (DCCT) showed that intensive metabolic control in type 1

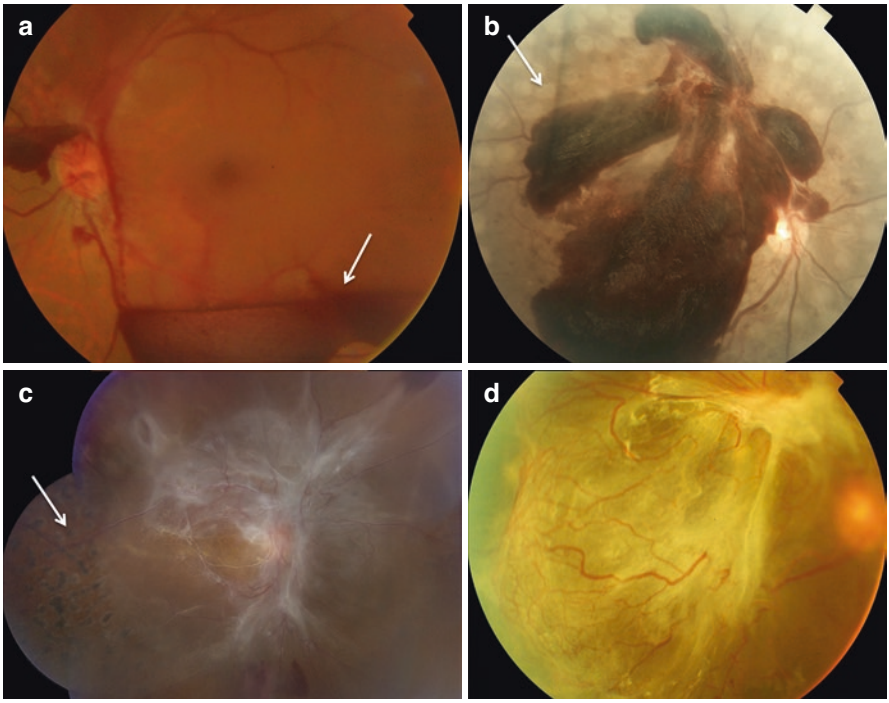

Fig. 17.4 Fundus photographs illustrating vision-threatening complications of proliferative diabetic retinopathy. (**a**): Vitreous and preretinal or subhyaloid (white arrow) hemorrhages. The hemorrhage may sometimes be dense, obscuring visualization of the underlying retina. (**b**): Large and dark subhyaloid hemorrhage covering the entire posterior pole and macula. Note also the multiple round scars of previous panretinal laser photocoagulation (PRP, white arrow). (**c** & **d**): Massive proliferation of fibrous bands and fibrovascular tissue leading to traction and retinal detachment of the macula. The scars of previous panretinal laser photocoagulation (PRP) are also seen in this frame (white arrow in **c**)

diabetics reduced the risk of developing retinopathy by 76% and slowed progression of retinopathy by 54%. Furthermore, intensive glycemic control was associated with reduction in the incidence of macular edema and the need for panretinal and focal laser photocoagulation [18]. The UKPDS showed that intensive blood glucose and blood pressure control slowed progression of retinopathy in type 2 diabetics [20].

As mentioned before, two large clinical trials, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) [51] and ACCORD [22], demonstrated that hyperlipidemia control with fenofibrate reduces the risk of progression of retinopathy by up to 40%. Multiple studies have demonstrated that angiotensin-converting enzyme (ACE) inhibitors reduce the incidence and risk of progression of diabetic retinopathy in patients with type 1 diabetes [24–26, 52].

In addition to optimizing metabolic status and blood pressure control, eye-specific treatments are needed in patients with vision-threatening complications of

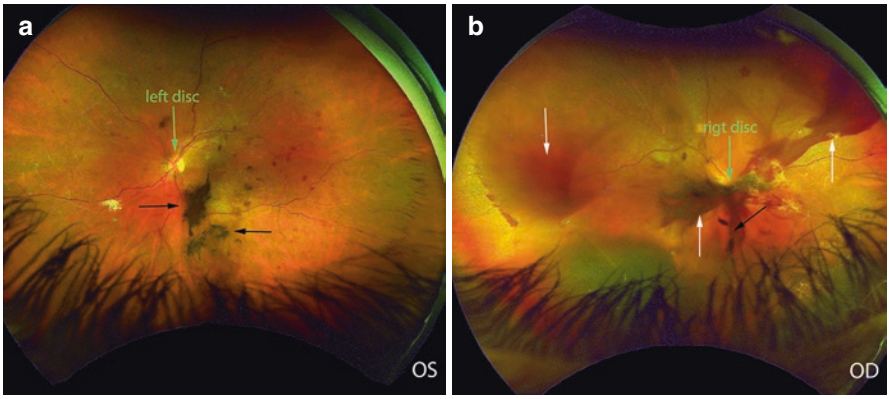

Fig. 17.5 Optom™ photos (**a** and **b**) of a patient bilaterally depicting multiple intravitreal hemorrhages of varying ages and DR changes in the background. Black arrows: old hemorrhages in OU; white arrows: hemorrhages in OD at varying stages of resolution with changing colors from red to maroon to brown. Green arrows mark the optic nerve disks bilaterally; the right disk is partially covered by an overlying intravitreal hemorrhage. Eyelashes in both photos and the dark greenish black areas inferiorly seen in the right frame are artefacts

Table 17.1 The American Academy of Ophthalmology recommendations on the frequency of eye examinations for different stages of diabetic retinopathy [50]

Status of retinopathy	Follow-up (mo)
No retinopathy or rare microaneurysms	12
Mild to moderate NPDR without macular edema	6–12
Mild/moderate NPDR with macular edema that is not clinically significant	4–6
Mild/moderate NPDR with clinically significant macular edema	2–4
Severe/very severe NPDR	2–4
PDR	2–4
Inactive/involuted PDR without macular edema	6–12

diabetes (proliferative diabetic retinopathy and macular edema). The Diabetic Retinopathy Study (DRS) was a prospective, randomized clinical trial evaluating laser panretinal photocoagulation (PRP) treatment (Figs 17.4 b and c) to one eye of patients with advanced non-proliferative diabetic retinopathy (NPDR) or PDR in both eyes. The primary outcome measurement was severe visual loss, defined as visual acuity of less than 5/200 on two consecutive follow-up examinations 4 months apart. The DRS demonstrated a 50% or greater reduction in the rate of severe visual loss in eyes treated with PRP compared to untreated control eyes during a follow-up of 5 years [53], especially in eyes with high-risk PDR. Within the last decade, randomized clinical trials have also established the efficacy of anti-VEGF agents in the treatment of high-risk PDR. Anti-vascular endothelial growth factor (VEGF) agents

were shown to be non-inferior to PRP and were associated with a better functional and anatomic outcome compared to PRP [54, 55].

The choice of treatment (PRP vs anti-VEGF agents) entails proper case selection depending on several variables such as the ability of the patient to comply with follow-up, the presence of comorbidities, the extent of tractional elements associated with PDR, cost, and the presence or absence of diabetic macular edema.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that focal/grid laser photocoagulation for clinically significant diabetic macular edema (CSME) substantially reduced the risk of moderate visual loss. In addition, it increased the chance of visual improvement, decreased the frequency of persistent macular edema, and caused only minor visual field loss [47].

A large body of scientific evidence has implicated vascular endothelial growth factor (VEGF) in the pathophysiology of diabetic macular edema. Multiple studies have shown that intravitreal injection of the anti-VEGF antibodies, *bevacizumab*, *ranibizumab*, and *aflibercept*, alone or in combination with other treatments, improves visual acuity by an average of one to two lines on a Snellen chart, with an improvement of three or more lines in 25 to 45% of patients over a period of 2 years. These results are significantly better than the outcome of laser treatment alone with a comparable safety profile [56–58]. Although these three agents are all extremely efficacious, they may have a slight variability in efficacy depending on the baseline visual acuity. For example, aflibercept may have a slightly better effect in eyes with worst baseline visual acuity of 20/50 or worse [58]. Due to their superior therapeutic effect compared to laser and their excellent safety profile, anti-VEGF agents are now the first line of therapy for fovea involving diabetic macular edema. Moreover, these agents were also found to have an additional favorable disease modulating effect in that they were found to decrease the severity of diabetic retinopathy in general in approximately 30–40% of treated eyes [56–62].

Glucocorticoids are known to reduce retinal inflammation and may have a role in restoring the integrity of the blood–retina barrier. Therefore, intravitreal injection of steroids has been tried for the treatment of diabetic macular edema in multiple studies. Intravitreal injection of triamcinolone has been associated with equivocal results in the treatment of diabetic macular edema [63–65]. Fluocinolone acetonide intravitreal implant has been shown to be effective in improving vision and resolution of macular retinal thickening in patients with refractory diabetic macular edema [66–68]. The implant is available in two different sustained delivery forms that result in a long-term effect of approximately 3 years: a surgically implanted delivery system [66] as well as an insert that is injected intravitreally in the office [67, 68]. A dexamethasone intravitreous drug delivery system has also been shown to be effective in the improvement of vision and reduction of central retinal thickness in eyes with persistent diabetic macular edema with a lower side effect profile [69, 70]. Steroid implants have been shown to be most effective in cases of diffuse and chronic diabetic macular edema. However, steroid implants are associated with a significantly higher risk of cataract formation and glaucoma development in treated eyes compared to anti-VEGF agents. Some patients may require surgery to treat such side effects [59–70]. The advantage of steroid implants compared to currently available

intravitreal anti-VEGF agents is in their long-term duration effect, which may last between 3 months for the dexamethasone implant [70] and 3 years for the *fluocinolone acetonide implants* [66–68]. On the other hand, intravitreal anti-VEGF agents may require frequent injections as frequently as every month in some patients, which represents a significant treatment burden for both patients and physicians. Therefore, steroid implants may help reduce that burden because of their long-term effect and significantly less frequency of injections particularly in the subgroup of patients who are pseudophakic and/or have chronic macular edema [71]

Many of the approaches to DR treatment, however, are employed after the disease is symptomatic. In the last couple of years, a new class of antidiabetic drugs is utilized early in the disease that inhibits SGLT2 and thereby decreases reabsorption of glucose from the renal proximal tubules, thereby increasing the glucose excretion [72].

It is promising that with these drugs, blood glucose is lowered and metabolic and hemodynamic risk factors like elevated blood pressure and obesity, which are tightly linked to diabetic microangiopathy, are effectually bettered. This approach might have the potential to directly protect against microvascular complications and could represent a likely treatment option for early DR. Randomized controlled clinical trials are needed to investigate the effectiveness of SGLT2 inhibitors in the prevention or deferral of diabetic microangiopathy in the retina as well as elsewhere [73].

In addition to laser and pharmacotherapy, a group of patients with diabetic retinopathy will require surgical management to restore vision or prevent further visual loss. Pars plana vitrectomy, which involves surgical removal of vitreous opacities and proliferative retinal tractional membranes, is indicated in patients with dense, non-clearing vitreous hemorrhage, tractional retinal detachment involving the macula, diffuse diabetic macular edema associated with vitreomacular traction, or combined tractional and rhegmatogenous (derived from the Greek word *rhegma*, which means a rupture or break) retinal detachment (RRD) [74–80]. RRD arises when a tear in the retina occurs and leads to fluid accumulation between the neurosensory retina and the underlying retinal pigment epithelium.

Other Ocular Manifestations

In addition to the retina, diabetes can affect other parts of the eye, including the conjunctiva, tear film, cornea, and iris. Patients can present with conjunctival microaneurysms, dry eye, decreased corneal sensation, poor corneal wound healing, as well as neovascularization of iris/anterior chamber angle.

Dry eye syndrome is more common in diabetics secondary to decreased tear film, abnormal tear lipid layer, higher tear osmolarity, and glucose level [81, 82]. Worsening of dry eye symptoms may correlate with the severity of diabetic retinopathy [83].

Diabetics have reduced corneal sensation as part of diabetic polyneuropathy. As corneal innervation provides protective and trophic functions, diabetics can develop

neurotrophic keratopathy. Confocal biomicroscopy studies in vivo have confirmed the reduction in the number and branching of corneal nerves as well as increase in the tortuosity of sub-basal corneal nerve plexus [84, 85]. Changes in sub-basal nerve plexus of diabetic corneas appear to be related to progression of diabetic retinopathy and peripheral neuropathy. Therefore, corneal confocal microscopy can be used as an adjuvant technique for the early diagnosis and assessment of diabetic neuropathy [86].

Last but not least, diabetic papillopathy, a relatively rare and benign ocular complication of diabetes mellitus, is worth mentioning [87, 88]. Ischemia of the optic nerve is a likely mechanism for this pathology; however, this process is independent of the ischemia of the retina [89]. Diabetic papillopathy presents with optic disk edema, which may vary from minimal to extensive with hemorrhages and exudates even to the degree of forming a "macular star." Papillopathy of diabetes may be a difficult entity to diagnose as it can mimic both papilledema secondary to increased intracranial pressure and anterior ischemic optic neuropathy (AION). The setting and absence of systemic findings associated with increased intracranial pressure such as headache and tinnitus help differentiate papilledema from diabetic papillopathy. When diabetic papillopathy is bilateral or detected in a young diabetic patient as conventionally occurs, it is not likely to be mistaken for AION [87]. However, some cases may present unilaterally or asymmetrically in older patients. In such cases, differentiating diabetic papillopathy from AION may be challenging. During the acute phase, there may be loss of central vision, enlarged blind spot, or other field defects. However, unlike AION, these usually resolve, and the prognosis is usually good without chronic impairment of vision. The visual prognosis might be poor in older patients with type 2 diabetes [89].

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Chapter 18
Pregnancy and Diabetes

Anna Marie Burgner and Natalie McCall

Introduction

The kidneys are a central contributor to the extraordinary adaptation of physiologic changes that occur in a woman during pregnancy. During normal pregnancy, a woman's kidney size, renal plasma flow, and glomerular filtration rate (GFR) all increase [1]. Pregnancy represents a state of both volume expansion and vasodilation with plasma volume increasing by more than 1 L and yet a decrease in blood pressure of up to 10 mmHg by the second trimester [2, 3]. There is a remarkable orchestration of changes in the hormonal milieu that occurs to allow all these physiologic alterations to occur. There is a significant upregulation of renin-angiotensin-aldosterone system with an early increase in prorenin due to production from ovaries and the decidua and increased estrogen produced by the placenta leading to increased production of angiotensinogen, ultimately causing a significant increase in angiotensin II [4]. However, blood pressure falls due to increased vascular expression of the angiotensin II type 2 receptor, an increase in production of nitric oxide, and the release of the hormone relaxin by the ovaries.

However, in women with chronic kidney disease (CKD), reproductive health care can pose multiple challenges, in part due to CKD's effects on the aforementioned hormone milieu. Fertility declines as CKD progresses, some types of contraception can affect proteinuria and hypertension, medications commonly used to treat CKD are teratogenic, and an ill-timed pregnancy can lead to disease progression. In addition, pregnant women with CKD are at a much higher risk of preeclampsia and delivering a preterm baby, in addition to other pregnancy complications that we will discuss below. However, good preconception care and prenatal care can improve the chances of good outcomes [5].

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As the prevalence of diabetes mellitus (DM) in women of reproductive age continues to increase, the preconception and prenatal care of the pregnant woman with diabetic kidney disease is extremely important for nephrologists, endocrinologists, and obstetricians to be knowledgeable in. In this chapter, we will discuss the risks of pregnancy to women with diabetic kidney disease and their infant, the long-term effects of gestational diabetes on kidney disease, the management and treatment of CKD during pregnancy, and the role of preconception counseling,

Maternal Pregnancy Outcomes

Type 1 (T1) diabetes and type 2 (T2) diabetes in pregnancy are associated with a considerably increased rate of adverse obstetric outcomes, and the number of pregnancies in T1 and T2 diabetic women has increased in the past few decades [6, 7]. Studies have demonstrated that the most common maternal complications associated with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) include increased risk of preeclampsia, preterm delivery, and need for cesarean section [7–9]. Women with diabetes deliver 2–3 weeks earlier than women without diabetes [7]. The most common reasons for need of obstetric interventions and preterm delivery include fetal distress, macrosomia, and preeclampsia.

CKD is also associated with higher rates of maternal complications. These complications are similar to those seen in diabetic pregnancies and include higher rates of preeclampsia, preterm delivery, and delivery by cesarean section [10, 11]. The risk of these complications increases as kidney function worsens, with the highest risk occurring in women with end-stage kidney disease (ESKD). Despite the increased risk of these complications, CKD does not appear to increase the risk of maternal death in developed countries [11]. Preeclampsia is the leading cause of maternal death worldwide, causing 14% of maternal deaths [12].

Not surprisingly, women with CKD from diabetic kidney disease are at a higher risk of adverse pregnancy outcomes than women with diabetes uncomplicated by kidney disease. However, the risk of developing preeclampsia and premature delivery is higher in women with non-diabetic kidney disease than diabetic kidney disease [11]. The major risks of pregnancy in diabetic kidney disease include exacerbation of hypertension, preeclampsia, worsening proteinuria, preterm delivery, delivery by cesarean section, and progression of kidney disease [13–15].

Preeclampsia is the most frequent complication of pregnancies in women with diabetic kidney disease. The degree of proteinuria at conception affects the risk of preeclampsia; with women with higher levels of proteinuria having higher rates of preeclampsia. In studies that have compared pregnant women with normoalbuminuria, microalbuminuria (30–300 mg/24 h) and macroalbuminuria (>300 mg/24 h), the rate of preeclampsia increased from 5–7% in women with normoalbuminuria to 38–42% in women with microalbuminuria to as high as 60–64% in women with macroalbuminuria [14–17]. Preeclampsia in women with microalbuminuria or macroalbuminuria is often severe, with early development leading to preterm delivery before 34 weeks [18].

The development of preeclampsia does not just represent increased short-term pregnancy risks to the woman. There are also multiple long-term, significant cardiovascular and nephrologic risks that the woman is at risk for after a diagnosis of preeclampsia. Preeclampsia is associated with a significant increased risk in the development of CKD and ESKD [19, 20]. The more episodes of preeclampsia that a woman has, the higher these risks are. In addition, preeclampsia increases the risk of hypertension, coronary heart disease, heart failure, and stroke with these risks appearing to be higher in the first 10 years after a diagnosis of preeclampsia [21].

For most pregnant women with diabetic kidney disease, pregnancy does not appear to cause progression of CKD. If kidney function is well preserved and proteinuria is suppressed at the beginning of pregnancy, progression of CKD is unlikely [15]. However, in women with a reduced GFR of <40 mL/min/1.73 m^2 and proteinuria >1 g/24 h, the risk of permanent worsening of kidney function is much higher [22–24]. Coexisting poorly controlled hypertension can also increase the risk of permanent worsening of kidney function at a higher GFR.

Fetal Pregnancy Outcomes

In the early twentieth century, rates of fetal mortality in pregnancies of women with diabetic kidney disease were reported to be as high as 30–60% [25]. Over the past few decades, fetal survival rates have improved dramatically to approximately 95% [13]. Despite improvements in fetal survival rates, neonatal morbidity and mortality remain a challenge in pregnancies of diabetic women. Babies born to diabetic mothers continue to have a higher prevalence of major congenital malformations, fetal macrosomia (birth weight > 4000 g), and to be born large for gestational age (>90th percentile of birth weight). They also have an increased prevalence of stillbirth and infant death as compared to babies born to non-diabetic mothers [6, 7, 9].

Major congenital malformations have been shown to occur up to two to three times more often in diabetic pregnancies than with non-diabetic women [8]. The most common congenital malformation reported is fetal macrosomia, but cardiovascular anomalies, urogenital anomalies, and neural tube defects are also reported. Babies born large for gestational age or with fetal macrosomia have a higher incidence of birth injuries associated with large fetal size such as Erb's palsy and shoulder dystocia [8, 26]. Although not statistically significant, there is a suggestion that the incidence of congenital malformations is significantly lower in planned pregnancies [26].

Perinatal mortality in diabetic pregnancies is largely due to an increased risk of stillbirth that can be up to four times higher than in non-diabetic pregnancies [8]. The mechanism for an increased risk of stillbirth is not understood but postulated to be due to maternal and fetal chronic hyperglycemia that is associated with chronic fetal hypoxia. Unfortunately, despite improvements in other aspects of neonatal morbidity, stillbirth rates have not changed over the past 30 years [8, 26, 27].

Despite risk for large or macrosomic babies in diabetic pregnancies, women with diabetic kidney disease have an increased risk for babies to be born with lower birth weight, small for gestational age, and/or intrauterine growth restrictions. This

occurs in both diabetics with microalbuminuria and worsens with worsening kidney disease [13–15, 17, 18, 28]. In diabetic kidney disease, 26.3–50% of babies born were small for gestational age compared to 0–12% of babies born to non-nephrotic mothers [13–15, 17, 18, 28].

Stillbirth rates and perinatal mortality are comparable between pregnancies in women with diabetic kidney disease and women with diabetes without kidney disease. Rates of major malformations are also similar between groups [14]. However, women with diabetic kidney disease are more likely to deliver babies prematurely. There is also a suggestion of increased perinatal morbidity with increased rates of jaundice and respiratory distress in babies born to women with diabetic kidney disease, although not statistically significant [17, 18]. As many more pregnancies in women with diabetic kidney disease are complicated by small-for-gestational age babies instead of macrosomic babies, obstetric complications like shoulder dystocia and Erb's palsy are not reported.

Just as preeclampsia leads to both short- and long-term complications in the mother, infants born prematurely are at increased short- and long-term risks. In the short term, there is increased risk of mortality, respiratory distress, cardiovascular abnormalities, hypothermia, necrotizing enterocolitis, sepsis, retinopathy of prematurity, intraventricular hemorrhage, and neurodevelopmental disabilities such as cerebral palsy [29–31]. Most notably for this chapter, in the long term, infants born prematurely are at a higher risk of developing both CKD and cardiovascular disease in their lifetimes [32, 33]. Approximately two-thirds of nephron development occurs in the third trimester with kidney development concluding around 34 to 36 weeks' gestation [34]. Prematurity and low birth weight are known risk factors for the development of secondary focal segmental glomerulosclerosis, and one meta-analysis found that infants with a low birth weight had a 70% increase in relative risk for the development of CKD [33, 35]. Prematurity and low birth weight associate with low nephron number that has been shown to increase the risk of hypertension in some populations, predisposing these children to cardiovascular disease [36].

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as glucose intolerance after onset of pregnancy. It commonly resolves after pregnancy but has been shown to increase the risk of developing T2DM, hypertension, and cardiovascular disease later in life [37]. There are also concerns for an increased risk of developing CKD. A large meta-analysis was not able to show an increased risk for the development of CKD in the general population, but a subgroup analysis did suggest black women with a history of GDM are at a higher risk of developing CKD [20]. Another study with long-term follow-up of women with GDM in pregnancy did find higher eGFR levels 9 to16 years postpartum, suggesting early glomerular hyperfiltration and kidney disease [38]. This suggests strict risk factor management including mitigating obesity, hypertension, and T2DM in this population can be a potential target to decrease the risk of CKD later in life.

Table 18.1 Summary of the safety of medications in pregnancy for the treatment of CKD from diabetic kidney disease

	Safe	Limited data	Unsafe
Antihypertensives	Methyldopa Labetalol Nifedipine Hydralazine Beta-blockers [a]diuretics	Amlodipine Doxazosin	Angiotensin-converting enzyme inhibitors Angiotensin receptor antagonists
Immunosuppressants	Corticosteroids Hydroxychloroquine Azathioprine Cyclosporine Tacrolimus	Rituximab[b] Eculizumab[c]	Mycophenolate mofetil Cyclophosphamide Sirolimus/everolimus
Anemia in CKD	Iron Erythropoietin		
Mineral bone disease	Calcidiol analogues Calcitriol analogues Calcium carbonate Calcium acetate	Sevelamer Lanthanum Cinacalcet	
Anti-thrombotic/ anticoagulants	Aspirin Low-molecular-weight heparin		

[a]Diuretics should be used carefully due to risk of maternal effective arterial volume depletion and theoretic uteroplacental blood flow compromise
[b]Avoid if other treatment options are available due to risk of neonatal B cell depletion
[c]Benefits for organ-threatening disease are likely to outweigh risk

Treatment of Diabetes and CKD from Diabetic Kidney Disease During Pregnancy

Treatment of DM as well as the complications of CKD from diabetic kidney disease is an important consideration during pregnancy. Several medications that are typically used in the treatment of women with diabetic kidney disease are teratogenic, so close attention to the medication list is critical (see Table 18.1 below). In addition, part of the treatment of the pregnant woman with diabetic kidney disease includes treatment to prevent complications of pregnancy such as preeclampsia.

Preeclampsia Prevention

Women with diabetic kidney disease are considered at high risk for the development of preeclampsia. DM, CKD, and hypertension are all considered high-risk criteria for the development of preeclampsia, and the patient with diabetic kidney disease frequently has all three of these diseases, so preventative strategies should be considered mandatory [39]. Low-dose aspirin (60–150 mg/day) has been shown to reduce the incidence of severe, early-onset preeclampsia, particularly when initiated

before 16 weeks' gestation [40–42]. Current guidelines recommend initiating aspirin therapy between 12 and 28 weeks' gestation [43, 44]. In women with diabetic kidney disease and low calcium intake, calcium supplementation should also be considered based upon a meta-analysis that analyzed trials with at least 1 gram per day of supplementation of calcium [45]. Treatment of hypertension has not been demonstrated to decrease the risk of preeclampsia, but treating hypertension is important to decrease the risk of severe hypertension that increases the risk of adverse cerebral events such as stroke [39].

Antihyperglycemic Treatment

Insulin is the recommended therapy during pregnancy for both T1DM and T2DM. Despite many oral antihyperglycemics being safe for use in individuals with CKD, all oral agents lack long-term safety data in pregnancy [46]. The use of other agents (metformin, sulfonylureas, thiazolidinediones, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, meglitinide inhibitors) is controversial due to concerns for transplacental passage of the drug and/or the drug metabolites and increased insulin resistance in pregnancy. Drug regimens including subcutaneous long- and short-acting insulins are recommended to achieve optimal glycemic control [47].

To achieve glycemic control during pregnancy, it is recommended that diabetic women self-monitor their fasting and post-prandial blood glucose. The A1c target in pregnancy is <6.5%, and the fasting and post-prandial glycemic targets are listed below and are consistent between American Diabetes Association (ADA) and American College of Obstetricians and Gynecologists (ACOG) guidelines [46, 48]. The risk of hypoglycemia is high with intensifying insulin regimens, and these glycemic targets should be relaxed if hypoglycemic episodes occur.

Fasting <95 mg/dL (5.3 mmol/L).
One-hour post-prandial <140 mg/dL (7.8 mmol/L) OR.
Two-hour post-prandial <120 mg/dL.

Hypertension Treatment

Hypertension in pregestational DM, especially in the presence of kidney disease, increases the risk of preeclampsia, preterm delivery, uteroplacental insufficiency, and stillbirth [49]. The goal blood pressure in the setting of pregnancy and diabetic kidney disease is unclear. Hypertension control during pregnancy has been shown to decrease the risk of development of severe hypertension but does not appear to significantly reduce the incidence of other adverse outcomes [50–52]. However, hypertension is a known risk factor for the progression of CKD as well as the

development of cardiovascular disease, so the American Diabetes Association recommends a target blood pressure of 120–135/80–85 for pregnant women with DM in the interest of long-term maternal health [46]. The International Society for the Study of Hypertension in Pregnancy recommends a target blood pressure of 110–140/85 mmHg for pregnant women with chronic hypertension [53].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) remain the cornerstone of the treatment of diabetic kidney disease in non-pregnant women [54]. Despite positive effects for hypertension and proteinuria in non-pregnant diabetics, ACE inhibitor and ARB use is contraindicated in pregnancy. There is some data that suggests an association between these agents and congenital malformations if given in the first trimester [55, 56]. When exposure occurs in the second and third trimesters, they can cause fetal kidney failure, oligohydramnios, death, intrauterine growth retardation, respiratory distress syndrome, pulmonary hypoplasia, limb defects, persistent patent ductus arteriosus, or cerebral complications [57]. Therefore, ACE inhibitors and ARBs should be stopped before conception or at the first positive pregnancy test. In addition, mineralocorticoid receptor antagonists, atenolol, and nitroprusside should all be avoided during pregnancy [58].

Antihypertensives known to be safe in pregnancy include methyldopa, labetalol, nifedipine, hydralazine, diltiazem, clonidine, and prazosin [46, 58]. Methyldopa, labetalol, and nifedipine are typically considered as first-line options [58]. Diuretics such as furosemide and hydrochlorothiazide are typically considered as second-line agents and reserved for women with significant volume overload including pulmonary edema, such as you might see in a patient with CKD. Diuretics have a theoretical risk of causing maternal intravascular volume depletion leading to oligohydramnios and fetal growth restriction; although this has not been proven in studies, they should still be used with close monitoring [59, 60].

Anemia of Chronic Kidney Disease

Anemia is common in pregnancy. First due to the physiologic effects of increased plasma volume in pregnancy resulting in lower hemoglobin concentrations. Beyond normal physiologic effects, iron deficiency is a common cause of anemia in pregnancy. Iron deficiency anemia is associated with increased risk of preterm birth, low birth weight, and small-for-gestational-age newborns [61]. Women with moderate to severe CKD may also have anemia of CKD related to a relative deficit of erythropoietin [62].

Both oral and IV iron supplementations are considered safe in pregnancy. The World Health Organization recommends supplementing 30–60 mg/day of elemental iron starting 3 months before and throughout pregnancy and increased to 120 mg/day in the setting of anemia [63]. IV iron should be considered when hemoglobin levels are <8 g/dL or if the woman is not tolerating oral iron supplementation. The goal ferritin and transferrin saturations are similar in CKD/ESKD in non-pregnant

and pregnant patients with a transferrin saturation of >30% and with a serum ferritin level of 200–300 ng/dL [64].

Erythropoietin (EPO) is believed to be safe for both the mother and the fetus in pregnancy. In vitro studies suggest that recombinant erythropoietin does not cross the placenta [65, 66]. The dosing strategy resembles regimens in non-pregnant patients and is based on the patient's weight. Goal hemoglobin is the same as in non-pregnant patients with a goal to maintain hemoglobin 10–11 g/dL. The risks of EPO administration include flu-like symptoms, conjunctival inflammation, seizures, increased risk of thromboembolic events, and hypertension. Of particular concern is the risk of hypertension in pregnancy with EPO administration, but this is generally responsive to antihypertensive therapy or slightly lowering hemoglobin/hematocrit goal. Gradual correction (2–3% rise per week) and frequent monitoring of response to EPO therapy (every 1–2 weeks) and blood pressure can additionally mitigate these risks [67, 68].

Mineral Bone Disease of CKD

Mineral bone disease in CKD is normally managed with the use of phosphorus binders, vitamin D analogues, and calcimimetics. Vitamin D deficiency is common in pregnancy and is associated with increased risk of preeclampsia and gestational diabetes. There are physiologic changes of vitamin D metabolism in pregnancy, and circulating calcitriol levels are observed to increase during pregnancy [69]. Data on supplementation of vitamin D in pregnancy are inconsistent, but maintenance doses of 400–1000 IU are considered safe during pregnancy. For women with serum calcidiol (25-OH-vitamin D) levels of <20 ng/mL, repletion with cholecalciferol 20,000 IU per week is recommended [70]. Once serum calcifediol levels are replete, activated vitamin D analogues (alfacalcidol, calcitriol) can be continued in pregnancy at a dose that is guided by ongoing measurement of vitamin D, parathyroid hormone, calcium, and phosphorus levels [64, 68, 71].

Severe hyperphosphatemia is not common in pregnant mothers with CKD. In pregnant patients on dialysis, the increased amount of dialysis that is needed in pregnancy usually obviates the need for phosphorus binder use. In cases of CKD in pregnancy where hyperphosphatemia persists, calcium phosphate binders (calcium carbonate, calcium acetate) are preferred. Non-calcium phosphate binders (sevelamer hydrochloride, lanthanum carbonate) and calcimimetics (cinacalcet) are not considered safe in pregnancy due to limited data [64, 70].

Postpartum Treatment

The specialized care of the pregnant patient with diabetic kidney disease does not conclude when she has successfully delivered her infant. Diabetes and blood pressure control remains important in the postpartum period and is affected by the

woman's decision of whether or not to breastfeed. Multiple antihypertensives have been shown to have no adverse effects in the setting of lactation, of which, most notably for the woman with diabetic kidney disease are the ACE inhibitors captopril and enalapril [58]. Labetalol and nifedipine can also be continued postpartum. Insulin resistance of pregnancy quickly disappears after delivery, so insulin requirements substantially decrease with delivery and monitoring for hypoglycemia is very important [46]. Statins should continue to be withheld during lactation.

Preconception Counseling

Women with diabetic kidney disease have to make complex, difficult reproductive choices. An ill-timed pregnancy can lead to progression of CKD, increased maternal and fetal risks, and exposure of the fetus to teratogenic medications. Thus, it is critical for their health-care providers to provide guidance and to empower women with all of the knowledge they need to make these choices. This knowledge includes the potential risks of pregnancy, how to time pregnancy to decrease risks, fertility considerations, and a review of their medications for teratogenic effects. We have previously outlined the potential risks of pregnancy to both the mom and the infant above, and we have summarized them in Table 18.2. Here, we will focus on timing the pregnancy, fertility considerations, and review of medications.

Preconception control of glycemia, hypertension, and proteinuria is important for improving outcomes and should form a base for pregnancy timing. Poor glycemic control increases the risk of congenital malformations, preeclampsia, and

Table 18.2 Summary of pregnancy counseling by CKD stages [5]. Reproduced with permission from https://www.sciencedirect.com/science/article/pii/S0272638619307371

Pregnancy counseling considerations	Stage 1 CKD	Stage 2 CKD	Stage 3 CKD	Stage 4–5 CKD	Transplantation	Intensive HD
% progression	8%	13%	16%	20%	Loss of graft Function Possible with Scr >1.5 mg/dL	NA
New onset HTN	8%	18%	47%	50%	54%	12%
Worsening proteinuria or preeclampsia	21%	38%	87%	70%	25–30%	20%
Average birth weight, g	2967	2484	2226	1639	2572	2118
Low birth weight (<2500 g)	13%	18%	19%	50%	42%	44%
Average gestational age	38	36	34	34	36	36
Preterm delivery						
<37 weeks	24%	51%	78%	89%	50%	65%
<34 weeks	7%	21%	38%	44%	20%	41%

Abbreviations: *CKD* chronic kidney disease, *HTN* hypertension, *NA* not applicable, *Scr* serum creatinine

preterm delivery [72]. The American Diabetes Association 2020 standards of care recommends a preconception Hgb A1c of <6.5% as it is associated with the lowest risk of congenital abnormalities [73]. Small studies in women with diabetic kidney disease have suggested that reduction of proteinuria and strict control of blood pressure with an ACE inhibitor preconception may also improve maternal and fetal outcomes [16, 74, 75].

While pregnancy risks increase as a woman's CKD worsens, fertility declines, so it is likely to be more and more difficult for a woman to get pregnant as her diabetic kidney disease progresses. Fertility does improve with improved kidney function such as what happens when a woman with advanced CKD or ESKD undergoes a kidney transplant or starts an intensified dialysis regimen [76, 77]. Given the increasing risks with advanced CKD as well as diminished fertility, women with advanced CKD may be best supported by waiting until a kidney transplant is performed, age permitting. Current recommendations suggest that if a woman waits at least a year after kidney transplant to become pregnant and if she has had no episodes of rejection in the previous year, has adequate allograft function with a serum creatinine less than 1.5 mg/dL, has minimal or no proteinuria, is on pregnancy-safe therapeutic levels of immunosuppression, and has had no recent infections that could affect the fetus, pregnancy should not jeopardize allograft survival [78]. If age does not permit, utilizing an intensive dialysis regimen can improve fertility as well as pregnancy outcomes [79].

Contraception counseling is an important part of proactive family planning as it allows for women to time their pregnancy for the best possible outcomes. In addition, some contraceptives can worsen blood pressure and proteinuria and thus affect the woman's underlying kidney disease. Unfortunately, few women with CKD receive pregnancy or contraception counseling [80, 81]. Contraceptive choices are the same for healthy women and women with CKD. They include, in order of increasing effectiveness, barrier methods, hormonal methods, intrauterine devices, and sterilization. See Table 18.3 for a summary of the pros and cons of each of these methods. Most notably estrogen-containing contraceptives are considered relatively contraindicated in women with DM. Estrogen-containing contraception has been shown to increase blood pressure by as much as 8/6 mmHg [82]. In addition, studies have shown worsening proteinuria in women on estrogen, which could hasten the decline of kidney function in women with diabetic kidney disease [83]. Before starting an estrogen-containing contraceptive, a patient with diabetic kidney disease should be counseled on these risks and should be monitored for signs of uncontrolled hypertension or worsening kidney disease.

Medication counseling is a critical part of preconception counseling. Many medications that are core to treating a woman with diabetic kidney disease are teratogenic, namely, ACE inhibitors, ARBs, and statins. Newer, emerging treatments for diabetic kidney disease including sodium-glucose linked transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists have not been studied in pregnant women, but animal studies have shown adverse pregnancy outcomes with these agents [84]. Women of reproductive potential should all be counseled on the teratogenic effects of these medications and be told to avoid pregnancy while taking these medications. In women planning pregnancy, these medications should

Table 18.3 Summary of pros and cons of different contraception choices [5]. Reproduced with permission: https://www.sciencedirect.com/science/article/pii/S0272638619307371

Contraception option	Pro	Con
Estrogen/ progestin combination	Multiple options to fit a patient's preferences (pills, patch, vaginal ring); effective	Increases the risk for VTE; cannot use in women with Significant CVD and smokers older than 35 years; SLE, DM, HTN, and hypertriglyceridemia are relative contraindications
Progestin only	Less risk for VTE than estrogen/ progestin combination	Not as effective as estrogen/progestin combination if not taken consistently within a 3-h window each day
Barrier methods	Male latex condoms are the only options outside of abstinence that decrease the risk for transmission of sexually transmitted diseases	Higher failure rates than all other methods, but improved if used with a spermicide
IUD	No medication to remember taking; effective	May cause peritonitis in patients on PD; rare cases of uterus perforation; expulsion occurs in w5% of women
Sterilization	Can be either the female patient or her male partner; very effective with low failure rate	Should be considered permanent

Abbreviations: *CVD* cardiovascular disease, *DM* diabetes mellitus, *HTN* hypertension, *IUD* intrauterine device, *PD* peritoneal dialysis, *SLE* systemic lupus erythematosus, *VTE* venous thromboembolism

be stopped prior to conception. In the setting of an unplanned pregnancy, these medications should be stopped immediately upon confirmation of pregnancy. In addition, while doing preconception medication counseling, this is a good time to discuss the role of aspirin for preeclampsia prophylaxis.

Special Considerations: Kidney Biopsy During Pregnancy

While DM represents the most common cause of kidney disease, women with DM can have other causes of their kidney disease. These other causes can present during pregnancy, and in a woman who has not undergone regular screening preconception, it can be difficult to distinguish between diabetic kidney disease and other causes of proteinuric kidney disease. Preeclampsia needs to be considered in the differential if the woman is past 20 weeks' gestation. Other potential causes may be suggested based upon history, physical, and laboratory testing. Rarely a kidney biopsy is indicated during pregnancy to establish the cause of kidney disease. The decision to biopsy during pregnancy versus waiting till after delivery is typically based upon the stability and severity of the kidney dysfunction, the current stage of pregnancy, and the suspected underlying disease. Pregnancy is not a contraindication to kidney biopsy [85]. There does appear to be an increased risk for biopsy

complications when compared to the postpartum period [86]. However, this same systematic review also reported that biopsy during pregnancy led to therapeutic changes in almost two-thirds of patients.

Conclusion

Pregnancy represents an astounding orchestration of different physiologic changes in a woman's body that lead to several kidney-related adaptations. Not surprisingly, women with CKD, including those with diabetic kidney disease, are at increased risk of adverse pregnancy outcomes. However, with good preconception care, prenatal care, and postnatal care, better outcomes can be seen. Preconception counseling is therefore of utmost importance in all women with diabetes, including those with diabetic kidney disease, that are of childbearing potential.

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Chapter 19
Kidney Transplantation and Kidney Pancreas Transplantation

Sixto Giusti and Vecihi Batuman

Introduction

Diabetes is a global health emergency, with 425 million people affected in 2017 and a projection for 629 million by 2045. Nearly half develop diabetic kidney disease, and its prevalence is rising progressively in parallel with the overall diabetes epidemic, primarily driven by type 2 diabetes [1]. In a recent report based on data from 142 countries, the global percentage of the prevalent end-stage renal disease (ESRD) patients with diabetes increased from 19.0% in 2000 to 29.7% in 2015 worldwide, while the percentage of incident ESRD patients due to diabetes increased from 22.1% to 31.3% [2]. Type 2 DM is now the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [3] and accounts for nearly 95% of all cases of DKD [4]. According to the 2020 United States Renal Data System (USRDS), prevalent ESRD among all patients with a diagnosis of DM exceeded 300,000 in 2018 in the USA, representing ~38% of all patients on dialysis [5]. Similarly, data from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) show that nearly 40% of patients on transplant waiting list in the USA had DM in 2019 [6] (see Fig. 19.1).

Type 2 DM is a major risk factor for the development of cardiovascular (CV) and kidney disease and is responsible for a significant number of hospitalizations, morbidity, and mortality. Kidney transplant has emerged as the preferred mode of renal replacement for ESRD, including patients with diabetic kidney disease. Transplant

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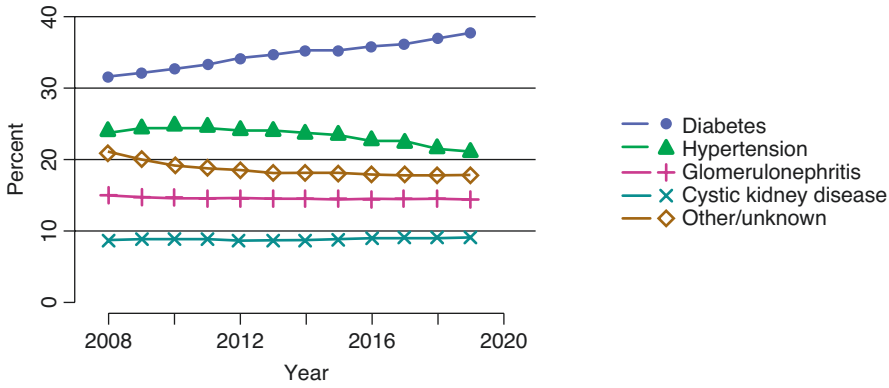

Fig. 19.1 Distribution of adults waiting for a kidney transplant by diagnosis. Candidates waiting for transplant at any time in the given year. Candidates listed at more than one center are counted once per listing. Active and inactive patients are included [6]

provides both better quality of life and survival advantage compared to dialysis [7, 8]. For example, receiving a deceased donor kidney increases a patient's chances of survival by twofold and a living-donor graft by fourfold compared to those who remain on the waiting list [9]. In an earlier analysis, transplant increased the projected life expectancy in kidney transplant recipients by 10 years compared with those who remained on dialysis [8].

Kidney and/or pancreatic transplantation has now proved to be the treatment of choice for those patients. Kidney and pancreas transplantation not only solves the problem of organ failure but also achieves insulin independence and reverses the metabolic complications of diabetes. Combined kidney and pancreas transplantation has the best long-term outcome in patients with advanced or end-stage kidney disease [7].

In the past, pancreatic transplant was not offered to type 2 DM patients. However, as later data showed that simultaneous pancreas-kidney (SPK) transplant has resulted in similar outcomes in both type 1 and type 2 DM patients, there is increasing acceptance of type 2 DKD patients for this modality. Still, pancreas transplant is rarely offered to type 2 DM patients; the rate of pancreas transplant in type 2 DM patients increased from 2% in 1995 to only 7% in 2010 [10]. There was some further modest increase after the 2014 revision in the pancreas allocation system (PAS) (see Fig. 19.2). According to the Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients (OPTN/SRTR) 2019 annual report, the total number of pancreas transplants in 2019 was 1015, slightly lower than the previous year, but remained somewhat flat for the past 5 years [11]. Most of these involved simultaneous pancreas-kidney (SPK) transplants followed by pancreas-after-kidney (PAK) and pancreas transplant alone (PTA) [11].

Although the recently introduced agents, mainly the SGLT2 inhibitors, raise the expectations that they will further slow the progression of DKD to advanced stages, there will still be a need to implement renal replacement for many patients. The

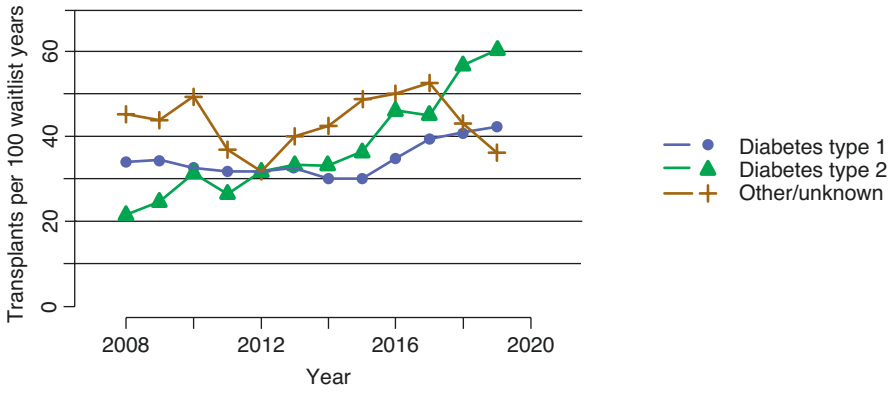

Fig. 19.2 Deceased donor pancreas transplant rates among adult wait-list candidates by diagnosis. Transplant rates are computed as the number of deceased donor transplants per 100 patient-years of wait time in a given year. Individual listings are counted separately [11]

purpose of this chapter is to briefly outline the transplant options for patients with advanced or end-stage diabetic kidney disease.

Transplant Options for Patients with Diabetic Kidney Disease

Diabetic kidney disease represents an increasing percentage of chronic kidney disease populations worldwide. The demand for renal replacement therapy is also on the rise as cases of diabetes have reached epidemic proportions [1, 2, 6]. Kidney transplantation has emerged as the clearly superior alternative for all ESRD of any etiology, especially for DKD, which carries a higher CVD risk and other comorbidities [1, 12–14]. Kidney transplantation is now an established modality and becoming increasingly available, with nearly 300,000 transplants performed since 1970 [9]. However, demand remains high such that barely a quarter of patients on the wait list receive a deceased donor kidney transplant within 5 years [6]. Although there is a recent trend toward a slightly increased availability of living-related donor kidneys, only a small fraction of patients benefit from this alternative [6].

Transplant options (Fig. 19.3) include kidney transplant alone, living or deceased donor (KT), simultaneous pancreas and kidney (SPK) transplant, and pancreas-after-kidney (PAK) transplant [7, 15, 16]. These treatment options generally offer markedly superior survival benefits for ESRD patients, including those with diabetic kidney disease. One-year KT survival in diabetic patients is now near 90% for deceased donors (DD) and 96% for living donors (LD) [7]. Pancreas transplantation has become increasingly successful in recent years due to advances in surgical outcomes and immunosuppression protocols [16–19]. One-year pancreas graft survival is now nearly 95% when performed as a simultaneous pancreas-kidney (SPK) transplant and 86% when performed as a pancreas after KT (PAK). In one single center,

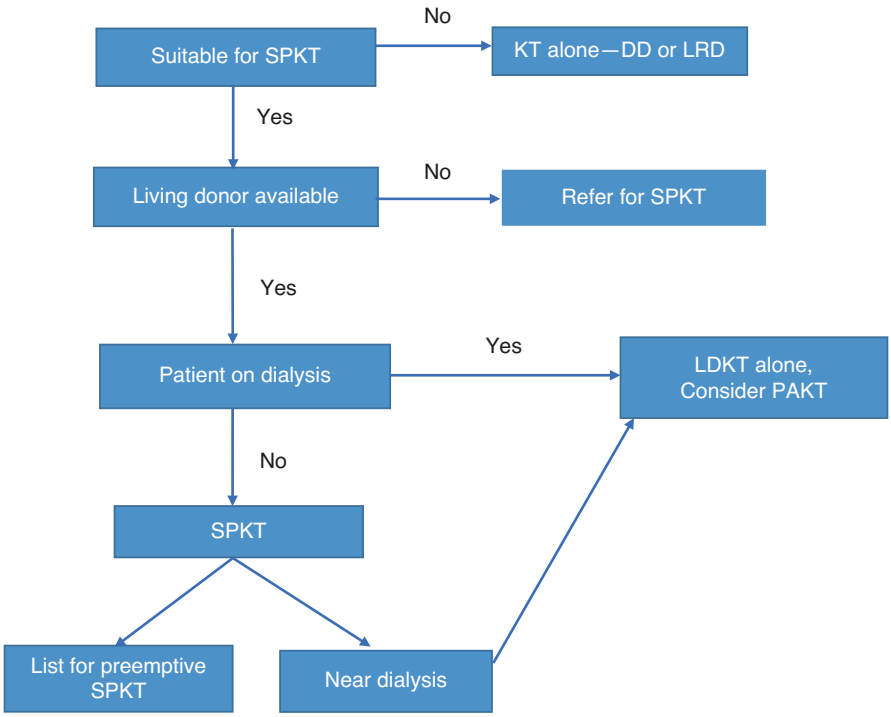

Fig. 19.3 Options for kidney transplant for patients with diabetic kidney disease. Adapted from A.C. Wiseman [16]. (*KT* kidney transplantation, *DD* deceased donor, *LRD* living-related donor, *SPKT* simultaneous pancreas-kidney transplantation, *LDKT* living-related kidney transplant, *PAKT* pancreas after kidney transplant)

mortality risk for diabetic patients was two- to threefold lower in those who received a pancreas transplant [6, 7, 20]. Other centers report similarly successful long-term outcomes [21, 22].

During the early years of transplantation, DKD was considered a relative contraindication for transplant because of the higher cardiovascular risk and obesity. This attitude has now reversed since Wolfe et al. demonstrated that renal transplantation provided a marked survival advantage for diabetic ESRD patients and reduced mortality by 73% compared with patients remaining on the wait list. The projected life expectancy was more pronounced for younger diabetics (presumed type 1 DM) with a gain of 17 years, and the gain was also significant even for patients older than 60 years (presumed type 2 DM) [8, 13]. Long-term follow-up analyses confirm superior outcomes and significant survival benefit for ESRD patients associated with type 1 DM [23].

The evidence supports that preemptive transplant is superior to dialysis or to transplant after initiation of dialysis and results in improved recipient survival [1, 3, 24]. Patients in the USA qualify for kidney transplant listing when their glomerular filtration rate (GFR) is <20 ml/min or when they have initiated maintenance

dialysis. Despite the distinct advantages of preemptive transplant, the rates remain disappointingly low in the USA [25]. Lack of clear guidelines on the timing of referral, pre-dialysis patient education, and socioeconomic factors are among the key barriers [25].

Transplant programs have considered obesity [body mass index (BMI) >30–35 kg/m2] as a relative contraindication for transplantation in diabetic patients because of inferior outcomes for both KT and SPK transplant, mainly due to surgical complications. Some centers view only morbid obesity (BMI >40 kg/m2) as an absolute contraindication. Recent advances in bariatric surgery can ameliorate this contraindication and make even obese type 2 DM patients eligible for transplantation [13].

Patient Selection and Kidney Transplant

For optimal outcomes, a careful pre-transplant evaluation and risk screening are essential. Each modality has its advantages and disadvantages depending on patient selection (Table 19.1). As the waiting list for kidney transplantation continues to grow, the need for selecting appropriate candidates for transplant becomes fundamental. To maximize the success rates of transplant, a careful review and evaluation of coexisting medical and psychosocial comorbidities should be performed to intervene, if possible, before the procedure [26].

It is important to evaluate patients carefully for contraindications including recent or active malignancy, active infection, advanced atherosclerotic cardiac and

Table 19.1 Comparison of transplant options for diabetic kidney disease

Modality	Pros	Cons
DDKT	Superior survival compared to dialysis options	Graft and patient survival not as good as other transplant options
LDKT	Better graft and patient survival; can be done before initiating dialysis or it reduces time on dialysis	Does not help with glycemic control
SPK	Achieves insulin independence; median pancreas graft survival of >10 years	More complex surgery with higher complication and mortality rates
PAK	Achieves insulin independence	Requires two separate surgeries, increased early post-op mortality after pancreas transplant
PTA	Achieves metabolic control, prevents microvascular complications including DKD	Suitable only for insulin-dependent diabetics without kidney disease
Islet cells	Prevents diabetic kidney disease, no surgery involved	Technique still not fully established engrafting is short-lived, requires repeat procedures

DDKT deceased donor kidney transplant, *LDKT* living donor kidney transplant, *SPK* simultaneous pancreas-kidney transplant, *PAK* pancreas after kidney transplant. Adapted from A. C. Wiseman [15]

vascular disease, alcohol-drug dependence, psychiatric disease, and morbid obesity [7, 13]. If significant coronary artery disease is present, transplantation can still proceed after appropriate therapy, which may include coronary artery revascularization. As noted above, severe obesity is no longer an absolute contraindication. Morbidly obese patients can become eligible for transplant after bariatric surgery [13].

The current guidelines suggest that transplant candidates should be evaluated carefully and in an unbiased multidisciplinary setting, involving physicians, surgeons, psychologists, social workers, financial counselors, and dietitians, and sometimes the patients. This process may take considerable resources and time depending on the extent of testing needed for each patient. At the end of the evaluation, patients should be discussed at a multidisciplinary Selection Committee for a consensus agreement on the final listing [27].

As the demand for kidney transplant is rising, there is a shortage of available kidneys [6]. Living donation accounts for one-third of kidney transplants performed in the USA, showing a remarkable increase in the annual number of living donors from 1988 to 2004, although there is a recent trend toward a decline [28–30]. Family members have usually been the main source of living donations, although unrelated donations from friends and coworkers have recently increased. Altruistic anonymous donations from strangers are also increasing. Potential living donors need a comprehensive and cautious evaluation to minimize the risks in a healthy altruistic donor who is willing to undertake a major surgical procedure to help another [31]. Kidney paired donation, a national United Network for Organ Sharing (UNOS)-sponsored swapping of incompatible donors, has facilitated multiple living donor transplants, but the impact on the number of transplants has been modest [6, 28, 29].

Pancreas Transplantation

The first human pancreas transplant was performed in 1966 by Dr. Lillehei at the University of Minnesota [32]. The procedure was performed simultaneously with a kidney transplant in a young female with diabetic kidney disease. Unfortunately, the patient could remain insulin-free for only a few weeks. Although other pancreas transplants were performed over the next few years, the success rates were initially low. But later improvements in surgical techniques, immunosuppressive medications, and organ donor management have allowed pancreatic transplantation to become a well-accepted and commonly performed procedure [21].

Pancreas transplantation in conjunction with kidney transplantation, either simultaneously or after kidney transplantation, has proved valuable especially for DKD patients with type 1 DM and for some type 2 patients as well [7, 17, 33]. Pancreas transplant alone in type 1 DM patients before the onset of kidney disease may be particularly helpful in preventing kidney disease and other microvascular complications of diabetes and avoid the need for renal replacement [34, 35]. Based on 2004 to 2015 data, patient survival rates for SPK, PAK, or PTA ranged from 96

to 99% at 1 year, 89 to 91% at 5 years, and 70 to 80% at 10 years postoperatively [20].

Pancreatic transplantation can achieve improvements in metabolic disorders, including glucose and glucagon metabolism. Secondary complications of diabetes also show improvement, including improvement of left ventricular function and reversal of diastolic dysfunction [36]. Improvements in DKD [37], peripheral and autonomic diabetic neuropathy, possible diabetic retinopathy [37, 38], and serum triglyceride and low-density lipoproteins are also among the expected benefits [39].

Simultaneous pancreas-kidney (SPK) transplant initially carries a high mortality risk relative to living donor kidney recipients through 18 months posttransplantation, likely related to the surgical procedure complications. But the risk improved after the early postoperative period with better long-term outcomes [40]. A UNOS database review of all adult pancreas and kidney-pancreas transplants between 1996 and 2012 showed that graft survival was the best in adults 40–49 years of age [40].

Indications for Pancreas Transplants

The most common indication for a pancreatic transplant is insulin-dependent diabetes mellitus (IDDM). In most cases, patients have classic type 1 diabetes mellitus, an autoimmune disease with the presence of anti-insulin or anti-islet cell antibodies. Patients who develop IDDM from previous pancreatic resections or chronic pancreatitis have also received pancreas or islet cell transplants [41–43]. Many of these patients will have complications of IDDM, including hypoglycemic unawareness, diabetic ketoacidosis, as well as other organ sequelae such as kidney disease, retinopathy, and neuropathy [38, 39].

In the past, type 2 diabetes mellitus was considered a contraindication for pancreatic transplant, despite its proven success in type 1 diabetics. The presence of considerable overlap of clinical presentation of both types especially in the setting of renal failure, over-reliance on the presence of detectable C peptide, which is no longer considered reliable in determining DM type, and incomplete understanding of the pathogenesis were probably the main barriers [44]. Recently, there has been recognition of adult-onset diabetes that is insulin responsive [45–47]. Although these patients may previously have been characterized as type 2 diabetics, they show features of type 1 patients. They often are not obese, and they develop ketoacidosis and retinopathy. Some have even demonstrated late onset of insulin antibody development. Syndromes such as latent autoimmune diabetes in adults (LADA) or maturity-onset diabetes of the young (MODY) fall in this category [1, 45–48]. Such patients were previously classified as type 1½ diabetics, but recognition of these syndromes would allow these patients to benefit from a pancreas transplant as well. These diabetes variants clinically behave similarly to type 1 diabetes and benefit from pancreas or islet cell transplantation. There is growing evidence that these specific categories of type 2 diabetes patients with overlapping features of type 1

diabetes may benefit from a pancreas and kidney transplant. Increasing numbers of transplants are now offered to such patients [13, 41, 49, 50].

In most instances, pancreas transplants are performed in conjunction with a kidney transplant, either simultaneous (SPK) or pancreas after kidney (PAK), with good success rates [13, 33, 51]. The presence of diabetic renal disease with a GFR of less than 20 mL/min/1.73 m^2 or with the need to initiate dialysis is an indication for a kidney transplant as well.

The workup for a transplant candidate is exhaustive and like that of the kidney transplant recipient (see above) may consume considerable time and effort. Identification and management of the various sequelae of diabetes before the planned surgery are essential to minimize the risk of perioperative complications, including graft failure, infection, and death. In most centers, candidates are usually younger (<50 years of age) and non-obese (BMI <30). Results of pancreas transplants have not been as good in older or obese patients [52, 53].

Pancreatic Islet Cell Transplantation

Pancreas alone or islet cell transplant has emerged as another option for type 1 diabetics or MODY or LADA cases without renal disease. Successful pancreas transplant or beta islet cell replacement achieves excellent glycemic control and prevents the microvascular complications of diabetes including retinopathy, neuropathy, and kidney disease [34, 35, 54, 55]. There has been a long-standing interest in islet cell replacement since the turn of the nineteenth century, but the modality has not been clinically feasible until the development of the Edmonton Protocol in 2000 [56]. The harvested cells are transplanted via the portal vein and engraft in the liver and can achieve insulin independency. However, many challenges remain. Often, repeat islet cell infusions are necessary. Harvesting adequate numbers of cells is inefficient and often requires multiple donors. In the case of non-autologous transplants, immune reactivity and the need for anti-rejection treatment may be a problem [11, 56, 57]. There is ongoing active research in multiple fronts, including genetically modified islet cells, encapsulating islet cells in protected lattices, xenotransplants using genetically modified porcine cells, or using pluripotent stem cells [56, 58, 59]. With continued progress in this non-surgical technique, we can imagine a breakthrough in the treatment of diabetes and preventing its devastating complications including kidney disease.

Posttransplant Diabetes Mellitus (PTDM)

A major complication of kidney transplantation is the development of posttransplant posttransplant diabetes mellitus, which poses an important risk factor for cardiovascular disease and other diabetic complications, including kidney disease after transplantation [60, 61]. New onset diabetes mellitus in the posttransplantation setting (PTDM), regardless of the timing of detection or whether it was present undetected prior to transplantation or not, develops in 10–40% of patients [62–64] (see Fig. 19.4).

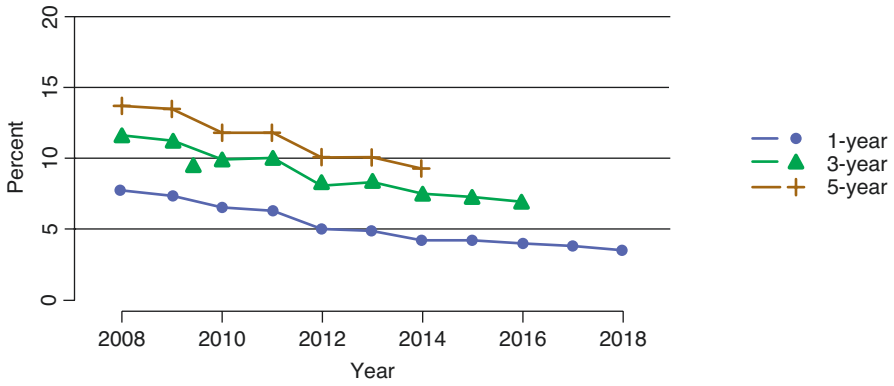

Fig. 19.4 Posttransplant diabetes among adult kidney transplant recipients. Percentage of adult deceased donor kidney recipients who were nondiabetic at transplant and developed diabetes post-transplant. Posttransplant diabetes is reported on the Transplant Recipient Follow-up form. Death and graft failure are treated as competing events [6]

Multiple factors contribute to the increased risk of PTDM. Immunosuppressive medications including steroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors are the main offenders. Higher doses of steroids have been associated with increased risk of PTDM. Both tacrolimus and cyclosporine also can increase the risk of PTDM, with a higher risk associated with tacrolimus than cyclosporine [64]. Other factors predisposing to PTDM include pre-transplant impaired glucose tolerance [65], obesity [66], hypomagnesemia [67], increased age (≥40 to 45 years), African American race, and deceased donor kidney transplantation [63, 65, 66, 68].

Posttransplantation diabetes mellitus (PTDM) leads to increased rates of cardiovascular disease mortality [68, 69], graft rejection, and decreased survival. Diabetic complications, such as ketoacidosis, hyperosmolar hyperglycemic state, neuropathy, diabetic kidney disease, and infection, can also occur [68, 70]. Often glycemic control can be achieved successfully using oral agents, especially dipeptidyl peptidase-4 (DPP-4) [71, 72]. Similarly, a recent meta-analysis showed that SGLT2 inhibitors effectively lowered HbA1c, reduced body weight, and helped preserve kidney function in transplant patients with PTDM and good kidney function without adverse events [73]. Optimal glycemic control and cardiovascular risk management improved outcomes markedly since 1996 [70, 74].

Summary and Conclusions

When measures to forestall kidney disease fail and patients reach advanced stages requiring renal replacement therapy, transplantation is distinctly superior to either peritoneal or hemodialysis. Transplant options include deceased donor or living donor kidney or combined pancreas and kidney transplant (simultaneous or

pancreas after kidney transplantation). Simultaneous pancreas-kidney transplant replaces kidney function and corrects the underlying metabolic disorder and affords the best survival advantage in the long run despite an initial increase in postsurgical mortality. Pancreas transplant alone is an option for type 1 and other forms of insulin-dependent diabetes patients and can prevent serious microvascular complications of diabetes, including kidney disease. Pancreatic islet cell transplantation is a nonsurgical technique with various configurations in experimental stages that promise optimal insulin independence but is not yet widely available clinically.

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Chapter 20
Diabetic Kidney Disease and Covid-19

Luis D'Marco

Introduction

Diabetic kidney disease (DKD) is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM), and approximately 30–40% of these patients develop DKD. In this regard, chronic kidney disease (CKD) is associated with all-cause and cardiovascular mortality in patients with DM. Furthermore, patients with DM are prone to infections due to immune dysfunctions [1]. Besides, patients with DKD express a chronic systemic inflammation that contributes to the immunosuppressed state that accounts for infectious complications, determining the morbidity and mortality associated with these patients.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease in 2019 (COVID-19) pandemic, has emerged as one of the most significant infectious diseases of this century. Although governments everywhere plan for pandemics because their impact can cause sharp shocks to economies and societies, the COVID-19 pandemic represents a real challenge and will require a substantial surge in health system capacity [2, 3]. Interestingly, this novel coronavirus can be transmitted quite efficiently, affecting healthy adults and the elderly with higher rates of complications than other pandemics [4].

Evidence reported that COVID-19 represents a real threat for those patients with comorbidities such as diabetes, obesity, hypertension, and cardiovascular and kidney disease [5, 6]. Indeed, more severe cases with higher mortality rates have been reported in older patients and those with chronic illnesses, such as cardiovascular disease. Thus, patients affected with CKD, mainly those with DKD, are prone to be

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affected since the rate of all types of infections and cardiovascular disease is more common than the general population [7]. The vulnerability of diabetic patients to infections with different viruses is well known. The evidence includes studies from the 2009 influenza A (H1N1) pandemic [8], SARS-CoV [9], and Middle East respiratory syndrome coronavirus (MERS-CoV) [10].

Diabetic Kidney Disease and SARS-CoV-2: An Immunological Approach

Currently, the rapid spread of the SARS-CoV-2 pandemic, especially among DKD patients, deserves closer scrutiny. However, as with many other conditions, marked alterations in the immune system have been observed in those patients affected by kidney diseases. Beyond the immune system impairment, special attention must be focused on the uremic state, excessive oxidative stress status due to the retention of a plethora of toxins, and the accumulation of oxidative products that could worsen the patient's condition once the patient gets infected.

It is known that SARS-CoV-2 targets the respiratory cells; however, other organs might also be affected by the invasion of the virus, namely, the kidneys and heart, among others. Furthermore, COVID-19 is considered an endothelial disease. A recent investigation identified that kidneys are organs with a high vulnerability of damage according to angiotensin-converting enzyme 2 (ACE2) expression [11]. Besides, arterial smooth muscle and myocardial cells are also susceptible to SARS-CoV-2 damage (Fig. 20.1).

Of note, angiotensin-converting enzyme inhibitors (ACEi) do not inhibit ACE2 since ACE and ACE2 are different enzymes with two different active sites [12, 13]. Moreover, although angiotensin II type 1 receptor blockers (ARB) can upregulate ACE2 in experimental models, the evidence is not always consistent and differs among the diverse angiotensin II type 1 receptor blockers [12]. Although the literature is still controversial, ACEi/ARB treatment does not affect the morbidity and mortality of COVID-19 combined with cardiovascular disease [14]. To date, the actual evidence is unclear regarding a direct mechanism of kidney involvement of COVID-19. Nevertheless, mechanisms including a cytokine storm syndrome through sepsis pathways or direct viral renal tubular cell injury have been reported (Fig. 20.2) [15, 16]. At present, the main expression of renal damage in COVID-19 patients appears to be acute. However, some cases of albuminuria/proteinuria and/or hematuria may be associated with endothelial dysfunction observed in these patients (Fig. 20.3) [17, 18].

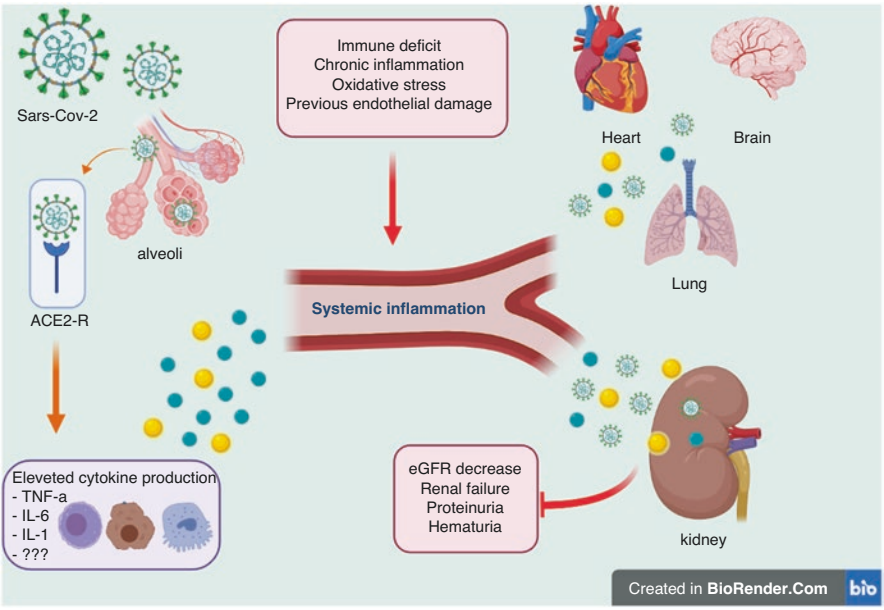

Fig. 20.1 SARS-CoV-2 binds to the ACE2 receptor (ACE2-R). In some cases, the elevated cytokine production leads to an acute over chronic systemic inflammation. Susceptible patients, such as those with CKD and DKD, preexisting immune deficiency, and other chronic conditions, are prone to the well-known "cytokine storm" observed in COVID-19. Similar to other organs, the kidneys are susceptible to be affected since they express the ACE2-R. Besides acute renal involvement, there is growing evidence that proteinuria and/or hematuria with CKD progression may be associated with the chronic endothelial dysfunction observed in these patients

Diabetic Kidney Disease and SARS-CoV-2: A Therapeutics Approach

Beyond the recommended classical or new therapeutic agents commonly used in the treatment of DM and management of COVID-19, the possible benefits of many of these approaches require some discussion. Currently, the management of diabetic patients acutely affected by COVID-19 is complex and not clearly defined. First, improving glycemic control should be of utmost importance in patients with COVID-19 and preexisting type 2 (T2) DM. Thus, the goal of "organ protection" raised during the SARS-CoV-2 pandemic may be achieved through the pleiotropic effects of various therapeutic regimens directed against this novel coronavirus (Fig. 20.4).

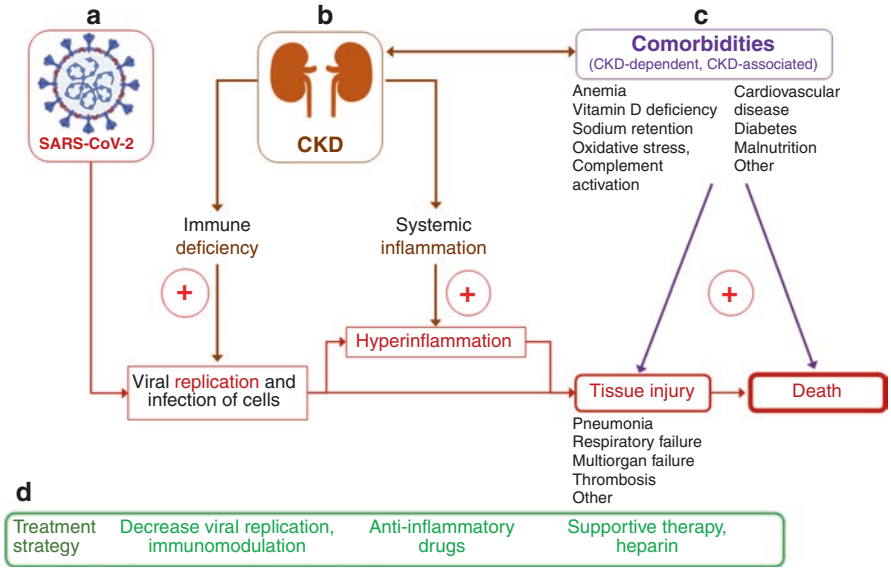

Fig. 20.2 Interaction between SARS-CoV-2 and CKD. (**a**) Infection by SARS-CoV-2 results in viral entry into cells and viral replication, causing tissue injury. Tissue injury is aggravated by a severe inflammatory response, eventually leading to death. (**b**) CKD is characterized by both evidence of immune deficiency, which may facilitate viral replication and expansion, and systemic inflammation, which may aggravate hyper-inflammation observed in severe cases. (**c**) Furthermore, CKD is frequently associated with comorbidities dependent or associated with CKD, such as diabetes. These comorbidities may also contribute to a more severe disease leading to death. Thus, there is a biological plausibility supporting the empirical evidence of higher mortality of COVID-19 in CKD patients. (**d**) Current therapy aims to decrease viral replication and boost antiviral defenses, limiting hyper-inflammation and supporting measures and thrombosis prevention. Currently, these measures are similar for CKD and non-CKD patients. Research is needed for the optimization and individualization of the therapeutic approach to the CKD state. Adapted from D'Marco et al. [16]

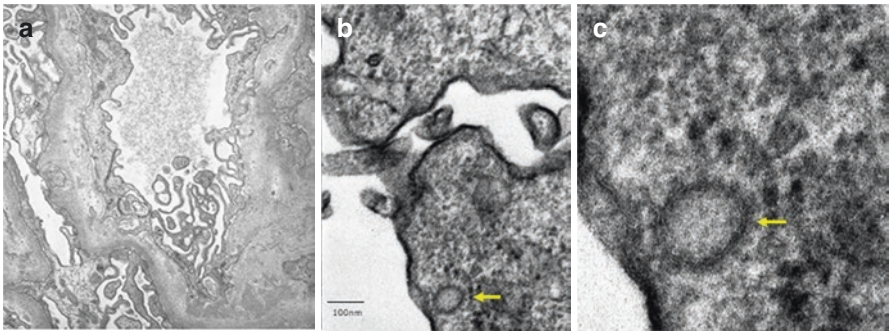

Fig. 20.3 An ultrastructural study from a patient who developed acute IgA glomerulonephritis after COVID-19. Electron-dense deposits with mesangial and para-mesangial location (**a**). Viral particles with a double contour membrane and a crown of 120 nm diameter in podocyte cytoplasm (arrows) (**b** and **c**). Adapted from Perez et al. [18]

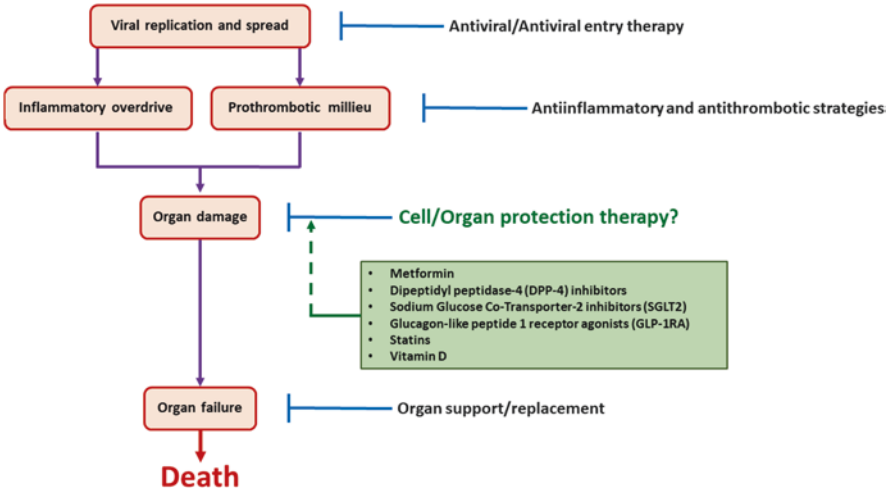

Fig. 20.4 The pathogenic basis of current therapeutic approaches to COVID-19 and the potential uses of antidiabetics and other drugs used in diabetic kidney disease patients. Adapted from Fernandez et al. [32]

Metformin and DPP-4 Inhibitors

Metformin, a first-line antidiabetic drug in the T2DM therapeutic arsenal, has antiproliferative and immunomodulatory effects. Emerging evidence found that treatment with metformin in T2DM patients with COVID-19 is not harmful and could possibly be beneficial. In the CORONADO trial (Coronavirus Disease and Diabetes Outcome), Cariou et al. showed that patients on metformin treatment had a lower death rate than all other antidiabetic agents [19]. Similarly, Luo et al. performed a retrospective study in patients with COVID-19 and suggested that in-hospital mortality was significantly lower in those receiving metformin [20]. Of interest, metformin activates AMP-activated protein kinase (AMPK) by causing its phosphorylation and regulates glucose and lipid metabolism [21]. Thus, downstream of AMPK, activation of PI3K/AKT/mTOR pathway seems to play a major role in MERS-CoV infection [22]. Therefore, metformin may offer benefits in T2DM patients with COVID-19 by indirectly mediating the mTOR pathway.

Dipeptidyl peptidase-4 (DPP-4) inhibitors exert a hypoglycemic effect by inhibiting the degradation of endogenous peptides such as glucagon-like peptide 1 (GLP-1), a glucose-dependent insulinotropic peptide. There is evidence that DPP-4 inhibitors offer a wide range of cardiovascular benefits by ameliorating risk factors such as high blood pressure, postprandial lipemia, inflammation, oxidative stress, and platelet aggregation [23, 24]. Previous evidence identified that DPP-4 was a functional receptor for MERS-CoV and may also participate in SARS-CoV2 infection despite not being its primary entry receptor [25]. Thus, targeting DPP-4 has been considered as a pharmacologically reasonable strategy in COVID-19 cases

[26, 27]. It was also noteworthy that DPP-4 was also involved in inflammatory and immune functions [28]. It is unclear whether DPP-4 inhibition or modulation should be the most appropriate strategy. However, DPP-4 may represent a potential target for preventing and reducing the risk and the progression of the acute respiratory complications that T2DM may add to the COVID-19.

Sodium-Glucose co-Transporter-2 (SGLT2) Inhibitors

SGLT2 inhibitors are oral hypoglycemic agents for patients with T2DM [29]. One member of the class, dapagliflozin, was also recently approved in Europe for patients with T1DM. They block SGLT2, a high-capacity/low-affinity glucose transporter located in the S1 segment of proximal renal tubules, responsible for 90% of glucose reabsorption [30]. In diabetic patients, SGLT2 expression increases up to threefold. However, this effort to preserve glucose by preventing urinary excretion further deranges glucose homeostasis. SGLT2 inhibition results in excretion of 50–60% of filtered glucose, roughly corresponding to 60–100 g/day, and loss of the associated calories (76,77).

Beyond the hypoglycemic effects, SGLT2 inhibitors have shown unexpected clinical benefit regarding heart and kidney protection both within and outside the context of T2DM, suggesting potential intrinsic organ protective effects. This notion is supported by preclinical data that suggest a range of potential mechanisms of action, not limited to hemodynamic effects. These mechanisms of action may impact cell resistance to diverse stressors by decreasing oxidative stress and inflammation. Of note, recent evidence has shown that an SGLT2 inhibitor (dapagliflozin) decreases lactic acid generation and reverses acidosis inside the cells during hypoxia, thus contributing to the prevention of cell injury in the setting of cytokine storm of COVID-19 diabetic patients [31]. Thus, SGLT2 inhibitors may be potentially beneficial as organ protective agents in COVID-19 [32].

Glucagon-like Peptide 1 Receptor Agonists (GLP-1RAs)

GLP-1RAs are a pharmacological family of peptides that stimulate the human GLP-1 receptor and are known as incretin mimetics and improve glucose homeostasis through enhancing glucose-dependent insulin secretion. Moreover, GLP-1RAs offer the potential for adequate glycemic control in multiple stages of DKD without an increased risk of hypoglycemia and with additional benefits in weight reduction and cardiovascular and renal outcomes [33].

Recent evidence found that liraglutide, a long-acting GLP-1RA, increased the expression of ACE2 in the lungs and heart, which also raised the interest in patients with COVID-19 [34]. Like DPP-4 inhibitors, GLP-1RAs exerted anti-inflammatory effects by interfering with NF-kB signaling pathways [35]. Likewise, GLP-1RAs

were associated with a significant reduction in inflammatory cytokine in the respiratory epithelium in animal models infected by the respiratory syncytial virus [36]. Further evidence is needed to clarify the possible benefits regarding the uses of GLP-1RAs in the context of the SARS-CoV-2 infection.

Statins and Vitamin D: Common Drugs Used in Diabetic Patients

Statins are lipid-lowering drugs with pleiotropic effects frequently used in patients with cardiovascular risk. They have shown benefit in managing inflammatory and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. Furthermore, due to their immunomodulatory properties, they have been used to treat various infectious diseases such as community-acquired pneumonia and influenza. Hence, the pathophysiological foundations supporting the use of statins as an adjunctive treatment in patients with COVID-19 have been suggested [37].

Vitamin D (VitD) is a hormone regulating calcium and phosphate homeostasis. At the same time, it exerts many other essential extra-skeletal functions. Thus, this hormone plays a critical role in a host of physiologies, including proper functioning of the immune system and modulation of inflammatory responses. VitD deficiency and insufficiency are common and are linked to many pathophysiological states such as DM, allergies, and autoimmune diseases and recently have also been associated with worse COVID-19 clinical outcomes. Of note, lower levels of VitD are also more common in patients with CKD and T2DM [38]. Moreover, there is solid evidence that VitD deficiency may be a prominent element of DKD [39].

Recent reports have shown that low VitD levels are associated with an increased risk of COVID-19 infection; in fact, individuals deficient in VitD have a 54% greater SARS-CoV-2 positivity rate [40, 41]. Therefore, due to beneficial effects outside COVID-19 and possible protective impacts in SARS-CoV-2 infection, VitD supplementation is likely a safe and cost-effective intervention that could decrease morbidity and mortality [42].

Conclusions

What can we expect regarding this new pandemic crashing with the old known diabetes pandemic? As we observe in our daily clinical practice, some post-COVID-19 DKD patients progress to more severe CKD stages. Unfortunately, many are also at imminent risk of needing renal replacement therapies (RRT) or even death. The evidence supports the notion that diminished immune defenses and other renal-related risk factors make diabetic patients more prone to infections. Finally, the

crash of these two pandemics will surely affect greater numbers of patients with diabetic kidney disease and result in higher mortality rates associated with the COVID-19 pandemic.

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Part III
Treatment and Prognosis

Chapter 21
Glycemic Control

Armand A. Krikorian and Angela Pauline P. Calimag

Introduction

Diabetes mellitus (DM) affects almost 1701 million people worldwide, with estimates of around 20 million people in the USA. Likewise, chronic kidney disease (CKD) is recognized worldwide as a significant public health problem. An estimated 50 million people worldwide are affected; in the USA, it is estimated to affect almost 20 million people. As such, both are considered as major public health problems that are associated with considerable morbidity and mortality [1].

CKD is commonly associated with diabetes mellitus and is considered a diabetic microvascular complication. The progression of CKD to end-stage kidney disease (ESKD) leads to significant morbidity. Hence, therapeutic regimens based on understood pathophysiologic mechanisms of CKD in DM are continually being developed to delay or prevent its progression.

The cornerstone of these therapies is the management of glycemia, which can be even more challenging for patients with CKD as several medications used for glycemic control are contraindicated in advanced CKD. In addition, the risk of hypoglycemia can be more pronounced in patients with CKD.

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Assessment

Estimation of Kidney Function and Staging of Diabetic Kidney Disease

Fundamental to the prevention of diabetic kidney disease is screening. Patients need to be screened annually for diabetic kidney disease, which can be detected by measuring serum creatinine and urine albumin [2, 3]. In diabetic kidney disease, the earliest detectable change is the presence of albuminuria, with a 24-h urine albumin as the gold standard diagnostic test. Nevertheless, the more convenient urine protein/creatinine ratio is the recommended test of choice. There are patients, however, who do not exhibit albuminuria, for whom other markers of kidney disease come into play such as creatinine and estimation of glomerular filtration rate (GFR).

We can estimate the chronic kidney disease level for all patients with DM by utilizing serum creatinine-based equations such as the Modification of Diet in Kidney Disease (MDRD) equation or the Cockcroft-Gault equation to estimate the GFR.

Table 21.1 shows CKD staging based on current KDIGO guidelines [2, 3].

Glycemic Target

Glycemic targets and treatment approaches need to be individualized and modified depending on multiple factors such as patient age, life expectancy, type of diabetes, duration of diabetes, risk of hypoglycemia, and other comorbidities [4–6]. Table 21.2

Table 21.1 GFR categories in chronic kidney disease

CKD 1 (GFR >90 mL/min per 1.73 m^2)
CKD 2 (GFR 60 to 89 mL/min per 1.73 m^2)
CKD 3 (a- GFR 45 to 59 mL/min per 1.73 m^2) (b- GFR 30 to 44 mL/min per 1.73 m^2)
CKD 4 (GFR 15 to 29 mL/min per 1.73 m^2)
CKD 5 or ESRD (GFR <15 mL/min per 1.73 m^2)

Table 21.2 Recommended glycemic targets

HbA1c values (%)	</=6.5	</=7.0	7.1–8.5	>8.5
	Patients with type 2 diabetes, no severe comorbidities, and low risk for hypoglycemia	Preferred for most patients with type 1 and type 2 diabetes	Patients with diabetes, multiple comorbidities, and high risk for hypoglycemia or those with hypoglycemia unawareness	AVOID except under extreme circumstances

Adapted from references [2, 5–7]

outlines the recommended glycemic targets based on the current evidence. While it is true that intensive glycemic control reduces the development of microvascular complications in patients with type 1 and type 2 diabetes, there remains a significant risk of developing hypoglycemia and increased all-cause mortality with tighter control. Different societies have offered guidelines on optimal HbA1c targets for glycemic control, ranging from <6.5% by the American Diabetes Association to 9% in special older adults by the American Geriatrics Society [2, 6, 7].

UKPDS, DCCT, and Kumamoto

The landmark trials of the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study in type 2 diabetes confirmed that microvascular complication risk is reduced with improved glycemic control.

The Diabetes Control and Complications Trial (DCCT) demonstrated that in patients with type 1 diabetes, strict glycemic control prevents up to approximately 70% of microvascular complications. Specifically, it can delay the onset of retinopathy, diabetic kidney disease, and neuropathy as well as delay the progression of any existing microvascular complications. In the primary-prevention cohort, the development of retinopathy was 6.0% vs. 24. 1% (RR, 0.26; 95% CI 0.15–0.38; $P < 0.001$), while in the secondary-intervention cohort, the progress of retinopathy was seen in 21.2% vs. 40.6% (RR, 0.46; 95% CI 0.34–0.61; $P < 0.001$). For microalbuminuria, which they defined as urinary albumin excretion of >/= 40 mg/24 h, there was a 34% reduction ($P = 0.04$) in the primary-prevention cohort, while in the secondary-intervention cohort, there was a noted 43% reduction ($P = 0.001$) as well as a 56% reduction ($P = 0.01$) for albuminuria which was defined in the study as urinary albumin excretion of >/= 300 mg/24 h. This, however, increased the risk of hypoglycemia by 62 versus 19 episodes per 100 patient-years ($P < 0.001$) with 54 hospitalizations in 40 patients versus 36 hospitalizations in 27 patients to treat for severe hypoglycemia [8].

The United Kingdom Prospective Diabetes Study (UKPDS) compared the efficacy of different treatment regimens on glycemic control as well as microvascular and macrovascular complications among patients with type 2 diabetes. In this study, it was noted that maintaining intensive glycemic control defined as having a goal fasting glucose less than 108 mg/dl with a reduction of 11% of HbA1c (median 7.0% vs. 7.9%) over a median of 10 years is associated with 25% reduction in microvascular complications. Comparison between intensive and conventional glycemic control for the development of microvascular complications (retinopathy requiring photocoagulation, vitreous hemorrhage, and kidney failure) showed a significant reduction in microvascular complications with 8.6 vs. 11.4 (RR, 0.75; 95% CI 0.60–0.93; $P = 0.0099$). There was, however, no noted significant effect on macrovascular disease or diabetes-related mortality (death from Myocardial Infarction, stroke, Peripheral Artery Disease, kidney disease, hyper- or hypoglycemia, and sudden death), 10.4 vs 11.5 (RR, 0.90; 95% CI 0.73–1.11; $P = 0.34$), or all-cause mortality, 17.9 vs 18.9 (RR, 0.94; 95% CI 0.80–1.10; $P = 0.44$) [9].

The Kumamoto study, which randomized patients with type 2 diabetes between intensive and conventional therapies, demonstrated delayed onset and progression of microvascular complications that include retinopathy, diabetic kidney disease, and neuropathy. These were observed in non-insulin-dependent diabetes mellitus patients with the following glycemic thresholds: Hba1c <6.5%, fasting blood glucose <110 mg/dl, and 2-h postprandial blood glucose concentration < 180 mg/dl. There was 40% risk reduction in severe non-proliferative or proliferative retinopathy. In the primary-prevention cohort, there was 100% risk reduction for albuminuria and 62% for microalbuminuria, while in the secondary-intervention cohort, there was 100% risk reduction for albuminuria and 52% for microalbuminuria [10].

ACCORD, ADVANCE, and VADT

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) are three subsequent trials conducted on patients with long-standing type 2 diabetes using stricter HbA1c targets than UKPDS. All three trials were able to demonstrate a similar positive impact of intensive glycemic control on diabetic kidney disease [11].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial failed to demonstrate a reduction in cardiovascular events with intensive therapy. This trial had to be concluded earlier because it showed that in patients with type 2 diabetes, intensive glycemic control with a target of HbA1c of <6% was associated with increased all-cause mortality and CV mortality while intensive glycemic control reduced the incidence of diabetic kidney disease by 21% [12].

Similarly, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) failed to demonstrate cardiovascular benefit with intensive therapy; however, it did show a modest reduction for albuminuria, which was their surrogate marker for microvascular complications. The trial concluded that sulfonylurea-based intensive glycemic control with a target of HbA1c levels </= 6.5% was associated with a 23% reduction in the risk of microvascular events. Compared with conventional therapy, intensive glycemic control was associated with a reduction of major microvascular events (new or worsening kidney disease or retinopathy, 9.4% vs 10.9% (HR, 0.86; 95% CI 0.77–0.97; P = 0.01); new or worsening kidney disease, 4.1% vs 5.2% (HR, 0.79; 95% CI 0.66–0.93; P = 0.006); new-onset macroalbuminuria, 2.9% vs 4.1% (HR, 0.70; 95% CI 0.57–0.85; P < 0.001); and new-onset microalbuminuria, 23.7% vs 25.7% (HR, 0.91; 95% CI 0.95–0.98; P = 0.02)). Unlike the ACCORD trial, ADVANCE did not show an increased risk of mortality, however, it did show that intensive glycemic control was associated with an increased risk of severe hypoglycemia and hospitalization [13].

The Veterans Affairs Diabetes Trial (VADT), which is a study performed on a population of elderly males with poorly controlled type 2 diabetes whose average HbA1c was approximately 9.4%, concluded that intensive glycemic control with rosiglitazone and insulin had no significant impact on mortality or macrovascular

endpoints. It did show only a modest improvement in albuminuria, the surrogate marker used for the microvascular endpoint of kidney disease [14].

Management

The choice of therapies for diabetes management must be individualized as well based on patient factors and the medications' mechanism of action, taking into consideration their pharmacokinetics and pharmacodynamics. The choice of therapy also depends on tolerability, adverse effect profile, ease of use, and cost to optimize patient adherence.

Non-insulin Medications

The primary classes of anti-diabetic drugs include biguanides, sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors (AGIs), sodium-glucose co-transporter-2 inhibitors (SGLT2), glucagon-like peptide 1 receptor (GLP-1) agonists, and amylin agonists. For the sake of discussion, we will be classifying them further into oral and parenteral; we will also be including other drug classes that have antihyperglycemic effects. See Table 21.3 for non-insulin medication properties and dose adjustment in chronic kidney disease.

Oral

Biguanides

This class is the recommended first-line therapy for the management of type 2 DM. While it originally included metformin, phenformin, and buformin, the latter two have long been withdrawn from the market due to their increased risk of causing fatal lactic acidosis. For patients with type 2 DM, metformin can be used as monotherapy or in conjunction with other oral agents or insulin and is generally not recommended in patients with type 1 DM.

The molecular mechanism of action of metformin is complex, and studies have shown that it acts primarily through inhibition of complex I in the mitochondrial respiratory chain. This causes an increase in the AMP:ATP ratio, thereby increasing adenosine monophosphate-activated protein kinase (AMPK) activity. This leads to diverse pharmacologic effects, including reduction of gluconeogenesis and lipogenesis, increase in fatty acid as well as enhancement of insulin sensitivity in liver and peripheral tissues. The inhibition of the mitochondrial respiratory chain also leads

Table 21.3 Non-insulin medication properties and dose adjustment in chronic kidney disease

Medication class and drugs	Mechanism of action	HbA1c reduction	Major metabolic pathway	Renal dosing	Dialyzable
Oral					
Biguanides					
Metformin	Prevents hepatic gluconeogenesis through mitochondrial oxidation inhibition. Promotes peripheral tissue glucose utilization	1–2%	Renal	Dose reduction in eGFR <45 ml/min Avoid in patients with serum creatinine >1.5 mg/dl or eGFR <30 ml/min	Yes
Sulfonylureas					
1. First generation: (a) Tolbutamide, tolazamide, acetohexamide, chlorpropamide 2. Second generation: (b) Glyburide, glipizide, glimepiride, gliclazide	Stimulates pancreatic beta-cell insulin secretion	1.5–2%	Hepatic	Avoid in eGFR <60 ml/min	No
Meglitinide analogues					
Mitiglinide, repaglinide, nateglinide	Stimulates pancreatic beta-cell insulin secretion	0.5–1.5%	Hepatic	No specific dose adjustment	Repaglinide – No, nateglinide – Yes
Thiazolidinediones					
Rosiglitazone, pioglitazone	Decreases insulin resistance by acting on the peroxisome proliferator-activated receptor-γ. increases peripheral tissue glucose utilization. Decreases hepatic gluconeogenesis	0.5–1.4%	Hepatic	No specific dose adjustment	No
Alpha-glucosidase inhibitors					
Acarbose, miglitol, voglibose	Prevents intestinal breakdown of oligosaccharides decreasing postprandial hyperglycemia	0.5–0.8%	Acarbose, voglibose – Fecal miglitol – Renal	Avoid in creatinine clearance <25 ml/min	Acarbose – No, miglitol – Yes

Table 21.3 (continued)

Medication class and drugs	Mechanism of action	HbA1c reduction	Major metabolic pathway	Renal dosing	Dialyzable
Dipeptidyl peptidase-4 inhibitors					
Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	Reduction of hyperglycemia inducing incretin effects	0.5–0.8%	Sitagliptin – Renal, vildagliptin – Hepatic/ renal, alogliptin – Renal, linagliptin – Biliary, teneligliptin – Hepatic/ renal, anagliptin – Renal		Sitagliptin – Yes, saxagliptin – Yes, vildagliptin – Yes, alogliptin – Yes, linagliptin – No, teneligliptin – Yes, anagliptin – No
SGLT2 inhibitors					
Canagliflozin, Dapagliflozin, Empagliflozin	Increases glucose elimination through the urine	0.9–1%		No dose adjustment in eGFR >60 ml/min. Do not initiate in eGFR between 30 and 45 ml/min. Contraindicated in eGFR <30 ml/min	Unknown
Parenteral					
Glucagon-like peptide 1 receptor agonists					
Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	Stimulates pancreatic insulin secretion, decreases glucagon release, and slows gastric emptying	0.5–1%	Exenatide – Renal		Exenatide and liraglutide – No, Albiglutide, dulaglutide, and semaglutide – Unknown
Amylin analogues					
Pramlintide	Decreases glucagon release and slows gastric emptying. Promotes satiety	0.3–0.6%		No dose adjustment in creatinine clearance >15 ml/min	No

Adapted from references [11, 53–56]

to an increase in the anaerobic metabolism of glucose in the cell cytoplasm, causing the production of lactic acid [15, 16].

Metformin is a hydrophilic cation with low lipid solubility. It is not bound to albumin or plasma proteins, giving it a bioavailability of around 50–60% and a high volume of distribution. Maximum plasma concentration is achieved by the immediate release form about 1–3 h after ingestion, with the extended release form reaching peak levels in about 4–8 h. Its half-life is about 6 h [15, 17–19]. Given its hydrophilic nature, metformin needs organic cation transporters to be distributed into tissues and enter cells as it cannot diffuse through cell membranes. The plasma membrane monoamine transporter (PMAT) that is expressed on the luminal side of enterocytes mediates the absorption of metformin in the intestine. Also, organic cation transporter (OCT) 3 expressed on the brush border of enterocytes contributes to intestinal uptake. Another transporter, OCT1, expressed on the basolateral membrane and cytoplasm of enterocytes, is implicated in the facilitation of transfer into the intestinal fluid. Both OCT1 and OCT3 are also expressed on the basolateral membrane of hepatocytes mediating hepatic uptake of metformin. OCT2 expressed at the basolateral membrane of kidney epithelial cells in the kidney tubules facilitates the uptake of metformin from the circulation into kidney epithelial cells. From there, multidrug and toxin extrusion proteins (MATEs) 1 and 2 K located in the apical membrane of kidney proximal tubule cells excrete metformin into the lumen. The liver does not metabolize metformin; hence, the only route of elimination is through active tubular secretion in the kidney [15, 17–19].

Therapy with metformin is primarily endorsed as first line upon the diagnosis of DM. Metformin reduces HbA1c by 1.0–2.0% [20, 21]. The current recommendation for the maximum dosage is 2550 mg. In 2016, the Food and Drug Administration (FDA) modified its criteria for the use of metformin, highlighting GFR as a better measure of kidney function compared to serum creatinine. Specifically, metformin can be started for patients with eGFR >60 mL/min/1.73 m^2. For those with eGFR between 45 and 59 mL/min/1.73 m^2, metformin can be continued safely with close follow-up of kidney function every 3–6 months. In patients with eGFRs between 30 and 45 mL/min/1.73 m^2, the recommendation is to avoid initiating metformin and maintain those already on it on doses no more than 1–1.5 g daily, or a 50% reduction of their daily dose with close follow-up every 3 months is recommended. Metformin is not recommended in patients with eGFR <30 ml/min/1.73 m^2 [22]. It is important to discontinue therapy with metformin and monitor patients who are at risk of developing acute kidney failure such as hypotension, shock, sepsis, and acute myocardial infarction and during the use of nephrotoxic agents, including radiographic contrast. Patients who have excessive alcohol intake, as well as liver failure, are recommended not to be started on this medication as they are predisposed to develop severe lactic acidosis.

Sulfonylureas

The first sulfonylureas were discovered in the 1940s when some sulfonamides were noted to cause hypoglycemia in experimental animals. Since then, several sulfonylureas have been developed and are classified into two generations. First-generation

sulfonylureas are tolbutamide, tolazamide, acetohexamide, and chlorpropamide, most of which are no longer in use, while second-generation sulfonylureas are glyburide, glipizide, and glimepiride [23].

Sulfonylureas are unique as a class as they have the same mechanism of action but varied pharmacokinetic properties. Sulfonylureas are primarily insulin secretagogues. They exert their secretagogue effect by binding to an adenosine triphosphate (ATP)-sensitive potassium channel protein receptor on the membrane of the β-islet cells; this receptor is mainly composed of two subunits – KIR 6.2, which is a pore-forming subunit, and SUR, which is a drug-binding subunit. Once it binds to the receptor, they block potassium inflow causing depolarization of the cell membrane. This causes an influx of calcium into the cytosol, which in turn causes exocytosis of insulin due to the contraction of the actomyosin filaments. Secondarily, it also stimulates hepatic gluconeogenesis and increases the number and sensitivity of insulin receptors [20 , 21, 23, 24].

Sulfonylureas are highly bound to albumin with a volume of distribution of approximately 0.2 l/kg. As mentioned earlier, sulfonylureas have varied pharmacokinetic properties. Hence, they differ in dosage, rate of absorption, duration of action, and elimination.

Sulfonylureas can lower HbA1c by 1–2% [20, 21]. They are usually well tolerated; however, they can cause significant hypoglycemia and undesired weight gain [23]. As such, the use of sulfonylureas with active metabolites is limited in patients with impaired kidney function, as a decline in the estimated glomerular filtration rate (eGFR) increases the risk of hypoglycemia due to inadequate clearance. Sulfonylureas with inactive metabolites – gliclazide and glipizide – can be safely used at eGFR levels >30 ml/min with appropriate monitoring. Glibenclamide is generally avoided when eGFR is less than 60 ml/min, while glimepiride may be used in reduced doses with eGFR between 30 and 60 ml/min [24]. Sulfonylureas contain a SO2NH2 moiety. However, they are classified as non-sulfonyl arylamines, and there is little evidence of cross-allergy between them and sulfonamide antibiotics.

Meglitinides

Meglitinides are a family of insulin secretagogues, which are amino acid derivatives that are structurally different but act similarly to sulfonylureas. The medications in this class include mitiglinide, repaglinide, and nateglinide [25].

Their mechanism of action includes binding to receptors on the membrane of β-islet cells inhibiting adenosine triphosphate (ATP)-sensitive potassium channels. These receptors are similar to the sulfonylurea protein receptor subunit (SUR1/KIR 6.2), causing depolarization and gating of the voltage-sensitive calcium channels [20, 26]. This increases the calcium concentration intracellularly, which, in effect, stimulates insulin exocytosis. However, unlike sulfonylureas, they stimulate rapid and dose-dependent insulin release; hence, they have a more rapid and shorter duration of action, enabling it to mimic the physiologic insulin release pattern in patients without diabetes [21, 25].

Repaglinide is highly bound to albumin and alpha-1 acid glycoprotein and is mainly metabolized in the liver by cytochrome P450 isoform 3A4. Ninety percent of its metabolites are excreted in bile and only trace amounts in the urine. Nateglinide is absorbed in the gastrointestinal tract in a dose-dependent manner. It is metabolized via the cytochrome P450 isoforms 2C9 and 3A4 [27]. Approximately 30% is eliminated unchanged in the bile and urine, and eventually, about two-thirds are excreted in the feces and one-third in the urine.

Meglitinides as a class are eliminated mainly via non-kidney routes; hence, they are well tolerated and less likely to induce adverse effects such as hypoglycemic events in patients with mild to moderate kidney insufficiency [20, 26].

In clinical studies, meglitinides decrease HbA1c levels by 0.5–1.5%, comparable to biguanides and sulfonylureas [20].

Thiazolidinediones

It was 1975 when several analogues of clofibrate were noted to display hypoglycemic effects in diabetic mice, but it was not until 1982 when the first thiazolidinedione (TZD), ciglitazone, was discovered. TZDs owe their oral hypoglycemic effect by improving insulin sensitivity through increased transactivation or trans-repression activity of peroxisome proliferator-activated receptors (PPARs), a family of nuclear receptors [28]. This family of nuclear receptors is comprised of several isoforms, namely ζ, c/γ, and γ. The three different isoforms of the PPAR family differ in tissue distribution and ligands. PPAR-ζ is mainly found in the liver and skeletal muscle and also found in the kidney and brown adipose tissue as well as in the heart and intestines. PPAR-γ is highly expressed in white adipose tissue. However, it is also expressed in the skeletal muscle, liver, epithelial tissues, and macrophages. PPAR-∝/γ is ubiquitous [29, 30].

Thiazolidinediones were developed as synthetic ligands that directly activate the γ subtype of PPAR. Once activated, the receptor forms a heterodimer with an activated retinoid X receptor (RXR) to locate peroxisome proliferator response element (PPRE) sequences in the promoter region of target genes [20, 21].

Stimulation of PPAR-γ increases peripheral insulin sensitivity in the liver and skeletal muscle. TZDs have been postulated to have other pleiotropic effects, which include a reduction in the production of pro-inflammatory cytokines and increased production of adiponectin from adipose tissue [28]. The average HbA1c reduction from TZDs is 1.0–1.5%.

Several TZDs such as rosiglitazone and pioglitazone were developed and marketed, while others such as troglitazone were withdrawn from the market due to hepatotoxic effects. The use of TZDs fell out of favor when the FDA restricted their use under a Risk Evaluation and Mitigation Strategy due to concerns for increased cardiovascular events based on the results of the RECORD study. While this was eliminated in 2016, TZDs remain associated with increased fluid retention and hence have limited use in patients with advanced CKD.

Dipeptidyl Peptidase-4 Inhibitors

The first dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) were approved for use in diabetes in 2006. Currently, there are four DPP-4 inhibitors available in the USA, namely, alogliptin, linagliptin, saxagliptin, sitagliptin, with a fifth one available in Europe (vildagliptin).

After a meal, the small intestines secrete peptide hormones called incretins, the main ones being glucagon-like peptides 1 and 2 (GLP-1/2) and a glucose-dependent insulinotropic peptide (GIP). These incretins, in turn, increase pancreatic β-cell insulin secretion. However, this insulinotropic effect is dependent and limited by the level of glycemia [31]. At glucose concentrations lower than 90 mg/dL, the insulinotropic effect of GLP-1 is nil. Another action of GLP-1 is the inhibition of pancreatic α-cell glucagon secretion [32]. In patients with DM, the secretion of GLP-1 is decreased as well as reduced sensitivity to GIP [33]. GLP-1 also has a short half-life of 2 min, and it is degraded by a glycoprotein enzyme called dipeptidyl peptidase-4 (DPP-4). DPP-4, also known as CD26, is classified as an exopeptidase that cleaves peptides after the second position from the NH2-terminus. Dipeptidyl peptidase-4 (DPP-4) inhibitors, therefore, suppress degradation of GLP-1 and GIP [20, 21].

DPP-4 inhibitors may be utilized in patients with CKD stages 1–3 or eGFR >30 ml/min with appropriate monitoring and dose adjustments with decreasing eGFR. Linagliptin is an exception as it is predominantly eliminated by the hepatobiliary route and does not need dose adjustment in ESKD.

DPP-4 inhibitors cause a modest reduction of HbA1c of 0.5–0.8% [31].

Alpha-Glucosidase Inhibitors

Currently, three α-glucosidase inhibitors have been developed: acarbose, miglitol, and voglibose, with only the first two available in the USA [34]. α-Glucosidase is a type of glucosidase located in the brush border of the small intestine. They are enzymes that act to selectively hydrolyze terminal (1 → 4)-linked α-glucose residues (starch or disaccharides) to release a single α-glucose molecule, which is then quickly absorbed in the gastrointestinal tract [20, 34]. α-Glucosidase inhibitors act by reversible competitive inhibition as they are structurally similar to disaccharides or oligosaccharides, and they attach to the carbohydrate-binding site of the α-glucosidase, thereby inhibiting the activity of α-glucosidase in the mucous membrane of the small intestine. Because of its mechanism of action, α-glucosidase inhibitors preferentially lower postprandial glucose levels [21, 35].

The first-generation α-glucosidase inhibitor acarbose is a pseudo tetrasaccharide. Its structure consists of maltose bridged to acarvosine and has an excellent specificity for α-glucosidases, as well as increasing GLP-1 release due to inhibition of carbohydrate absorption. Miglitol, on the other hand, is a derivative of nojirimycin (1-deoxynojirimycin or N-OH-ethyl nojirimycin). This short-acting reversible competitive α-glucosidase inhibitor is almost wholly absorbed in the small intestine.

Voglibose was shown to facilitate the mobilization of GLP-1, aside from inhibiting α-glucosidase. Hence, it lowers both fasting and postprandial blood glucose [35].

Monotherapy with α-glucosidase inhibitors lowers HbA1c levels by 0.5–0.8% [20, 21, 34, 36]., and they have been associated with a high prevalence of GI side effects, including bloating and flatulence.

Sodium-Glucose Co-transporter-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a newer class of oral diabetes medications introduced in 2013. The current SGLT2 inhibitors approved for use are canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. SGLT2 is a low-affinity, high-capacity glucose transporter located in the first segment (S1) of the proximal tubules where it reabsorbs approximately 90% of the filtered glucose by the kidney glomeruli. SGLT2 inhibitors competitively inhibit SGLT2-mediated glucose reabsorption by reducing the plasma glucose kidney threshold, causing glycosuria, effectively lowering plasma glucose levels [37, 38].

They have been shown to reduce HbA1c by 0.5–1% [20, 21], and their half-life is approximately 10.6–13.3 h. Their efficacy is dictated by glomerular filtration: SGLT2 inhibitors reduce glomerular hyperfiltration and restore tubule-glomerular feedback. However, they have also been shown to increase creatinine and decrease eGFR, notably in patients with kidney impairment. It is recommended that therapy with SGLT2 inhibitors be discontinued or not initiated in patients with eGFR in the range of 30–60 ml/min/1.73m^2. They are also contraindicated in patients with type 1 diabetes and ketosis-prone insulin-dependent patients with type 2 diabetes [38–40]. Recent trials have shown that some SGLT2 inhibitors, such as empagliflozin, exhibit cardioprotective effects while others, such as empagliflozin, canagliflozin, and dapagliflozin, may slow the progression of chronic kidney disease [41–44].

Parenteral

Glucagon-Like Peptide 1 Receptor Agonists

Gastrointestinal peptide (GIP) and glucagon-like peptides 1 and 2 (GLP-1, GLP-2) are incretins, peptide hormones released in the small intestine in a glucose-dependent manner. Their presence results in increased insulin secretion from β-cells of the pancreas and concomitantly reduces pancreatic α-cell glucagon secretion, minimizing prandial glucose excursions. Their other effects include decreased gut motility, increased β-cell proliferation, and inhibition of β-cell apoptosis. GLP-1 has a noticeably short half-life of 2 min due to the activity of the exopeptidase dipeptidyl peptidase-4 (DPP-4).

In patients with type 2 diabetes, the activity of GIP and GLP-1 is diminished. Glucagon-like peptide 1 receptor agonists that are resistant to the effects of DPP-4

have been developed and include exenatide, lixisenatide, dulaglutide, liraglutide, semaglutide, and albiglutide. Albiglutide has been withdrawn from the market due to limited prescribing [45].

GLP-1 agonists regulate insulin secretion by activating adenylate cyclase, which in turn increases cyclic AMP (cAMP) levels, followed by protein kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factor 2 (cAMP-GEF2). This increase in PKA causes ATP-sensitive potassium channels to close, depolarizing the cell membrane and activating L-type voltage-dependent calcium channels. This increase in cytoplasmic calcium induces mitochondrial ATP synthesis and exocytic release of insulin [20, 45].

All the GLP-1 agonists share the same mechanism of action but differ in their metabolism and elimination depending on the structure of the analogue. Dulaglutide, liraglutide, and semaglutide or collectively referred to as "glutides" are human GLP-1 analogues; they are eliminated via general proteolysis pathways. Exenatide is a synthetic homologue of exendin-4 found in Gila monster (*Heloderma suspectum*) and is 50% homologous with GLP-1. It is eliminated via generalized proteolysis by DPP-4. It is renally eliminated, while lixisenatide, which is also structurally like exendin-4, is eliminated via glomerular filtration, is reabsorbed in the tubules, and subsequently undergoes metabolic degradation [45, 46].

GLP-1 agonists are generally well tolerated, with a low risk of hypoglycemia when used as a monotherapy. They are associated with weight loss, improvement in blood pressure and lipid levels, reduced rate of decline of eGFR, and reduced albuminuria. Patients receiving GLP-1 agonists have experienced gastrointestinal adverse events such as nausea, vomiting, and diarrhea, and there is a reported association between intake of GLP-1 agonists and pancreatitis [46]. They should overall not be used in patients with creatinine clearance <30 ml/min/1.73 m^2. They are also not recommended for use in patients with a personal or family history of medullary thyroid carcinoma.

GLP-1 agonists lower HbA1c by 0.5–1% [21].

Amylin Analogues

Pramlintide is a synthetic soluble analogue of islet amyloid polypeptide (IAPP or amylin) [47]. It is a 37-amino-acid peptide chain neuroendocrine hormone co-secreted with insulin by the beta cells in the islet of Langerhans in response to meals [47–49].

Its mechanism of action is predominantly through the modification of hypothalamic glucose-regulation in a centrally mediated effect at the area postrema in the brainstem. This activates efferent neural pathways promoting satiety, suppressing pancreatic glucagon secretion by the pancreatic alpha cells, and slowing gastric emptying [20, 48, 49].

Pramlintide is given subcutaneously, immediately before a meal as an adjunct to a basal-bolus insulin regimen. About 40% of the drug is albumin bound. Although the kidneys predominantly clear it with a half-life of 40–50 min and a duration of

action of 3 h [48, 49], no dose adjustment is needed in patients with a creatinine clearance of 20–50 ml/min. Current guidelines indicate that it is approved for use for both type 1 and insulin-dependent type 2 DM [47, 49]. Compared to placebo, the reduction of HbA1c is typically between 0.3 and 0.6% [20], together with a 1–2 kg weight loss, as well as a reduction in bolus insulin requirement of about 50% [47].

Others

Dopamine Agonists

Bromocriptine, an ergot alkaloid dopamine 2 receptor agonist, has been used in conjunction with lifestyle changes in patients with type 2 DM [50]. Although its mechanism of action for glycemic control is mostly unknown, some authors purport that it influences the circadian control of nutrient metabolism by increasing hypothalamic dopamine levels congruous with diurnal glucoregulation, thereby contributing to the neural suppression of hepatic glucogenesis and improving peripheral tissue glucose utilization [20, 21, 50, 51]. It has been noted to lower plasma glucose levels and HbA1c by 0.1–0.5% as well as improve glucose tolerance in obese patients with type 2 DM [21].

In the circulation, bromocriptine is highly bound to albumin (90–96%). It is metabolized largely in the gastrointestinal tract via the bile and liver via the cytochrome P450 enzyme CYP3A4. Hence, caution is exercised in patients with hepatic impairment. Approximately only 6% of the drug is cleared via the kidneys, and it has not been adequately studied for patients with CKD [50, 51].

Bile Acid Sequestrants

Colesevelam is a modified poly-allylamine bile acid sequestrant. Its use in diabetes as an adjunct to metformin, sulfonylurea, or insulin confers a modest 0.5–0.6% lowering of HbA1c. Its mechanism of action is presumed to be via the interaction of bile acids bound to colesevelam with bile acid receptor-1 (TGR5) on L-cells along the gut, thereby promoting GLP-1 secretion [20]. Another mechanism is possibly through the inhibition of enterohepatic bile acid circulation, preventing activation of hepatic farnesoid X receptor (FXR) systems and bile acid receptor-1 (TGR5), thereby increasing hepatic glucose metabolism [21, 52].

Insulin

Pre-proinsulin is the single-chain precursor of insulin with a signal peptide present at the N-terminus. The signal peptide gets cleaved during insertion at the endoplasmic reticulum of the β cell of the islet of Langerhans, and this generates proinsulin.

Proinsulin is an inactive 74-amino-acid prohormone, which in turn gets cleaved into insulin and a biologically inactive c-peptide. Insulin is the active hormone composed of two chains – the A chain consisting of 21 amino acids and the B chain with 30 amino acids linked by disulfide bonds. The pattern of physiologic insulin secretion is biphasic or divided into two phases: there is a protracted release wherein the pancreas continuously releases low levels of insulin as a response to hepatic glucose output and the second phase, which is a pulsatile secretion in response to glucose elevations with meals [57, 58].

In patients with diabetes, insulin therapy should ideally mimic or recreate this physiologic biphasic pattern [57, 59]. The standard insulin formulations were limited during the earlier years of their development and are not able to duplicate endogenous insulin secretion. Hence, new insulin formulations that have pharmacokinetic and pharmacodynamic properties that allow for flexibility in dosing and administration have been developed in recent decades, and these allow for insulin regimens that can closely simulate endogenous insulin patterns.

Bolus or prandial insulin attempts to reproduce the second phase of physiologic insulin secretion in response to glucose elevations with meals. Basal insulin replicates the first phase of physiologic insulin secretion, which is the protracted release of insulin responsible for the regulation of lipolysis and in response to hepatic glucose output. And lastly, correction-dose insulin is given to address hyperglycemia, which occurs between meals.

Insulin preparations are classified according to their mechanism and duration of action. See Table 21.4 for insulin preparation properties and dose adjustment in chronic kidney disease.

Metabolism of insulin differs between endogenous and exogenous insulin owing to their difference in molecular weight. Endogenous insulin produced by the pancreas is metabolized through first-pass metabolism in the liver, while exogenous insulin is metabolized by the kidney. Hence, clearance of insulin is decreased as kidney failure progresses [60].

Another caveat of insulin therapy for patients on dialysis lies in the fact that insulin is dialyzable: it is adsorbed by the dialyzer membrane. The degree of intradialytic drop depends on the type of dialyzer membrane used [56].

Recommendation for Type 2 Diabetes Management in Chronic Kidney Disease

Given the myriad of available oral and parenteral medications for diabetes, there are various approaches to management that allow for tailoring treatment to patient-specific factors. Several organizations such as the American Diabetes Association and the American Association of Clinical Endocrinology have published clinical practice guidelines for the comprehensive management of patients with type 2 diabetes mellitus [4, 6]. This year the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup has released their clinical practice guideline for diabetes management in chronic kidney disease [62]. Recognizing that treatment plans need to be

Table 21.4 Insulin preparation properties and dose adjustment in chronic kidney disease

Preparation	Onset	Peak	Duration	Insulin dose modification
Rapid acting				
Insulin Lispro (Humalog) Insulin Aspart (NovoLog) Insulin Glulisine (Apidra) Technosphere inhaled regular insulin (Afrezza)	5–10 min	1–1.5 h	3–4 h	CKD 1 and 2 – None unless the patient has hypoglycemic episodes For patients with hypoglycemic episodes: For BG <70 mg/dL – Decrease total daily dose (TDD) by 10–20% For severe hypoglycemia[b] – Total daily dose (TDD) by 20–30% CKD 3 – Decrease total daily dose (TDD) by 20–30% CKD 4 – Decrease total daily dose (TDD) by 40–50% CKD 5 – Decrease total daily dose (TDD) by 50–60% ESRD on hemodialysis (HD) – Insulin dose and timing preferably modified during dialysis and non-dialysis days
Short acting				
Regular insulin	30–60 min	2 h	6–8 h	Same as above
Intermediate acting				
Neutral protamine Hagedorn (NPH) insulin	2–4 h	6–7 h	10–20 h	Same as above
Long acting				
Insulin glargine (Lantus [U100], Basaglar [U100], Toujeo [U300]) Insulin Detemir (Levemir) Insulin Degludec (Tresiba)[a]	0.5–1 h	No peak	24 h	Same as above
Premixed				
70% insulin Aspart protamine/30% regular (70/30 insulin) 75% insulin Lispro protamine/25% insulin Lispro (Humalog mix 75/25) 50% insulin Lispro protamine/50% insulin Lispro (Humalog mix 50/50) 70% insulin Aspart protamine/30% insulin Aspart (NovoLog mix 70/30) 70% insulin Degludec/30% insulin Aspart (Ryzodeg)				Same as above

Adapted from references [6, 12, 53, 54, 58, 60, 61].

[a]Effective duration can be greater than 42 h

[b]Severe hypoglycemia is when a patient requires the assistance of another person to administer corrective measures

individualized and considering currently available therapies and the recently published guidelines, an algorithmic approach to treatment will assist clinicians in choosing the best individualized treatment plans for their patients as shown below in Fig. 21.1.

Recommendation for Management of Diabetic Ketoacidosis in End-Stage Kidney Disease

Diabetic ketoacidosis (DKA) is defined as blood glucose greater than 250 mg/dL, venous pH less than 7.3 or bicarbonate less than 15 mmol/L, and the presence of ketones in serum or urine [63]. DKA is less frequently reported in patients with ESKD on dialysis and requires a different approach to fluid, acid-base, and electrolyte imbalances [64, 65]. There is a plethora of evidence and guidelines on the management of DKA in patients without ESKD; however, these do not specifically address the management of DKA in ESKD patients on dialysis. The management of this subset of patients should be based on the fundamental understanding of the pathophysiology.

The primary insult that causes fluid, acid-base, and electrolyte imbalance in DKA is the relative deficiency in insulin to counter-regulatory hormones – namely, glucagon, cortisol, catecholamines, and growth hormone. This, in effect, triggers increased hepatic gluconeogenesis, increased glycogenolysis, and decreased uptake of glucose producing hyperglycemia. This also causes triglycerides to break down into free fatty acids and, in turn, beta-oxidation and eventual formation of ketone bodies that include acetone, acetoacetate, and 3-beta-hydroxybutyrate, hence ketosis and acidemia [63, 64].

Glucose is a solute, the excess of which causes hypertonicity. This increase in tonicity effectively causes intracellular fluid to move into the extracellular space. In patients with preserved kidney function, this induces osmotic diuresis causing significant hypovolemia [65, 66]. Sodium is also lost in the urine; although the proportion of fluid lost is higher, the osmotic shift of intracellular fluid into the extracellular space also brings about a state of dilutional hyponatremia. Consequently, total body sodium will be low although upon presentation, patients may either present as hypo-, normo-, or hypernatremic. Total body potassium is also essentially low due to excess excretion in the urine, yet hypertonicity causes intracellular potassium to move out into the extracellular space which, compounded by the effect of deficiency of insulin causing potassium to shift out of the cells, leads to some patients presenting with hyperkalemia.

In patients with ESKD who are either oliguric or anuric on kidney replacement therapy, the fluid and electrolyte shifts are altered due to the absence of osmotic diuresis as well as dialysis. Furthermore, this patient cohort is often in a persistent state of positive acid balance.

In these patients, an increase in tonicity also initiates increased extracellular volume from the osmotic movement of intracellular fluid to the extracellular space, though osmotic diuresis is minimal to absent. Hence, the primary determinant of

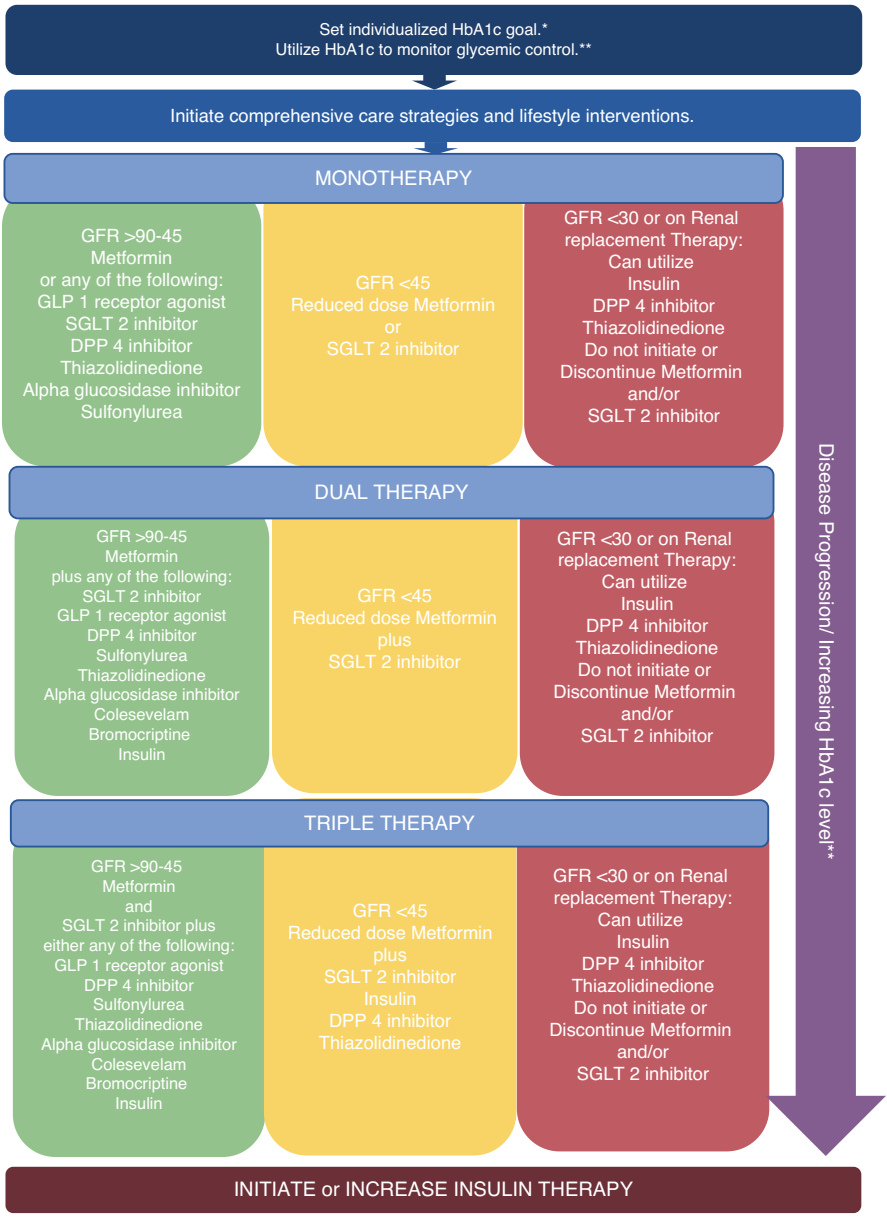

Fig. 21.1 Type 2 diabetes and CKD glycemic control algorithm
Adapted from references [4, 62]
*See Table 21.2 for recommended HbA1c goals
**Recheck HbA1c every 3 months after initiation of new therapy. If HbA1c not at goal, can escalate to the next level of therapy

tonicity in these patients is the level of hyperglycemia and extracellular volume unless the patient also has other sources of fluid losses such as Gastointestinal loss, fluid loss through the skin, a prolonged dwell time of hypertonic peritoneal dialysate, or through hemodialysis. It is also through this mechanism that total body sodium is unchanged while extracellular sodium is low due to dilution leading to these patients usually presenting with hyponatremia. Should they present with normo- or hypernatremia, fluid losses need to be suspected.

Patients with ESKD have difficulty excreting potassium. Coupled with the hypertonicity and insulin deficiency effects as discussed above, they rarely present with hypokalemia. Hence, it would be safe to assume that their total body potassium stores will be high; however, there are still cases when they can present with normo- or hypokalemia. Hyperphosphatemia is also common in patients with ESKD although they can also present with low serum phosphate depending on oral intake, adequacy of dialysis, or intake of phosphate binders. Its levels are less likely to be affected by glycemic status or tonicity; however, recognition of its deficiency is important as this may cause also neurologic manifestations.

Based on the key differences in pathophysiology, several authors have postulated that insulin infusion will improve all abnormalities seen in DKA in ESKD. Nevertheless, it is still practical to continuously monitor and determine if other interventions are required. The following are proposed recommendations for the management of DKA in ESKD on dialysis in the absence of current evidence-based guidelines [64, 65, 67, 68].

1. Once initial assessment is done and patient is stabilized, perform a complete history and physical exam looking for probable precipitating cause and other intercurrent illness.
2. Assess fluid status. Take note of patient's dry weight and compare it to their weight on presentation. Evaluate for other sources of fluid loss, especially if the patient is normo- or hypernatremic on presentation. If the patient is hypovolemic, use low-volume resuscitation with isotonic saline and reassess fluid status after every fluid bolus.
3. Be cautious in restarting hemodialysis. If necessary, hold hemodialysis unless there is evidence of significant hypervolemia, severe hyperkalemia, and persistent metabolic acidosis not corrected by insulin infusion. Peritoneal dialysis does not carry the same consequences of fluid and electrolyte exchange as hemodialysis and can be continued.
4. Do not give a bolus dose of insulin. Initiate insulin infusion at a lower rate considering the decreased metabolism of insulin in the liver and decreased kidney insulin clearance in ESKD patients.
5. Assume that the patient is in a persistent state of positive acid balance. Albumin adjusted anion gap may be higher. If persistently acidotic even on insulin infusion and hyperglycemia is corrected, look for other causes of acidosis.

See Fig. 21.2 for an algorithmic summary of the above recommendations.

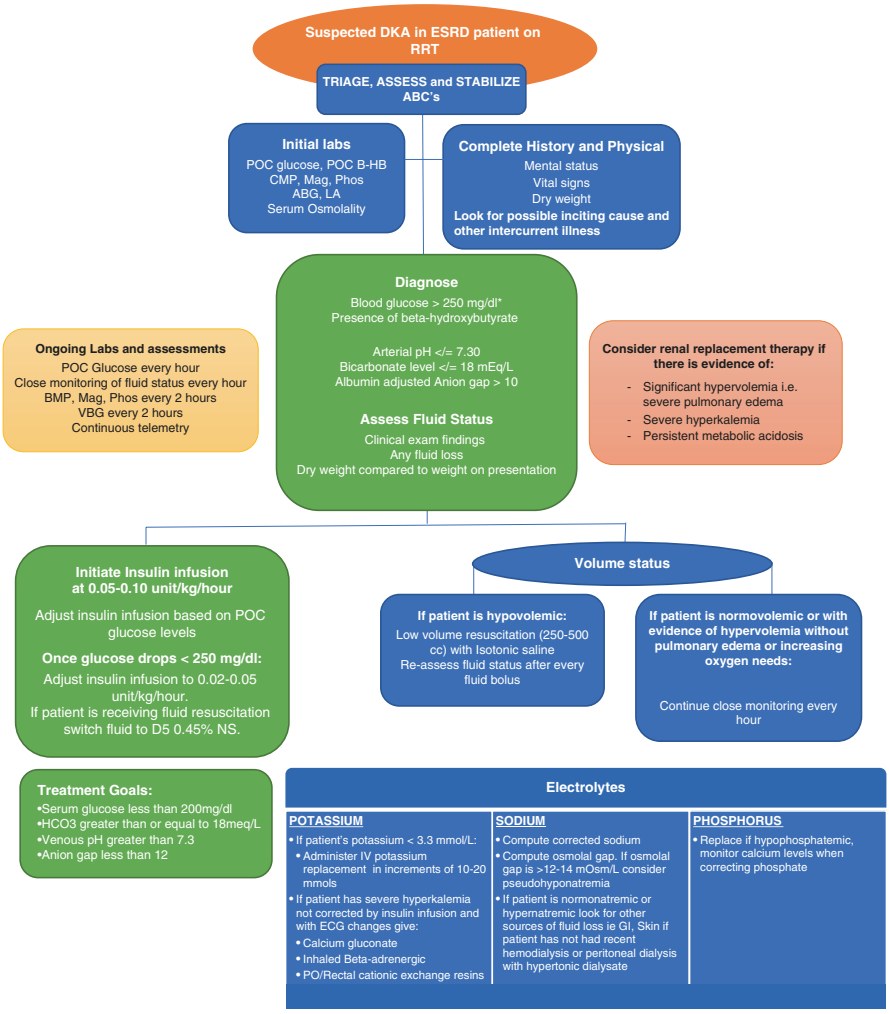

Fig. 21.2 DKA and ESKD management algorithm. (Adapted from references [63–65, 67])

Monitoring

Measuring Glycemic Control

The gold standard in measuring glycemic control is the measurement of glycated hemoglobin (HbA1c) as it reflects the average glycemic control over approximately 120 days, the average life span of erythrocytes. It should be noted, however, that in patients with chronic kidney disease, HbA1c level may not be accurate in assessing glycemic control. HbA1c may underestimate glycemic control as traditional

knowledge dictates that the life span of erythrocytes is shortened by 30–70% in chronic kidney disease, especially once serum creatinine levels reach >2.5 mg/dL. Medications that stimulate erythropoiesis, collectively known as erythropoiesis-stimulating agents (ESAs) such as epoetin alfa or darbepoetin alfa, which are frequently utilized in patients with chronic kidney disease, affect red blood cell turnover, increasing the percentage of immature red blood cells, effectively underestimating glycemic control.

To overcome these limitations encountered with HbA1c, other biomarkers have been developed, namely, 1,5-anhydroglucitol, fructosamine, and glycated albumin. 1,5-Anhydroglucitol measures the degree of urinary glucose excretion. Fructosamine refers to any glycated serum protein, which also includes glycated albumin, globulin, and lipoprotein. It reflects approximately 1–3 weeks of glycemic control. A caveat, however, with fructosamine depends on both the concentration of glucose and individual plasma proteins, which would be problematic in states wherein albumin levels may vary, such as chronic kidney disease, dysproteinemias, liver disease, pregnancy, and thyroid disease.

An alternative measure of glycemic control that is being studied and developed recently for use in patients with chronic kidney disease is glycated albumin. It is abundant in the body and sensitive to glycation. Its half-life is approximately 20 days and reflects glycemic control from the preceding 2–4 weeks. Its level is not affected by albumin levels since the ratio to total albumin is taken into account [11, 56, 69].

Hypoglycemia

Hypoglycemia is an essential and frequent adverse effect of glycemic control, as it causes significant morbidity and mortality. It is mostly associated with insulin, insulin secretagogues, sulfonylureas, and glinides. Prevention of hypoglycemia is crucial in the management of diabetes mellitus. The fear of experiencing hypoglycemia is one of the most significant barriers for people with diabetes in maintaining normoglycemia.

In April 2012, both the American Diabetes Association and the Endocrine Society assembled a new Workgroup on Hypoglycemia suggesting the following classifications of hypoglycemia in diabetes [6, 70]:

1. A plasma glucose concentration of </= 70 mg/dL (</= 3.9 mmol/L) on either self-monitored plasma glucose or continuous glucose monitor is used as the cut-off value for hypoglycemia in patients with diabetes.
2. Asymptomatic hypoglycemia is defined as a plasma glucose concentration of </= 70 mg/dL (</= 3.9 mmol/L) on either self-monitored plasma glucose or continuous glucose monitor that is not accompanied by typical hypoglycemia symptoms.
3. Probable symptomatic hypoglycemia is an event where a patient experiences symptom typical for hypoglycemia; however, plasma glucose concentration was not documented or measured.

4. Documented symptomatic hypoglycemia is an event where a patient experiences symptom typical for hypoglycemia with a plasma glucose concentration of </= 70 mg/dL (</= 3.9 mmol/L) measured on either self-monitored plasma glucose or continuous glucose monitor.
5. Pseudo-hypoglycemia is an event where a patient endorses experiencing symptoms typical for hypoglycemia with plasma glucose concentration; however, measured plasma glucose concentration is >70 mg/dL (>3.9 mmol/L) on either self-monitored plasma glucose or continuous glucose monitor.
6. Severe hypoglycemia is when a patient requires the assistance of another person to administer corrective measures.

The kidney plays a significant role in glucose homeostasis as both a substantial user and producer of glucose. The cells in the kidney cortex have gluconeogenic enzymes, whereas the kidney medulla cells have phosphorylating and glycolytic enzyme activity. Approximately 20–25% of glucose released into the circulation is from kidney gluconeogenesis during the fasting state. Kidney gluconeogenesis is also noted to increase after a meal, and it contributes to hepatic glycogen stores. Diabetic kidney disease carries an increased risk of hypoglycemia as kidney impairment leads to decreased kidney gluconeogenesis, and there is also reduced sympathetic response due to autonomic neuropathy. Kidney insulin clearance is reduced, and uremic toxins decrease insulin metabolism in the liver [2].

Hypoglycemia has also been associated with cardiac disturbances such as QT prolongation leading to ventricular arrhythmias and subsequent mortality. The ACCORD trial has demonstrated an increased association with all-cause mortality in intensive glucose control related to increased hypoglycemic events. Hence, prevention of hypoglycemia is crucial in this patient population [71, 72].

Summarized in Table 21.3 are various antihyperglycemic treatment options with recommended dose adjustments for the CKD population.

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Chapter 22
Computerized Clinical Decision Support

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Scope of the Problem

Epidemiology

Diabetes mellitus (DM) is the most common cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the United States [1, 2]. Diabetes affects approximately 36% of the nearly 37 million Americans with CKD and approximately 45% of the 509,014 Americans on dialysis [1, 2]. Patients with diabetes and CKD are at increased risk of cardiovascular and all-cause mortality [3, 4]. This mortality risk increases as kidney function deteriorates. The mortality for patients with ESKD and diabetes is estimated to be greater than 70% at 5 years [2]. In addition to these substantial health risks, Medicare spends approximately 35 billion dollars on fee-for-service spending for patients with ESKD annually [2].

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Early Recognition

The problem of chronic kidney disease in patients with diabetes is expected to worsen in the next two decades, as the incidence of diabetes increases. It has been estimated that by 2030, diabetes will reach pandemic proportions worldwide with over 366 million adults afflicted [5]. In order to slow the growing epidemic of kidney disease in patients with diabetes and improve outcomes in this population, the National Kidney Foundation (NKF) and National Institute of Health (NIH) have established programs that promote the early recognition and treatment of patients with diabetes and CKD [6, 7]. Established by the NKF in 1997, KEEP was a free community-screening program for adults designed to increase awareness of CKD among high-risk individuals, to provide free testing for kidney disease, to recommend a CKD treatment plan with educational information, and to provide referrals and ongoing support for follow-up [7, 8]. In total, 89,622 participants were screened, and the overall CKD prevalence was 26%, 17% had stage 3 CKD, and 1% had stage 4 or 5 CKD [9].

Established in 2000, by the NIH, the National Kidney Disease Education Program (NKDEP) was a program that promoted evidence-based interventions to improve CKD detection and management and that promoted the development of CKD treatment guidelines for primary care providers [10]. The program has carried forward an extensive collection of content that was developed during the program at www.niddk.nih.gov/health-information/community-health-outreach/information-clearinghouses/nkdep.

Proven Interventions

Many interventions have been proven to decrease cardiovascular risk and slow the progression of kidney disease in patients with diabetes and CKD. These interventions include the use of angiotensin inhibitors, use of sodium-glucose co-transporter 2 (SGLT2) inhibitors, strict blood pressure control and strict blood glucose control. Although not as rigorously supported, additional treatments such as cholesterol control, smoking cessation, dietary interventions and weight reduction may also slow the progression of CKD. When implemented together, these interventions have additive risk reduction benefits.

Angiotensin Inhibition The clinical benefits of angiotensin inhibition in the treatment of patients with diabetes and albuminuria have been shown in multiple large randomized controlled trials [11–16]. These benefits have included improved blood pressure control, regression of proteinuria, slower rates of kidney function decline, decreased rates of ESKD and decreased mortality [17]. Due to these benefits, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) for the treatment of patients with diabetes, hypertension, and albuminuria [18].

SGLT2 Inhibitors In patients with type 2 diabetes both with and without albuminuria, SGLT2 inhibitors have been shown to slow the rate of CKD progression and the risk of developing ESKD [19]. In the Canagliflozin and Kidney Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, 4401 patients with type diabetes, stage 2–4 CKD, and severely increased albuminuria despite angiotensin inhibition were randomized to canagliflozin 100 mg once daily or placebo [20]. Canagliflozin-reduced ESKD incidence, doubling of creatinine, heart failure hospitalizations, and all-cause mortality compared to placebo at 2.6 years. There are several risks of SGLT2 inhibition including a two- to fourfold increase in genital infections, a higher risk of lower limb amputations, and rarely Fournier's gangrene and euglycemic diabetic ketoacidosis [20, 21]. KDIGO currently recommends treating patients with type 2 diabetes, CKD, and an eGFR >30 ml/min per 1.73 m2 with an SGLT2i [18].

Blood Glucose Control Tight glucose control has been shown to prevent the development and progression of albuminuria [22–26]. Furthermore, large randomized controlled trials have shown that intensive glucose control slows decline in kidney function [23, 27]. Determining the optimal blood glucose to target treatment has been more difficult, as controlling hemoglobin A1c (HgBA1c) to a target of 6% or less has been associated with a higher risk of all-cause mortality [26]. KDIGO currently recommends an individualized HgBA1c target in patients with diabetes and CKD that ranges between 6.5% and 8.0% and the use of metformin and/or a SGLT2i to help reach this goal if eGFR >30 ml/min per 1.73 m^2 [18].

Blood Pressure Control Strict blood pressure control has been shown to slow the decline of kidney function in patients with diabetes and CKD in multiple prospective trials [28–30]. The optimal level of blood pressure to minimize risk remains uncertain. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines currently recommend targeting a blood pressure lower than 140/90 in nonalbuminuric patients with diabetes and CKD and targeting a blood pressure of less than 130/80 in albuminuric patients with diabetes and CKD [31].

Additional Therapies Additional interventions have shown limited benefit in the treatment of patients with diabetes and CKD. Salt restriction to ≤70 meq/day has been shown to enhance the anti-proteinuric effects of angiotensin inhibition [32]. Weight loss has been shown to decrease proteinuria in overweight patients with diabetes [33]. Cholesterol lowering with statins or fibrates may slow the rate of kidney function decline and progression of albuminuria [34, 35]. Smoking has been associated with the progression of kidney disease in patients with type 2 diabetes [36], and its cessation has been associated with a decreased risk of CKD progression [37]. Finally, decreasing dietary protein may mitigate the risk of ESKD and death in patients with diabetes and CKD [38].

Combined Therapy The potential additive benefits of intensive intervention in patients with diabetes and CKD have been shown in a prospective study of 160

white Danish patients, the Steno-2 trial [39]. In this study, patients were randomly assigned to multifactorial intensive therapy or standard therapy. Multifactorial intervention included dietary counseling, exercise, smoking cessation, targeting blood glucose to HgBA1C <6.5%, targeting blood pressure to <140/85 mmHg and < 130/80 mmHg for the last 2 years, ACE inhibitor therapy, targeting total cholesterol <190 mg/dL and < 175 mg/dL for the last 2 years, targeting triglycerides <150 mg/dL, aspirin, and vitamin therapy. After 7.8 years of follow-up, the intensive therapy group had a significant reduction in the primary composite cardiac endpoint, which included cardiac death, as well as a significant reduction in albuminuria [35]. At 13.3 years, including 5.5 years of observational follow-up, the intensive therapy group has a significantly decreased risk of all-cause mortality when compared to the control group [40].

Under-Recognition of CKD

Chronic kidney disease has been shown to be under-recognized in the general population, in populations at high risk for CKD, and in patients with diabetes [41, 42]. Cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2000 revealed awareness rates of 40.5%, 29.3%, 22%, and 44.5% in patients with stage 1, 2, 3, and 4 kidney disease, respectively [42]. Of the 274 patients with CKD who were unaware of their diagnosis, 68.8% were also noted to have a history of diabetes. In a more recent analysis of the KEEP database, which includes patients at high risk for CKD, awareness rates were found to be similarly low: 4.36%, 4.86%, 5.39%, 32.08%, and 44.87% in patients with stage 1, 2, 3, 4, and 5 kidney disease, respectively [41]. When patients from the KEEP database with diabetes were examined, only 9.4% of patients were aware of their CKD diagnosis [43].

Low rates of CKD documentation and coding have also been reported among primary care physicians [40–42]. Retrospective and cross-sectional chart reviews have revealed documentation rates between 4% and 38% in patients with moderate CKD [44, 45]. These low documentation and coding rates may be related to a lack of CKD knowledge. In a recent analysis by Navaneethan et al., only 36.5% of primary care physicians were aware of NKF guidelines for nephrology referral [46]. Furthermore, analysis of the KEEP database has revealed that only 12.3% of patients with CKD who met NKF nephrology referral criteria were actually seen by a nephrologist [47]. This is an important finding given the known benefits of early referral in patients with CKD [48, 49]. These benefits include cost savings and decreased morbidity and mortality rates [48]. In a retrospective study of the Veterans Health Administration clinic records, including 39,031 patients, consistent nephrology care was independently associated with a lower risk of death in patients with moderately severe to severe CKD [50].

Under-Treatment of CKD

As outlined above, several key interventions have been proven to slow the progression of CKD in patients with diabetes. Despite the proven benefit of these interventions, the majority of patients with diabetes and CKD are not receiving appropriate treatment. Analysis of the KEEP database, using data from 2005 to 2010, has revealed that target levels of blood pressure, blood glucose, and cholesterol were achieved concurrently in only 8.4% of patients. In patients with stage 1 and stage 2 CKD, 6.0% achieved these target levels; in patients with stage 3 CKD, 8.5% achieved these target levels; and in patients with stage 4 and stage 5 CKD, 9.0% achieved these target levels [47]. Interestingly, only 9.9% of patients with CKD co-managed by a nephrologist achieved target-level control. Similar studies have shown that rates of uncontrolled blood pressure exceed 50% in patients with CKD [51]. In a retrospective study of the NHANES database from 2003 to 2008, in which CKD awareness rates were only 7.4% among patients with stage 1 through 4 disease, awareness of CKD was not associated with improvements in BP control, ACEi/ARB use, or blood glucose control [52].

Given the importance of early diagnosis and treatment of chronic kidney disease in patients with diabetes and the known benefits of interventions, it is imperative that healthcare professionals increase their rates of guideline adherence. This includes improved rates of blood pressure, blood glucose, cholesterol control, ACEi/ARB use, metformin use, SGLT2i use, and the employment of multifactorial lifestyle interventions including dietary and weight-loss counseling and smoking cessation. Novel strategies to improve the treatment of patients with diabetes and patients with CKD have been employed but with only limited success. These strategies have included educational programs, multidisciplinary programs, behavioral interventions, telephone interventions, close follow-up by mid-level providers, and risk-communication interventions [53–59].

One potential strategy for increasing the adherence of patients and physicians to treatment guidelines is through the use of information technology interventions built into the electronic medical record (EMR) including the use of clinical decision support (CDS). The rest of this chapter will focus on the use of CDS to improve the care of patients with diabetes and CKD. We will first define CDS, we will then review the existing CDS systems that have been used to facilitate the treatment of patients with diabetes and CKD, and we will finish by discussing the characteristics of an optimal CDS system to help manage patients with diabetes and CKD.

Introduction to CDS

Clinical decision-making is part of the art of medicine. Deciding what diagnostic tests to order, when to initiate treatment, and how to treat is learned through countless hours of study and experience in medical school, residency training, and practice. Despite our

best efforts, healthcare professionals make medical errors on a daily basis, and adherence to guideline-appropriate treatment is poor. It has been estimated that more than 250,000 US deaths per year are due to medical errors [60]. Although healthcare professionals are often extremely bright, talented, and dedicated individuals, there are too many decisions to be made during a finite medical encounter. In addition, the growing body of medical literature makes it near impossible for healthcare professionals to stay completely up to date on studies that should be guiding their decisions. Computerized clinical decision support strives to improve the decision-making process of physicians.

CDS has been defined as the application of health information technology to aid clinical decision-making through the use of patient-specific electronic health information [61]. In the past decade, driven by US government incentives, there has been a dramatic rise in the number of US hospital adopting electronic health record systems and the number of these systems that use CDS [62]. In 2017, it was estimated that 40.2% of US hospitals had EMRs with advanced CDS capabilities [63]. This rise in the number of CDS systems has led to great heterogeneity in what is considered CDS. The most common features of these CDS systems are a clinical knowledge base, an integration of that clinical knowledge base with patient-specific information stored in the electronic medical record and a system by which recommendations are presented back to the clinician [64]. Additionally, the vast majority of these systems is now computerized. Due to this, for the remainder of this review, CDS systems will only refer to computerized systems.

Despite the heterogeneity of current systems, most appear to improve processes of care. In a recent systematic review by Kwan et al., 108 studies (94 randomized, 14 quasirandomized) were identified that reported on the effects of CDS on the processes or outcomes of care [65]. The authors found that CDS systems increased the proportion of patients receiving the studied care by 5.8%. The authors found great heterogeneity among studies with some studies reporting 10–62% increases. Substantial improvements in clinical outcomes were not found. The identified trials varied greatly with regard to the population studied, the clinical problem, the design and features of the CDS system used, and the clinical processes that were measured. Besides underscoring the breadth of CDS systems studied, this review also highlights the current problems with CDS research. In order to simplify the classification of CDS systems, we will only focus on clinically relevant aspects of CDS for the rest of this chapter.

Clinically Relevant CDS

CDS has been most commonly used to address clinical needs. The four most commonly described clinically relevant aspects of CDS systems include (1) the primary clinical problem for which CDS is being implemented, (2) the target audience for which recommendations are presented, (3) when recommendations are presented, and (4) how recommendations are presented and the control given to users in accessing or manipulating the recommendations [64].

(1) Primary Clinical Problem CDS systems have been used to improve the quality of care across multiple target areas. These areas have included preventive care, diagnosis, treatment, efficiency, and cost containment [63, 64]. With regard to preventive care, CDS tools have been studied as a means to improve immunization rates, cancer screening rates, and adherence to disease management guidelines for secondary prevention of cardiovascular disease [66–70]. In a systematic review by Souza et al. of the existing randomized CDS systems for primary preventive care, 41 trials were identified [69]. These CDS systems improved the screening and treatment of dyslipidemia in primary care but were less rigorously supported for use in cancer screening, vaccinations, and other preventive care. They also did not improve patient outcomes, safety, cost, or provider satisfaction. In a systemic review of CDS systems for cardiovascular disease prevention, 45 studies were identified with improvements found for clinical processes like screening, clinical testing, and prescribed treatment [70]. The authors did not find consistent improvements in clinical outcomes however.

CDS systems have been used to aid physician diagnosis. In radiology, CDS systems have improved image interpretation for a multitude of diseases including breast and lung cancer [71–73]. In internal medicine, CDS systems have been used to aid in the diagnosis of pneumonia through self-auscultation [74], diabetic proliferative retinopathy [75], tuberculosis [76], and acute coronary syndrome [77]. There are also many popular online diagnostic websites for both physicians and patients including WebMD®, AskMD®, and Symptify® [78].

CDS systems have been most extensively used to improve medical treatment. CDS systems have been used to alert physicians to drug-drug interactions, drug dosing errors, and non-adherence to treatment guidelines [77, 79, 80]. These systems have also been used to improve adherence to disease management guidelines in multiple chronic conditions including asthma, HIV, neonatal care, diabetes, and hypertension [81–86]. For the most part, CDS has improved the process of care in chronic conditions, but have not significantly improved patient outcomes [65, 87].

In addition to screening, diagnosis, and treatment, interventions implemented by CDS have been used to improve the efficiency of delivered care [88]. Examples of these interventions include care plans, order set guides, and drug formulary alerts [64]. These interventions have been designed to prevent duplicate testing and maximize cost savings. Few studies have examined the impact of these systems on efficiency and cost. Although difficult to implement and initially costly, CDS systems may eventually result in significant cost savings by decreasing hospitalizations, shortening length of stay, decreasing the frequency of drug adverse events, and eliminating duplicate or excessive tests [81, 89, 90].

(2) Target Audience CDS systems have been designed for use by physician, nurses, nurse-practitioners, physician-assistants, pharmacists, healthcare professionals in training, and patients [61, 63, 89]. The majority of the existing systems are targeted for healthcare provider particularly physician use [61]; however, increased interest in personal health records (PHR) has led to an integration of CDS in the form of shared decision-making [63]. An example of this is a Flu Tool that is incorporated

into the PHR at Vanderbilt University Medical Center which helps patients with flu symptoms to determine the level of care they need and then facilitates this care [91].

(3) When to Present Recommendations There has been considerable variation in when recommendations are presented to CDS users. Information has been presented prior to patient encounters, in real-time during patient encounters or after patient encounters. It appears CDS recommendations are most often followed when they are presented in real time; however, patient summaries or lists of high-risk patients may be useful before or after patient encounters [92, 93].

(4) How to Present Alerts and User Control of Alerts An area of extensive study in CDS implementation has been how to present recommendations or alerts to providers and the degree of provider control over these alerts. Considerations have included the format of alerts, how intrusive alerts and recommendations are to workflow, and how healthcare professional access and dismiss alerts [92–94].

The format of recommendations and alerts and their intrusiveness to workflow has varied greatly among CDS trials. CDS output has been presented as automatic pop-ups during a patient encounter that alert incorrect prescribing or inadequate treatment, a list of patients not meeting appropriate screening or treatment goals, or as passive guidelines that can assist providers with treatment. The format of alert presentation often varies according to the importance of information presented with pop-alerts that interrupt workflow presenting urgent information and passive lists conveying less urgent information.

The ease with which providers access and dismiss alerts has been described as its user control. CDS can vary with regard to user control from interruptive alerts that physicians cannot clear until the problem is noted and corrected to completely passive alerts that healthcare professionals access on demand [64]. Furthermore, the degree of user control can be matched to the intention of the alert. Alerts indicating severe drug-drug interactions are often interruptive alerts that must be addressed prior to completing an order, while alerts that guide optimal care of chronic illness are often passive reminders that physicians can choose to address. The degree of user control of CDS can dramatically impact a healthcare professional's impression of the CDS system and the resultant actions which they may take. Interruptive reminders may disrupt workflow and frustrate physicians, while passive reminders tend to be ignored. Furthermore, important interruptive reminders may start to be ignored if they appear too frequently or if CDS users deem them inaccurate or unnecessary, a phenomenon known as "alert fatigue."

"Alert fatigue" has the potential to prevent changes in provider practice [93]. The overall frequency of over-ridden alerts has been estimated to be as high as 96% [93]. Interruptive alerts have fared better than non-interruptive alerts. The frequency of providers over-riding drug interaction alerts has been found to be as high as 88%, and providers over-riding drug allergy alerts as high as 69% [95]. Importantly, these over-rides are often considered inappropriate through external review [96]. The frequency with which providers ignore non-interruptive alerts has been found to be

98.6% [97]. In designing future CDS systems, an integral component will be how to optimally configure user control of CDS output to the importance of the alert. In order to prevent "alert fatigue," it may become necessary to configure alert presentation and control to an individual provider's tendencies. For example, for a provider that regularly dismisses or ignores alerts, CDS systems could only present messages that are deemed urgent and make these messages difficult to dismiss or ignore [94].

Future Directions with CDS

In this brief overview of clinically relevant aspects of CDS interventions, we have introduced a variety of terms used to describe the existing designs of CDS. For the most part, although varied, current CDS systems have successfully improved provider practice. In a systematic review by Kawamoto et al., characteristics of CDS that successfully improved provider practice were described and included computer-based recommendations/alerts, automated alerts that did not disrupt workflow, and action-oriented recommendations [81]. Other characteristics of CDS that have been associated with success include delivering recommendations in a context other than electronic charting or order entry, requiring providers to give reasons when overriding recommendations and providing recommendations concurrently to patients and providers [93]. A recent review identified integration of media rich or interactive components as CDS features that can improve the quality of patient decision-making [98].

Despite improvements in provider practice, consistent improvements in clinical outcomes with CDS implementation have not yet been realized. As described in a review by Roshanov et al., CDS systems improved the process of medical care in 52–64% of studies, but only 15–31% of those studies led to an improvement in patient outcomes [93]. Furthermore, initial studies have shown significant costs associated with CDS implementation. In order to validate their adoption by healthcare systems, future CDS studies need to show improvements in patient outcomes as well as prove their efficiency and cost-effectiveness.

Existing CDS Systems for Diabetes, Hypertension, and CKD

There have been many studies addressing the effect of CDS systems on the care of patients with diabetes, hypertension, and chronic kidney disease. These interventions have addressed nephrologic care along different content areas with dramatically different CDS designs. Content areas have included preventive care, treatment, efficiency, and cost. We will now introduce the existing studies of CDS systems in patients with diabetes, hypertension, and CKD and end with a discussion of the optimal CDS system for patients with diabetes and CKD.

Preventing Adverse Drug Events in CKD

CDS systems have been used to check drug-drug interactions, drug allergies, and drug dosing in patients with kidney disease [89, 99]. These systems have been used in both acute and chronic kidney failure and in both outpatient and acute care settings [89, 99]. The ultimate goal of these systems is to reduce adverse drug events (ADEs), defined as drug-related patient injuries, though results thus far have been mixed [79].

Acute Kidney Injury (AKI) CDS has successfully improved medication dosing during episodes of AKI. In a study by McCoy et al., 1598 adult inpatients with an episode of AKI were randomized to a CDS system which consisted of a passive alert or an interruptive alert if one of at least 122 known nephrotoxic or renally cleared medications were dosed [100]. The interruptive alert but not the passive alert significantly improved the frequency with which providers modified or discontinued nephrotoxic or renally cleared medications during episodes of AKI. In a study by Pou et al., prescribing practices were compared pre- and post-implementation of a CDSS with interruptive alerts that warned prescribers of AKI in real time, in patients taking nephrotoxic medications [101]. The authors found that the CDSS intervention led to a significant improvement in how nephrotoxic drugs were prescribed.

CKD In a study by Chertow et al., the effect of CDS on prescriber practices and patient outcomes in hospitalized patients with CKD was evaluated [85]. The intervention consisted of real-time recommendations for drug selection, drug dosing, and drug frequency which appeared as alerts in the electronic medical record. This intervention was compared to controls, in which drug dosing information was available online but not incorporated real time into the ordering process, over four consecutive 2-month intervals (intervention – alternating with control) in a sample of 7490 patients with a creatinine clearance <80 mL/min. CDS was found to significantly increase the frequency of appropriate medication prescribing in patients with CKD to 51% compared to 30% in the control group. This included appropriate orders for dose changes (67 vs. 54%) and frequency changes (59 vs. 35%). There was also found to be a significant difference in length of stay in the intervention group versus control (4.3 vs. 4.5) days, but no difference in hospital costs or episodes of AKI with the intervention [102].

In a recent prospective, cluster randomized controlled trial, 514 physicians were randomized to a CDS tool to improve prescription for patients with kidney disease or usual care [103]. The CDS included 20 medications and detected situations where drug discontinuation or adjustment was needed in both the outpatient and inpatient settings. Alerts appeared at both initial prescription and with changes in kidney function over time. The CDS resulted in 4068 triggering conditions in 1278 unique patients (1579 were delivered to physicians in the intervention arm and 2489 were suppressed in the control arm). In the intervention arm, orders were appropriately adjusted 17% of the time versus 5.7% in the control arm.

In a review by Tawadrous et al., the effect of CDS systems on prescribing practices in patients with AKI and CKD was examined [89]. The review yielded 17 prospective studies of CDS. Of these 17 studies, 12 studies recommended drug dosing relative to the level of kidney function, and the remaining 5 recommended dosing in response to clinical parameters of serum drug levels. The majority of these studies improved clinician-prescribing outcomes by improving rates of appropriate dosing and/or frequency of medication as well as the time to modify inappropriate drugs. Overall in this review, CDS was found to decrease the rate at which patients developed AKI. However, patient-important outcomes, such as rates of adverse drug events and length of hospital stay, were not shown to improve.

The above studies demonstrate a clear role for CDS in improving clinician prescribing in terms of avoiding contraindicated medications and properly dosing medications in patients with kidney disease. Further research is needed to determine whether CDS improves clinical outcomes such as decreasing the frequency of drug adverse events and whether CDS can ultimately decrease costs.

CDS to Prompt Recognition of CKD

Despite mandatory estimated glomerular filtration rate (eGFR) reporting, only modest increases in CKD awareness among primary care providers have been realized [104, 105]. It is estimated that only approximately 30–40% with CKD patients are aware of their condition [106]. CDS systems may be used to improve provider recognition of CKD and have been integrated into outpatient primary care EMRs to prompt recognition of CKD in an effort to improve clinical outcomes. Two of these CDS systems were designed to provide comprehensive CKD care and will be discussed in an upcoming section, with only one study concentrated primarily on increasing recognition of CKD in a primary care [107, 108].

In a study by Abdel-Kader et al., the effect of a CDS plus an educational session for primary care providers versus an educational session alone on nephrology referral and proteinuria quantification was tested in primary care clinics throughout Canada [104]. The study was designed as a cluster randomized trial. The CDSS consisted of a passive alert in the EMR that would be activated for patients who had an eGFR <45 ml/min/1.73 m2 within 12 months of the patient's office visit and had not been seen by a university nephrologist. The first alert suggested a nephrology referral and provided the option to enter an order set containing an order for the referral. The second alert suggested ordering a spot urine albumin-creatinine ratio for patients who had not had a quantitative albuminuria/proteinuria assessment within the last year. The educational session and CDS prompt did not improve nephrology referrals or proteinuria quantifications between the intervention and control groups [104]. Although this study was an excellent example of a randomized controlled trial of a CDS system for patients with CKD, it had several limitations that limit its generalizability to all CDS systems for CKD. It was relatively small and underpowered, it was performed in university-based primary care clinics,

and finally and most importantly the CDS was designed with a passive, non-interruptive alert [105]. Given the high frequency with which providers ignore passive alerts, future trials of CDS to improve provider recognition of CKD should probably be designed with interruptive alerts that force provider recognition. These systems should also use a standardized and validated CKD phenotype. In order to encourage future use of CDSS to prompt provider recognition of CKD and to standardize this process, NKDEP has developed and validated an electronic CKD phenotype to prompt EHR-based identification of patients with CKD [109].

CDS Systems to Improve Blood Pressure Control

In a recent review of the effect of CDSS on cardiovascular risk factors, 11 studies were identified that examined the effect of CDSS on blood pressure and blood pressure target attainment [110]. In overall pooled analysis, CDSS led to a significant improvement in systolic blood pressure (−1.49 mmHg) and blood pressure attainment; however, the heterogeneity of the data was too high to be considered reliable. The authors also identified seven studies which examined the effect of CDSS on blood pressure and blood pressure target attainment in patients with type 2 diabetes. All studies were done in the primary care setting. Again, pooled mean systolic blood pressure and blood pressure attainment were improved with CDSS, and the heterogeneity of the data was too high to be considered reliable.

A good example of a CDSS intervention study to improve blood pressure was done by Hicks et al. [111]. In this cluster randomized trial performed in 14 primary clinics affiliated with a large academic medical center in Boston, practices were randomized to a CDS intervention designed to remind physicians of blood pressure treatment guidelines versus standard of care. Guidelines for blood pressure control were developed emphasizing disease-specific medication use. Patients were eligible for inclusion in the trial if they had a least one outpatient visit for hypertension in the preceding year to one of the clinics participating in the trial. The CDS consisted of a reminder to start an appropriate antihypertensive medication in patients with a diagnosis of hypertension in the problem list or with three blood pressure readings ≥140/90 who were not on an appropriate guideline-recommended medication for their disease class. The reminder was generated by an algorithm that was run in the electronic medical record which searched vitals, medications, allergies, and problem lists and cross-checked these patient-specific problems with a disease-specific algorithm. If the patient was not on a disease-appropriate medication, a reminder was given to the provider in the EMR. Paper printouts of the reminders were also given to providers prior to a patient encounter. Of 2027 eligible patients, 1048 were randomized to usual care, 786 to the CDS intervention, 120 to care with a nurse practitioner, and 73 to care with NP and CDS. Analysis of results revealed no significant improvement in blood pressure control between the CDS group and the control group; however CDS use did result in a significant increase in recommended medication prescribing. The lack of improvement in blood pressure was thought to

be due to the fact that the CDS was designed to remind physicians to prescribe an appropriate class of medication and not to intensify therapy. In fact 90% of patients in both groups were taking a guideline appropriate medication at the start of the study. The authors suggested that future CDS designs for hypertension management focus on intensification of therapy.

CDS Systems to Improve Diabetes Management

The largest percentage of CDS systems designed to treat chronic disease have been used to treat diabetes mellitus [93]. These CDS systems have added many advantageous elements to diabetes care including a standardized care process for providers with an emphasis on multifaceted risk reduction, improved continuity among providers due to a shared multidisciplinary EMR, and the ability to involve and empower patients in the care process through patient portals with accessible personalized health information [93]. Two examples of diabetes CDS studies with effective interventions include the TRANSLATE trial and the COMPETE II trial.

The TRANSLATE trial was a group randomized trial that tested the effect of a multicomponent diabetes intervention on diabetes care in 24 single specialty community primary care practices without an existing electronic medical record system [112]. In practices randomized to the intervention, a site coordinator and local physician advocate were assigned, an electronic diabetes registry was established, and a site coordinator was trained in its use. The electronic registry, based on coordinator and clinic staff input as well as a laboratory interface, generated reminders for unscheduled appointments (for foot exams, eye exams, etc.) and reminders that graphed HgBA1c, SBP, and LDL values over time and indicated whether a patient was at target. These reminders were given to patients at every visit. In addition, high-risk patients were contacted by study coordinators. Site coordinators updated physicians on their progress monthly. In this study of 7101 randomized patients, intervention practices resulted in significant improvements in SBP, HgBA1c, and LDL cholesterol from baseline to 12 months when compared to control. This study found that at 12 months, 15 more targets for SBP, HgBA1c, or LDL were achieved by the intervention compared to the control for every 100 individuals randomized.

In the COMPETE II randomized trial, Holbrook et al. tested the effect of a web-based diabetes tracker shared by both patient and provider on 13 diabetes risk markers [113]. Patients with diabetes were assigned to the intervention consisting of an electronic, web-based, color-coded, diabetes tracker that interfaced with the patient's electronic medical record and with a telephone reminder system or to standard care. The tracker monitored 13 diabetes-related quality variables for patients giving them targets for each variable as well as advice to help them reach these targets. In addition to the intervention, patients received monthly mailings of the tracker coder page with instructions to bring this page to their physician appointments as well as receiving monthly automated telephone reminders for medications, laboratory, and physician visits. A total of 511 patients were randomized into the trial, and these

patients were followed for an average of 5.9 months. The primary outcome for this study was an "improvement of process," defined as the difference between intervention and control with regard to a composite outcome of quality that was calculated based on achieved values of HgBA1c, blood pressure, LDL cholesterol, body mass index, albuminuria, foot check frequency, smoking, and physical activity index compared to targets. The process composite score increased significantly more in the intervention group than the control group. The authors also noted a small but statistically significant improvement in SBP control and HgBA1c between the intervention and control groups, but at the end of the 6 month study, only 19 patients or 7.5% of patients in the intervention group had SBP, HgBA1c, and LDL in target. The authors concluded that they achieved only modest improvements in outcome, attributing this to short follow-up and their focus on process outcomes.

Other trials of CDS systems in patients with diabetes have shown no improvements in clinical outcomes. In a cluster randomized trial of the effects of national computerized point-of-care CDSS in Belgium, 51 practices were randomized to the CDS system or usual care [86]. Using data taken before and after CDSS implementation, the CDS system did not improve HbA1c, LDL, or blood pressure after 1 year of follow-up. Systematic reviews of CDS systems have similarly found improvements in processes of care [114], without improvements in clinical outcomes [115]. Major findings from these reviews were (1) CDSS incorporated into the EMR led to a decrease in the variability of clinical care received between clinics and between providers at the same clinic; (2) multifaceted interventions, for example, those that also involved implementation of clinical case managers, improved outcomes to a greater degree than single interventions; (3) CDS tools that were interactive with patient portals and a greater number of features were associated with better outcomes; and (4) patients reported an increased sense of empowerment with CDS [114].

In conclusion CDS systems for diabetes have been shown to improve the clinical care process with multifaceted interventions and patient accessible options predicting the greatest success. Improvements in clinical outcomes however remain limited. Future studies should utilize a standard evaluation metric and include evaluation of hard clinical endpoints.

CDS to Treat CKD

There have been only four prospective studies examining the effect of CDS in patients with CKD. These trials identified patients with CKD from the EMR and then recommended treatment based on this designation.

In the first study by Fox et al., the effect of quality improvement measures implemented at two urban minority practice sites, one with an EMR and one with paper-based charting, was measured [107]. These quality improvement measures included the use of practice enhancement assistants, CDS, and academic detailing. A CDS

tool was designed based on NKF guidelines. This tool extracted laboratory elements from the EMR including eGFR, HgBA1c, medications related to CKD, as well as calcium, phosphorous, intact parathyroid hormone, and 25-OH vitamin D levels. Based on these current laboratory parameters, a recommendation reminder sheet was created for each patient with CKD seen by a specific provider. This reminder sheet included current laboratory parameters for the patient and recommendations for quality improvement to help the patient achieve NKF-defined CKD treatment goals. In the practice with EMR, the reminder sheet was placed in a physician's "to do" section as a passive task reminder, once approved reminder notes were placed into the EMR to improve CKD care including notes to diagnose CKD, discontinue harmful medications, and order appropriate diagnostic tests. In the paper-based clinic, the initial reminder sheet and reminder notes were placed in the paper-based chart. In addition to the CDS tools, the quality improvement intervention included the implementation of two practice enhancement assistants who would review charts and check for guideline implementation approximately every 3 months and make suggestions for meeting CKD guidelines. Inclusion criteria for CDSS implementation into the EMR included age older than 18 and estimated GFR (eGFR) < 60 mL/min, and 180 patients from both clinics met this criteria. The quality improvement project with CDS improved rates of CKD and anemia diagnosis and decreased the use of potentially harmful medications in CKD including metformin and NSAIDs. The authors also noted a small but significant improvement in eGFR at 1-year post-intervention.

In a study by Manns et al., the effect of an enhanced eGFR laboratory prompt was evaluated at 93 primary care clinics in Canada in patients older than 66 with an eGFR <60 mL/min and diabetes or proteinuria [108]. The enhanced prompt included education about the significance of CKD and management suggestions including recommendations to measure urine albumin-creatinine ratio (UACR), prescribe an ACEi or ARB in patients with diabetes or UACR>35 mg/mmol, reduce BP to <130/80 mmHg, reduce LDL cholesterol to <2.5 mmol/L, and target hemoglobin A1c to <7%. These recommendations were mailed to the provider. Primary care clinics were cluster randomized to receive a paper-based standard eGFR prompt which consisted of statement defining CKD and indications for nephrology referral or the enhanced prompt as described. The primary outcome was the proportion of patients who filled a prescription for an ACEi or ARB within 1 year of the first prompt being received by the physician. The authors found that the enhanced prompt did not improve ACEi or ARB prescribing practices in 5444 elderly CKD patients with diabetes or proteinuria. There was also no difference in the proportion of patients receiving a prescription for a new cholesterol-lowering drug or an additional antihypertensive medication from a different therapeutic class between groups for the year after the prompt was instituted. Although this was a large randomized trial, the design of the study and the intervention limit the generalizability of these findings. Treatment recommendations were not incorporated into the EMR and were not given at the time and place of the physician visit. Furthermore, 77% of patient had achieved the primary outcome and were on an ACEi or ARB, prior to

intervention suggesting minimal room for improvement [116]. Future studies of CDS in CKD should be designed with computerized systems that incorporate real-time recommendations into the EMR and be powered to detect improvements in clinical outcomes.

In another trial by Fox et al., 30 primary care practices comprising 6699 patients were randomized to CDS (10 practices) CDS plus practice facilitation (20 practices) [117]. The CDS group included the first four elements of the TRANSLATE model, target, use point-of-care reminder systems, get administrative buy-in, and network information systems, creating a practice population-based registry. The CDS and practice facilitation group also included site coordination, local physician champion, audit and feedback, team approach, and education. The authors found a significant difference in eGFR decline slopes in the intervention versus control group practices (0.95 vs. 0.01) and a significant difference in HbA1c slopes for patients in the intervention compared with control, but no other differences in any secondary outcomes (including avoidance of nonsteroidal anti-inflammatory medications, use of ACEis or ARBs, early recognition and diagnosis of CKD, blood pressure control, and smoking cessation) were found.

In the most recent prospective trial of a CDS system to improve care in patients with CKD, 524 adults with stage 3 CKD treated by 80 PCPs were randomized to usual care, eCDSS, or eCDSS PLUS [118]. The eCDSS was built into the EMR and followed PCP workflow. The initial phase prompted PCPs to check serum creatinine, cystatin C, and urinary albumin-creatinine ratio in order to risk stratify participants. For the low-risk group, an EMR alert notified the PCP and recommended retesting in 6 months. For high-risk group, an eCDSS SmartSet delivered individualized medication and dietary recommendations for blood pressure, potassium and proteinuria management, and cardiovascular risk reduction. The eCDSS also included education materials and suggested nephrology referral. If the eCDSS was ignored, it could be reinitiated for up to two subsequent PCP visits. In addition to above, in the eCDSS PLUS arm, a pharmacist followed up with participants within 2 weeks of their PCP visit to review and reinforce medication recommendations and deliver CKD-related recommendations. This encounter was documented in the EHR and sent to the PCP. A study nephrologist would also identify high-risk patients and ensure adherence to follow-up and nephrology referral. The primary clinical outcomes were change in systolic and diastolic blood pressure at the end of the intervention and 9 months after study completion. Secondary outcomes included PCP awareness of CKD and ACEi/ARB and statin use. eCDSS and eCDSS PLUS did not significantly improve blood control when compared to usual care.

There were also no significant differences in new ACEi/ARB or statin use by study arm.

PCP total and new awareness of CKD were significantly higher among intervention arms versus usual care. The majority of PCPs reported low or no burden from eCDSS on their practice. Unfortunately, there was no difference in eGFR decline among the study groups.

Optimal CDS for Diabetes and CKD

Caring for patients with diabetes mellitus requires attention to detail, close follow-up, and a multidisciplinary approach. Moreover, patients with diabetes and CKD represent a very high-risk sub-group that requires even more diligence. Physicians must remain up to date on the latest treatments for these patients, manage complex co-morbidities including psychiatric illness, and deal with challenging social problems. As we have previously documented, physicians are falling short in the care of patients with diabetes and CKD. Furthermore, the growing epidemic of patients with diabetes and CKD makes the future care of a large number of these patients daunting. It is obvious that physicians need help. We believe that the addition of computerized clinical decision support tools into the electronic medical record can greatly augment the care of patients with diabetes and CKD. In the previous section, we introduced studies examining the effect of CDS on diabetes, hypertension, and CKD care. In this section we will describe what we believe are characteristics of an optimal CDS system for patients with diabetes and CKD, characteristics we hope will improve patient outcomes not just processes of care.

Based on the successes and failures of the previously described CDS systems [92], we feel that the optimal CDS for diabetes and CKD should have several key systematic characteristics. These characteristics include integration into the existing EMR, real-time recommendations with minimal disruption to workflow, recommendations rather than assessments whenever appropriate, and customized alert messages with situation-specific user control. Furthermore we believe the optimal CDS for diabetes, and CKD should address five key functions: (1) identify patients with chronic kidney disease and those at high risk for progression to ESKD; (2) prevent drug adverse events; (3) identify patients who are not meeting diabetes, hypertension, or hyperlipidemia treatment goals; (4) make recommendations to help providers and patients reach treatment goals; and (5) engage patients with tools to help them better understand their condition and the rationale for their therapeutic plan. In the rest of this chapter, we will review how a CDS for patients with diabetes and CKD could be designed to optimally address these five functions.

Identifying High-Risk Patients

The optimal CDS system would automatically identify patients with diabetes as having CKD if their eGFR is less than 60 mL/min or if they have proteinuria, an inflammatory urine sediment or structural kidney abnormalities regardless of their eGFR. This identification process would be standardized based on identification criteria published by NKDEP [109]. A message would appear as an interruptive alert in the EMR at initial diagnosis and would subsequently appear as a passive alert (accessed by clicking an icon) only if a patient is determined to have CKD without clear documentation of this diagnosis. This alert could also include a link to

standard classifications of CKD or other educational materials for providers and patients.

This alert would be the first step in classifying patients with CKD who are at increased cardiovascular and kidney risk. Given the high prevalence of CKD in patients with diabetes, it will also be important to sub-classify patients in the highest-risk category and alert providers and patients to this. A more sophisticated risk stratification algorithm (described below) could be utilized to identify these patients. The charts of these patients would then be flagged with their high-risk status, possibly with an interruptive alert to prevent it from being overlooked. If a nephrologist or cardiologist is not seeing these patients, a recommendation for referral would be made by the system. Furthermore, more intensive care could be recommended for high-risk patients including protein restriction, bicarbonate or phosphate binder therapy, depression screening, insomnia screening, health psychology referral, CKD education referral, and kidney replacement planning.

Risk Prediction Using CDS Risk prediction is a potentially valuable tool in patients with diabetes and CKD, enabling physicians to stratify patients as low risk or as high risk for cardiovascular events and/or progression to ESKD. Determining which patients with diabetes and CKD are at high risk for progression to ESKD would enable either early preparation for dialysis, preparation for kidney transplant, or if the patient chooses end-of-life planning. Conversely, identifying patients at high risk for cardiovascular events rather than progression to end-stage kidney disease could prompt cardiology referral or end-of-life discussions and conserve valuable health resources that would otherwise be used preparing a patient for dialysis or transplant.

CDS has the potential to enable easier risk stratification of patients with diabetes and CKD by applying well-validated risk stratification equations to patient-specific health information in real time [58, 119]. Risk presentations could be expressed in the EMR as a numeric percentage, a risk category (high, medium, or low), or a graphical alert. This risk presentation could then be linked to other CDS interventions that recommend strategies for reducing cardiovascular and kidney risk and for preparing for end-stage kidney disease.

Risk presentation built into the EMR could also have beneficial effects for patients. Risk output could be printed out from the EMR or displayed through a patient-accessible portal and given to patients. These risk assessments could help patients make informed decisions regarding their care including kidney replacement planning and could motivate patients to improve their blood pressure, hemoglobin A1c, and cholesterol control through diet and exercise. These risk presentations would ideally be presented through simple risk graphics, which focus on frequencies and which are tailored to a population with low numeracy [120–122]. A comparable risk, such as the decrease in risk with appropriate treatment, could be displayed next to current risk, and strategies to decrease risk could also be provided for patients [120]. Face-to-face interactions would still be needed to help patients understand the data that is presented [123].

Preventing Drug Adverse Events

We have described previous CDS systems to decrease drug adverse events in patients with kidney disease [89]. The optimal CDS system for patients with diabetes and CKD would provide alerts for drug-drug interactions and drug dosing errors. For serious alerts, severe drug-drug interactions, or drug dosing errors, alerts would be interruptive and difficult to ignore. This format of alert has been shown to be more effective than passive alerts in modifying physician behavior [95]. In addition, interruptive alerts would appear when nephrotoxic medications such as aminoglycosides, NSAIDs, and intravenous contrast dye are ordered in patients with diabetes and CKD. The CDS system could also generate a printable list of nephrotoxic medications that could be given to high-risk patients.

For less severe drug interactions or dose recommendations, a passive alert would appear in the EMR. The user control of these alerts could be customized based on an ongoing review of the CDS system. Commonly ignored alerts could be made more passive with little to no interruption of workflow and ultimately could be removed from the CDS system. This would prevent "alert fatigue" and ensure continued support of the CDS by physician users.

Identifying Patients Not Meeting Treatment Goals

With the recent promotion of EMR by the federal government, it is believed the majority of patients with diabetes and CKD will have an electronic chart by 2014 [124]. From this electronic chart, it is imperative that key diabetes and CKD treatment parameters be easily searchable including, at minimum, HgBA1c, blood pressure, and LDL cholesterol. The ideal CDS system would be able to identify patients who are not meeting targets for these three variables. A provider would be flagged through a passive alert in real time that their patient is not meeting the target and would also get an email list of patients not meeting specific targets. If a patient with diabetes and CKD has not had the appropriate diagnostic work-up, recommendations for subsequent testing would be generated. These recommendations would ideally be linked to the guidelines that support them.

Recommendations to Help Providers Reach Treatment Goals

The most complicated part of implementing CDS for patients with diabetes and chronic kidney disease will be the generation of patient-specific recommendations for blood pressure, blood glucose, and cholesterol control. An additional level of sophistication would allow the provider and patient to set goals that might in some instances differ from the standard target, such as a higher blood pressure goal for a patient intolerant to attempts to lower blood pressure below 130/80 mmHg or a

patient who has developed symptomatic hypoglycemia with attempts at achieving a HbA1c at the recommended level. These patient-specific goals would remain as part of the record and would be used as the parameters for treatment recommendations.

Blood Pressure The optimal CDS system for patients with diabetes, CKD, and hypertension would provide recommendations for medication initiation and titration until blood pressure is at goal. In order to improve provider acceptance, recommendations would be based on up-to-date clinical knowledge and would be guided by patient-specific information.

The knowledge base would be generated from clinician review of recent randomized trials and would be continually updated. This knowledge base would also be supplemented by patient-specific information. For example, rather than recommending an angiotensin inhibitor for all patients, the CDS system would suggest an alternative medication or medication dosing in patients with an allergy to ACE inhibition and would recognize the patient previously treated with an ACEI or ARB who did not tolerate it for other reasons. This patient-specific feedback would be an integral component of such a CDS system. All medication recommendations would flow through a step-wise algorithm, which would be cross-checked with current medications and contraindicated medications until a specific medication or a dose increase is suggested. This would continue at each subsequent visit until the patient reaches a goal blood pressure of 130/80 (or other goals determined by provider and patient as discussed above).

HgBA1c The optimal CDS system for patients with CKD and diabetes would identify high-risk patients who are not at goal HgBA1c and would then provide therapeutic recommendations for providers. As described above, goal HgBA1c would be set based on patient-specific information, and HgBA1c goals higher than 7.0 would be set for older patients and patients with multiple prior episodes of symptomatic hypoglycemia. Alerts would recommend increasing or altering insulin therapy, adding a SGLT2-I and/or metformin if the eGFR is >60 mL/min, or recommending nutrition referral and specific diet plan for patients not at goal HgBA1c.

In order to optimize the diabetes treatment portion of such a CDS system, one would build on successful attributes of previous systems [114]. These attributes include multifactorial and multidisciplinary CDS recommendations and patient portals [114]. Such a CDS system would be used by a multidisciplinary team of providers including nephrologists, endocrinologists, cardiologists, nutritionists, and health psychologists. Patient-specific portals would allow patients and providers to jointly track patient-specific diabetes information. This portal would protect healthcare information and would ideally include the recommendations of providers. Furthermore, care coordinators could jointly tract patient information and help navigate patients to different appointments.

Cholesterol Management Previous studies have used CDS to successfully improve cholesterol management [125]. One can envision a CDS system that would alert physicians when the LDL level of their patient with diabetes and CKD is over goal.

The CDS would then recommend a multifactorial patient-specific plan to improve cholesterol levels. Again patients would be able to track their cholesterol management along with the physician using a patient portal with specific health information and recommendations.

Other Interventions An ideal CDS system would also suggest additional health management strategies for high-risk patients. This would include protein restriction for patients with advanced kidney disease, kidney replacement options for patients at high risk of progressing to ESKD, and referral to weight loss or smoking cessation clinic for obese patients and smokers. In addition, recommendations could be made by the CDS system to promote psychiatric and social health. These recommendations could include insomnia or depression screens; referral to educational interventions, which stress patient empowerment; or substance abuse rehabilitation. The goal through the implementation of these recommendations would be to improve the patient's quality of health by keeping them active and employed members of society.

Engaging Patients

Recently, patient health portals have gained increasing importance in hospital- and clinic-based EMRs. Patients are now able to access their recent studies and notes and are increasingly given computer-based information about these results in real time. The next frontier for clinical decision support **will be incorporation** into the patient health record. One potential application is risk prediction where patients may be presented with their future risk of a clinical event based on their current studies and treatment. Counseling and face-to-face interaction will need to be readily available to the patient so that they may accurately interpret and process these risks [123].

Several recent studies have tested the effects of electronic health interventions for patients with CKD including testing CDSS incorporated into patient health records [126, 127]. In a study by Navaneethan et al., 209 patients from six outpatient clinics were randomized to an enhanced personal health record (E-PHR), a patient navigator only, both, or usual care [126]. The E-PHR alerted patients to their CKD status, and when the alert was clicked, relevant education information was delivered. The authors did not find a significant change in their primary outcome (eGFR decline) or any of their secondary outcomes (CKD-related labs, referral for dialysis education, vascular access placement, emergency room visits, and hospitalization rates) at a 2-year follow-up. They did not however test the cost-effectiveness of their intervention.

Ensuring Success

Part of ensuring the success of a CDS system requires building on the success of previous systems. As mentioned, such an intervention would be computerized with real-time recommendations and would utilize customized alert messages with

situation-specific user control. As advocated by the Agency for Healthcare Research and Quality and Sirajuddin et al., the goal would be to provide the right alert, for the right patient, in the right format at the right time [128]. In addition, the CDS system would have several unique features that address the shortcomings of previous systems. The CDS would be multicomponent and multidisciplinary and would be able to be used and shared by all providers for a particular patient. Care would be comprehensive across a range of conditions that afflict patients with diabetes and CKD. The CDS would deliver recommendations for both providers and patients and would include patient portals where patients would be able to access their health information including treatment targets and recommendations for reaching these targets. All recommendations would be accompanied by links to supporting literature. The CDS system would include pathways for accessing additional resources that augment recommendations whenever possible such as involvement of nurse educators, care coordinators, and patient navigators in the patient's care. Finally, the CDS system would need to include support for the referral process workflow, an attribute recommended in interviews with primary care providers [129].

Monitoring Outcomes

The success of a novel CDS system such as that outlined here will need to be documented by the results of studies that demonstrate its efficacy in not only improving patient and provider practice but also in improving clinical outcomes and quality of life. Studies of such a CDS system will need to demonstrate improvements in hard clinical endpoints like progression to ESKD and all-cause and cardiovascular mortality. Other important clinical endpoints that should be measured include the percentage of patients being transplanted rather than receiving dialysis as well as the graft survival rates of transplanted patients. In addition to these clinical endpoints, important quality of life and user satisfaction markers should be measured.

The ideal CDS system will also need to demonstrate cost-effectiveness. Initial studies of CDS systems have shown that start-up can be costly, with the majority of the cost coming from clinician review and maintenance of the CDS knowledge base [130]. Future studies will need to demonstrate cost savings over time. Ideally if given enough time, optimal CDS systems would be self-sustaining with a decreased need for intensive clinical input. Ultimately, they could deliver care to multiple patients with minimal provider input and could become a viable option for care in low-income and resource-challenged settings. It is plausible that healthcare costs could be reduced by preventing the major morbidity and mortality associated with CKD and its progression to ESKD and the resultant need for kidney replacement therapy.

In conclusion CDS is a potentially valuable tool to improve the management of patients with diabetes and CKD. CDS can be used to identify patients with diabetes and CKD from the EMR, prevent drug adverse events, and make specific recommendations to help providers and patients reach treatment goals. Key features of

optimal CDS will be computerized, real-time, patient-specific recommendations that are integrated into workflow, multidisciplinary provider use, and patient portals. Ultimately the success of these systems will be defined by whether they improve ESKD and mortality rates as well as quality of life.

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Chapter 23
Antihypertensive Therapies

William J. Elliott

Introduction

Prevention of progression of diabetic kidney disease is a multi-faceted task and has been a "moving target" over the last several decades. Although the lifetime risk of developing end-stage kidney disease is now quite similar for people with either type 1 or type 2 diabetes (perhaps due to falling death rates from cardiovascular diseases) [1, 2], the earlier (and usually more precisely identified) age of onset of type 1 diabetes suggests they have a lower time-dependent risk of kidney disease. This had been reasonably well characterized in the decades before preventive measures were envisioned or widely available and has been discussed in Part I. From a clinical perspective, 5–10 years after diagnosis of type 1 diabetes, about 40% of individuals reproducibly excreted abnormal amounts of protein (especially albumin) in the urine (see Table 23.1 for the historical and 2012 Kidney Disease: Improving Global Outcomes (KDIGO)-recommended ranges and nomenclature [3, 4]). These amounts were typically small enough to escape detection by the traditional dipstick urinalysis, although special techniques were later developed to quantitate them. The 2012 term for this level of urinary albumin excretion is "moderately increased" albuminuria [3, 4], as many people were apparently confused by the older and now outdated term, thinking that it represented much smaller molecules of albumin that were excreted. Classically, this amount of urinary albumin did not yet meet the historical diagnostic criterion for "diabetic kidney disease" (which was >300 mg/d of albumin), and therefore many research projects were launched to determine if various therapies could retard progression to the defined threshold for urinary albumin excretion (which varied geographically, according to the units of common measurement: μg/min or mg/d). In people with type 1 diabetes, about 50% of those who produced 30–299 mg/d of albuminuria went on, over the next 10 years, to excrete

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Table 23.1 Historical comparison of important levels of urinary albumin excretion

Albumin excretion rate (mg/d)	Historical descriptor	Albumin/creatinine ratio (mg/g)	"New" classification (before "albuminuria")
< 30	"Normal"	< 30	"Normal to mildly increased"
30–300	"Microalbuminuria"	30–300	"Moderately increased"
> 300	"Macroalbuminuria"	> 300	"Severely increased"

Adapted from references [1, 3]

>300 mg/d of albumin (often producing a "positive dipstick test for proteinuria"). Several investigators have reported that individuals who cross this diagnostic threshold were more likely to have had an early detection of "moderately increased albuminuria" (or 30–299 mg/d) in the preceding decade. Detection of clinical proteinuria typically preceded a steady decline in glomerular filtration rate, with about 50% of these progressing to end-stage kidney disease over the next 7–10 years. Interestingly, but not well understood, *regression* of (usually short-term) moderately elevated albuminuria (30–299 mg/d) occurred in a substantial proportion of type 1 diabetic patients (range over the literature, 15–65%) [5]. However, once a patient developed >300 mg/d of albuminuria, regression back to <30 mg/d was not observed. The situation in people with type 2 diabetes is generally somewhat more complex, because the age of onset of diabetes is less certain, and those with type 2 diabetes are generally older (and therefore at higher risk for many other complications, including death). Despite all this, the degree of albuminuria at baseline was a significant, strong, and graded predictor of both cardiovascular events and mortality [6], as well as kidney outcomes [7] in meta-analyses of large cohorts.

It is now recognized, however, that urinary albumin excretion rates can be confounded by many parameters, including recent exercise, blood pressure control, urinary flow rate, urinary dilution, intravascular volume status, and dietary sodium intake. The intrinsic variability of albuminuria (even day to day) is such a major issue that the US Food and Drug Administration (FDA) has never recognized it as an appropriate surrogate endpoint for clinical trials, despite wide acceptance in the diabetes and kidney disease community [1–3]. Many improvements to methodology for specimen collection and analysis have resulted in the early morning first-voided urine as the currently recommended technique for estimating urinary albumin excretion [1–3]. Most clinical trials that use albuminuria as an endpoint require two successive determinations about the diagnostic threshold, in an attempt to minimize the intrinsic variability of the test.

Once the diabetic patient has reached the threshold of >300 mg/d of albuminuria (or albumin/creatinine ratio ≥ 300 mg/gm), some authorities claim that the diagnosis of diabetic kidney disease can be made; for example, Canadian health authorities reimburse physicians more for office visits for such patients, which is presumably why this diagnostic threshold was chosen by the Heart Outcomes Prevention Evaluation investigators [8]. Yet, even after the diagnosis is clear, there are several useful interventions to prevent an inexorable decline to end-stage kidney disease in people with diabetic kidney disease (see below and Chap. 11). Although some might

characterize these as "late interventions" for diabetic kidney disease, they are still worthwhile, as delay of dialysis or transplantation carries a large human and economic cost.

Interventions for Early Diabetic Kidney Disease

Glycemic Control

The most impressive results for control of blood glucose were seen in the Diabetes Control and Complications Trial (DCCT) [9] and its long-term follow-up, Epidemiology of Diabetes Interventions and Complications (EDIC) study [10]. This trial originally enrolled 1441 type 1 diabetic subjects with no retinopathy at baseline (1365 of whom had normal albumin excretion rates) and randomized them to an intensive vs. standard insulin regimen. After the first 6.5 years, the intensive therapy group (average A1c = 7.2%) had a significant 39% reduction in incident "albuminuria > 40 mg/d," as well as a significant 54% reduction in incident "albuminuria > 300 mg/d," compared to the standard therapy group (average A1c = 9.1%) [11]. Longitudinal follow-up showed a significantly increased risk of cardiovascular events in those who developed albuminuria, with a significant difference observed across randomized treatment groups [10]. In addition, those originally randomized to intensive glucose control were significantly less likely to develop incident "albuminuria > 40 mg/d" (7% vs. 16%), "albuminuria > 300 mg/d" (1.4% vs. 9%), or hypertension (30% vs. 40%). Follow-up 30 years after randomization showed a higher risk of development of impaired kidney function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) or cardiovascular events with any degree of albuminuria, but remission of albuminuria (once present) was not associated with improved outcomes [12]. Similar benefits were seen in a prospective, 7.5-year, Swedish trial that enrolled 102 type 1 diabetic patients: only 1 of 48 treated to an average A1c of 7.1% developed urinary albumin excretion >200 μg/min, compared to 9 of 54 treated to an average A1c of 8.5% [13], as well as a meta-analysis of smaller trials reported through 1993 [14]. Perhaps the most impressive report of the efficacy of glycemic control in type 1 diabetes comes from a series of eight patients who received pancreatic transplants, which led not only to persistent euglycemia but also striking reductions in albuminuria, 5 and 10 years later, with reversal of much of the glomerular pathology seen on biopsy during the transplant [15].

Clinical trial data about improved glycemic control and early kidney endpoints in type 2 diabetes are similar to those in type 1 diabetes but are somewhat less impressive, perhaps because of a smaller number of enrolled patients, a relatively short duration of follow-up, or small differences in achieved A1c levels across randomized groups. Many of these trials are discussed in more detail in Chap. 17. It is perhaps more efficient to summarize the data from seven trials involving 28,065 people with type 2 diabetes, as combined in meta-analyses. Subjects who received

the more intensive glucose control experienced a significantly reduced risk of developing albuminuria >30 mg/d (risk ratio, 0.86; 95% confidence interval [CI], 0.76–0.96) and albuminuria >300 mg/d (risk ratio, 0.74; 95% CI, 0.65–0.85), but *not* of doubling serum creatinine, end-stage kidney disease, or death [16]. Meta-regression analysis showed, as have many earlier observational studies, that greater differences in achieved A1c levels across randomized groups were associated with greater benefits on albuminuria (at both thresholds). It is likely that, since the Action to Control Cardiovascular Risk in Diabetes-Glucose trial showed significant harm (including death), associated with more intensive lowering of A1c [17], no further trials exploring aggressive lowering of A1c levels are likely to be performed in people with type 2 diabetes.

Inhibitors of the Renin-Angiotensin System

Although the first FDA-approved angiotensin-converting enzyme (ACE) inhibitor initially caused an increase in the incidence of dipstick-detectable proteinuria, essentially all subsequent studies have shown a strong antiproteinuric effect of all ACE inhibitors, angiotensin receptor blockers (ARBs), or aliskiren, a direct renin inhibitor. These effects on protein and albumin excretion appear to be independent of their blood pressure-lowering effects. As a result, they have been widely studied and are now nearly universally recommended for diabetic patients with persistent albuminuria [1, 3, 4], although this indication is not formally recognized by the US FDA.

Angiotensin-Converting Enzyme Inhibitors

After an extensive literature search, the Evidence Review Team for the 2020 KDIGO guideline for diabetes management in chronic kidney disease updated previous meta-analyses [18–20] and found 23 studies that compared an ACE inhibitor vs. placebo or "standard of care" (without a RAS blocker, hereinafter "control" group) in subjects with diabetes and chronic kidney disease [3]. Neither all-cause mortality nor cardiovascular mortality was significantly reduced in the combined ACE inhibitor arms, but the quality of evidence was generally poor, because of concern about inadequate randomization and possible selection bias. They also found nine studies [8, 21–28], involving 6780 subjects that reported doubling of serum creatinine, with a mean follow-up of 27 months (see Fig. 23.1). Overall there were 43 events per 1000 subjects in the "control" arm and 29 per 1000 in the ACE inhibitor arm, which provided a relative risk of 0.68 (95% confidence interval, 0.47–1.00). There was again a concern about inadequate randomization or blinding in some of these trials. More definitive was the comparison of progression from "moderately increased albuminuria" (generally 30–300 mg albumin/gram of creatinine) to "severely

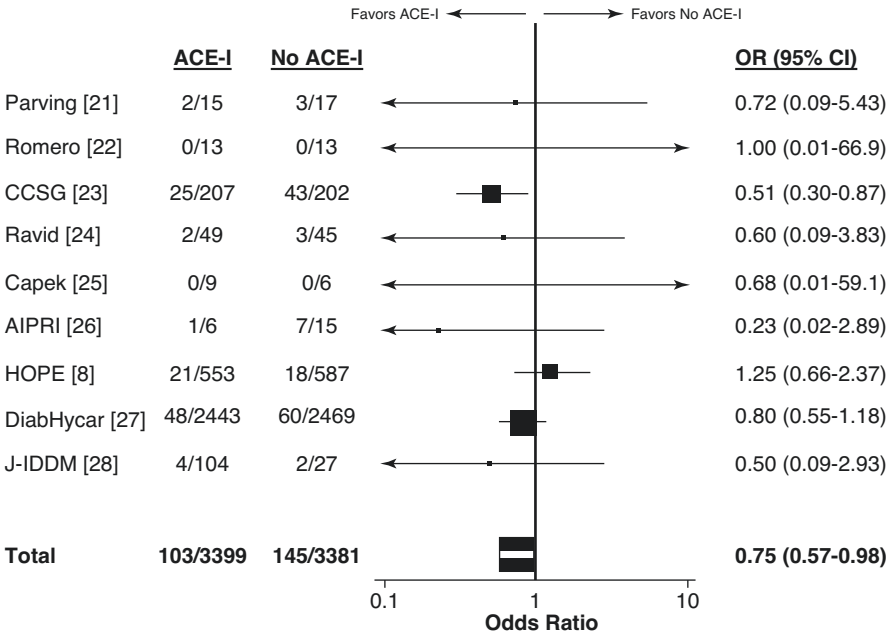

Fig. 23.1 Results of a random effects meta-analysis of nine randomized clinical trials in 6780 diabetic subjects comparing an angiotensin-converting enzyme inhibitor (ACE-I) or no ACE inhibitor, with the endpoint of doubling of serum creatinine. OR, odds ratio; 95% CI, 95% confidence interval; AIPRI, ACE Inhibition on Progressive Renal Insufficiency; CCSG, Captopril Cooperative Study Group; DIABHYCAR, Non-insulin-dependent DIABetes, HYpertension, microalbuminuria, proteinuria, CARdiovascular events, and ramipril trial; HOPE, Heart Outcomes Prevention Evaluation; J-IDDM, Japanese with insulin-dependent diabetes mellitus. These results differ from those of previous meta-analyses (e.g., [3, 18]) because a continuity correction and a random effects model were used

increased albuminuria" (generally >300 mg albumin/gram of creatinine), which was compared in 2036 subjects in 17 studies [8, 22, 27, 29–42], with a mean follow-up of 34 months (e.g., Fig. 23.2). In this comparison, the absolute incidence was 224 per 1000 subjects in the "control" group, but only 101 per 1000 subjects in the ACE-inhibitor arms, giving a relative risk of 0.45 and a 95% CI of 0.29–0.69.

Although not specifically involving "early" diabetic kidney disease, perhaps the most impressive trial in people with type 1 diabetes using doubling of serum creatinine as the primary endpoint was the Captopril Cooperative Study Group's comparison of captopril and placebo in 409 subjects [23], discussed in detail in Chap. 11. The clear, major benefit of the ACE inhibitor, not only in reducing the risk of doubling serum creatinine (the primary endpoint) but also the clinically important endpoint of death, dialysis, or kidney transplantation, as well as proteinuria (with eight captopril-treated patients experiencing a complete, long-term remission of proteinuria [43]), made it ethically difficult for others to evaluate the effects of other (newer) antihypertensive agents against placebo in patients with type 1 diabetic kidney disease. This historical situation left the door open to investigation of newer agents (e.g., ARBs) in type 2 diabetes.

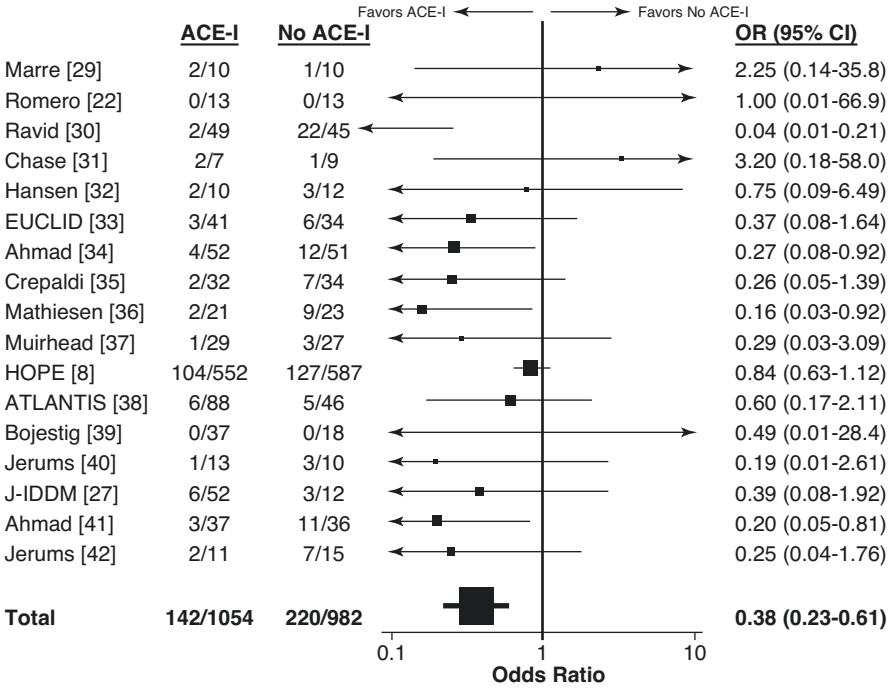

Fig. 23.2 Results of a random effects meta-analysis of 17 trials comparing an angiotensin-converting enzyme inhibitor (ACE-I) or no ACE-I on the transition of 2036 people with diabetes and "moderately increased albuminuria" (traditionally 30–299 mg/d or 20–199 μg/min) past the threshold for "severely increased albuminuria" (traditionally 300 mg/d or 200 μg/min). OR, odds ratio; 95% CI, 95% confidence interval; EUCLID, EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes; HOPE, Heart Outcomes Prevention Evaluation; ATLANTIS, Angiotensin-converting enzyme inhibitor Trial to Lower Albuminuria in NormoTensive Insulin-dependent Subjects; J-IDDM, Japanese with insulin-dependent diabetes mellitus. These results differ from those of previous meta-analyses (e.g., [3, 18]) because a continuity correction and a random effects model were used

Similarly, perhaps the most direct evidence for ACE inhibitors in delaying the progression of "moderately" to "severely" increased albuminuria comes from the MICRO-HOPE trial, in which ramipril was allegedly given at bedtime to minimize the potential confounding of its hypotensive effects [8]. After 4.5 years of follow-up, there was a significant 24% reduction in the development of "overt kidney disease" (defined as albumin/creatinine ratio of 36 mg/mmol, 300 mg/d of albuminuria, or 500 mg/d of proteinuria) in the group with baseline albumin/creatinine ratios >2 mg/mmol; the 9% difference in those with lower degrees of albuminuria was not significant across randomized groups.

Angiotensin II Receptor Blockers

The Evidence Review Team for the 2020 KDIGO guideline for diabetes management in chronic kidney disease found nine studies that compared an ARB vs. placebo or "standard of care" (without a RAS blocker, hereinafter "control" group) in subjects with diabetes and chronic kidney disease [3]. As with the ACE inhibitor meta-analyses, there were no significant differences between randomized groups for all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, or heart failure. However, based on four studies [44–47] involving 3280 subjects with a mean follow-up of 34 months, there were 280 subjects (per thousand) who doubled their serum creatinine in the "control" group, compared to only 235 (per thousand) in the ARB-treated group (see Fig. 23.3 for a similar meta-analysis); this provided a relative risk of 0.84 (95% CI, 0.72–0.98). As before, there were concerns about unbalanced randomization or selection bias. An even larger absolute and relative risk reduction was observed in their meta-analysis of five trials [37, 48–51] (see Fig. 23.4 for a similar meta-analysis) involving 899 subjects, with a mean follow-up of 23 months, for the ARB-treated group with respect to retarding the progression from "moderately" to "severely increased" albuminuria: 371 (per thousand) in the

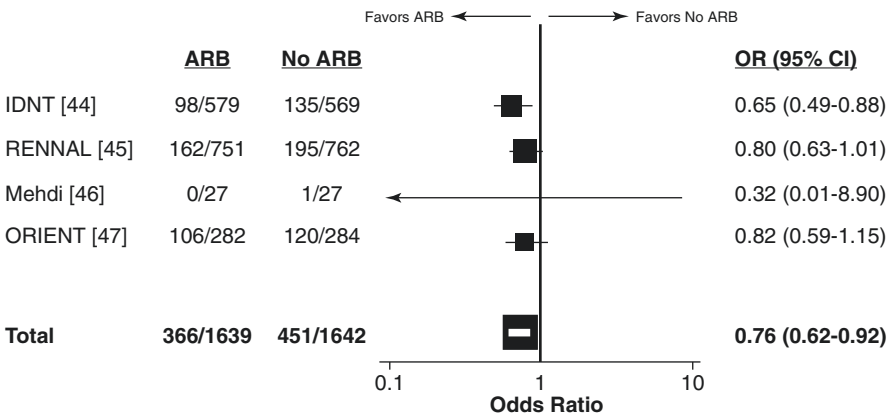

Fig. 23.3 Results of a random effects meta-analysis of four randomized clinical trials in 3281 diabetic subjects comparing an angiotensin receptor blocker (ARB) vs. no ARB, with the endpoint of doubling of serum creatinine. OR, odds ratio; 95% CI, 95% confidence interval; IDNT, Irbesartan Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; ORIENT, Olmesartan Reducing Incidence of Endstage renal disease iN diabetic nephropathy Trial. These results differ from those of previous meta-analyses (e.g., [3, 18]) because a continuity correction and a random effects model were used

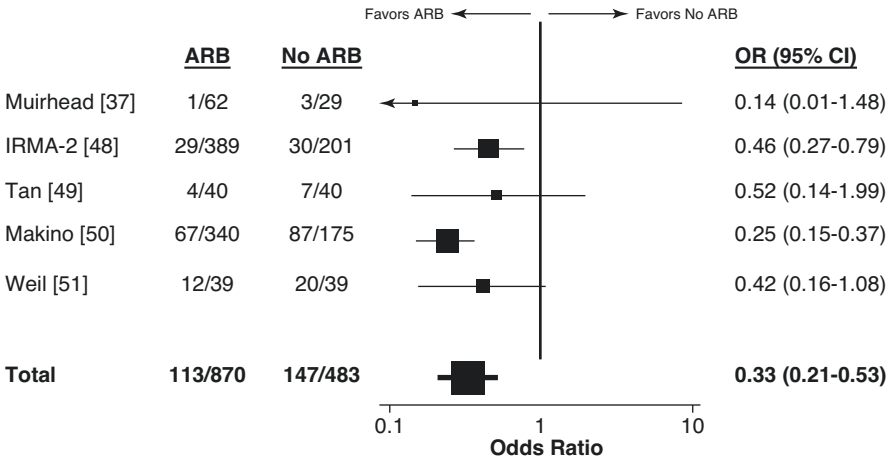

Fig. 23.4 Results of a random-effects meta-analysis of five trials comparing an angiotensin receptor blocker (ARB) vs. no ARB on the transition of 1353 diabetics with "moderately increased albuminuria" (traditionally 30–299 mg/d or 20–199 μg/min) past the threshold for "severely increased albuminuria" (traditionally 300 mg/d or 200 μg/min). OR, odds ratio; 95% CI, 95% confidence interval; IRMA-2, IRbesartan in patients with MicroAlbuminuria and type 2 diabetes. These results differ from those of previous meta-analyses (e.g., [3, 18]) because a continuity correction and a random effects model were used

"control" group, compared to 137 (per thousand) in the ARB-treated group. The relative risk for this endpoint was 0.37 (95% CI, 0.20–0.68), with some concern about imbalanced randomization.

The vast majority of the data about ARBs and diabetic kidney disease was obtained from trials that recruited diabetic subjects with hypertension. Although not done in patients with "early" diabetic kidney disease, perhaps the first most impressive and least confounded of these were the Irbesartan Diabetic Nephropathy Trial [44] and the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study [45]. As discussed in detail in Chap. 11, these two trials showed a significant 20% or 16% reduction, respectively, in their shared primary endpoint: a composite of doubling serum creatinine, end-stage kidney disease, or death, compared to placebo. In both trials, reduction in this endpoint was preceded by, and associated with, a significant decline in urinary albumin excretion. Elaborate statistical analyses suggested that the reduction in the primary kidney endpoint in each trial was independent of blood pressure lowering [52, 53]. This was perhaps easier to demonstrate in IDNT, which split its statistical power and included an amlodipine arm as a sort of "positive control" for its hypotensive effects, which were quite similar to those of irbesartan (141/77 vs. 140/77 mm Hg, respectively), yet irbesartan was superior to amlodipine (by 23%, P = 0.006) in prevention of the primary composite endpoint.

Perhaps the clearest conclusion about the dose-dependent ability of an ARB to prevent progression of albuminuria came from the Irbesartan Microalbuminuria Trial #2 [48], which randomized 590 subjects to placebo or irbesartan (150 or

300 mg/d), and followed them for 2 years for the development of albumin excretion rates >200 μg/min and a 30% increment from baseline. This endpoint was significantly prevented only by the 300 mg/d dose, although a trend was present for the 150 mg/d dose, compared to placebo. In a substudy of 133 subjects in this trial, a month after withdrawal of antihypertensive agents, blood pressure was unchanged in those originally taking placebo but returned nearly to baseline in the irbesartan-treated groups [54]. Perhaps more importantly, the urinary albumin excretion rate increased in the placebo and low-dose irbesartan groups but remained 47% below baseline in the high-dose irbesartan group, which suggested that the high-dose ARB had persistent long-term benefits, even after it was discontinued for a month. Even more interesting was the 2-year follow-up after the study's completion, which showed that individuals who experienced the greatest degree of reduction in urinary albumin excretion had the slowest rates of decline in glomerular function [55]. This is therefore one of the few trials in diabetics with initially normal to mildly increased albuminuria that has been able to link progression to moderately increased albuminuria and then to a decline in renal function, both independent of blood pressure changes. A subsequent meta-analysis (that included IRMA-2) also concluded that the anti-albuminuric effect of ARBs is dose-dependent [56].

Data are weaker for the ability of an ARB to prevent worsening of albuminuria in diabetic subjects without hypertension. In the RENAAL trial, 3.5% of enrolled subjects were normotensive [57]; in the more recent INNOVATION trial, 163 of 527 (or 31%) of the randomized subjects were similarly normotensive [50]. Subgroup analyses have led the KDIGO Clinical Practice Guideline writers to conclude that an ARB *may* be effective in diabetics with "moderately increased albuminuria" but without hypertension.

In diabetic patients with neither hypertension nor albuminuria, it is more difficult to justify a RAS blocker. When this was attempted in people with type 1 diabetes, neither losartan nor enalapril was associated with slowed progression of either albuminuria or histological changes in the kidney [58]. In people with type 2 diabetes without albuminuria and well-treated hypertension, telmisartan treatment reduced the incidence of "moderately increased albuminuria," but cardiovascular events were increased, allegedly due to an imbalanced randomization [59]. A meta-analysis of six trials with various RAS blockers in people with type 2 diabetes without albuminuria at baseline showed less progression of albuminuria, but most subjects were hypertensive [60].

Direct Renin Inhibitor(s)

More recently, a direct renin inhibitor has been used in clinical trials, but because of the prior proven efficacy of an ARB in preventing kidney endpoints in hypertensive type 2 diabetic subjects, the study design involved adding aliskiren (or placebo) to an ARB (or ACE inhibitor). The 6-month trial, in which all subjects received losartan, used urinary albumin excretion as the endpoint and was positive (showing a

20% reduction with aliskiren vs. placebo, $P < 0.001$), with only a small difference in blood pressures between the groups [61]. However, the long-term study, which layered aliskiren or placebo on either an ARB or an ACE inhibitor, was stopped prematurely at 2.7 years, because of excess hyperkalemia and hypotension in the aliskiren-treated group [62], despite a significant 14% reduction in the urinary albumin/creatinine ratio.

Aldosterone Antagonists

Spironolactone is often used as the fourth-line agent for the treatment of resistant hypertension, usually in combination with an ACE inhibitor or ARB. Although many such studies have shown a reduction in blood pressure, urinary protein excretion, and renal function, the most recent meta-analysis of 44 studies involving 5745 subjects suggests that these "benefits" are likely offset by an increase in hyperkalemia, acute kidney injury, and gynecomastia [63]. Now that effective potassium binders can reduce the severity and incidence of hyperkalemia, some of the objections to aldosterone antagonists may be mitigated.

The most recently FDA-approved aldosterone antagonist, finerenone, showed a dose-dependent decrease in albumin/creatinine ratio in subjects with chronic kidney disease and either heart failure [64] or diabetes with moderately increased albuminuria [65]. More importantly, in the 2.6-year-long, placebo-controlled trial in 5734 subjects with at least "moderately increased albuminuria" and estimated glomerular filtration rates (*e*GFRs) between 25 and 60 mL/min/1.73 m^2, adding finerenone to a maximally tolerated dose of a RAS blocker was associated with a significant 18% reduction in the primary composite endpoint of a sustained 40% reduction in *e*GFR, end-stage kidney disease, *e*GFR < 15 mL/min/1.73 m^2, or death from kidney causes [66]. As expected, albumin/creatinine ratios were significantly decreased, and hyperkalemia was somewhat more common (15.8% vs. 7.8%) in the finerenone-treated group. Whether this therapy's hyperkalemia can be effectively countered by orally administered potassium binders and whether it works as well in early diabetic kidney disease are interesting but unresolved questions.

Other Combinations of RAS Blockers

In addition to the unsuccessful long-term trial that added aliskiren to a RAS blocker in subjects with type 2 diabetic kidney disease [62], similar higher rates of adverse experiences (hyperkalemia, acute kidney injury, and an *increase* in albuminuria) were seen with the combination of full doses of telmisartan + ramipril in the Ongoing Telmisartan Alone or in Combination with Ramipril Global Endpoint Trial (ONTARGET), compared to either monotherapy alone [67]. When these results were combined to provide a meta-analysis of 85 trials involving 21,708 subjects,

progression of albuminuria from moderately increased to severely increased was significantly reduced by an ACE inhibitor vs. placebo and an ARB vs. placebo, but not the combination vs. monotherapy [19].

A more recent trial, the Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT), randomized 577 hypertensive Japanese or Chinese type 2 diabetic subjects with overt kidney disease (morning albumin/creatinine ratio > 300 mg/gm) to olmesartan or placebo for an average of 3.2 years [47]. The primary endpoint was the same as that of IDNT and RENAAL, but the major difference was that ~73% of subjects in both randomized groups *continued* therapy with an ACE inhibitor (although dose changes were prohibited by protocol). During follow-up, the olmesartan-treated group had significantly lower blood pressure (by 2.8/1.6 mm Hg, on average) and a highly significant reduction in urinary albumin excretion (−24.9% at 144 weeks compared to baseline vs. –3.1% compared to baseline in the placebo group, P = 0.005), but a non-significant reduction in the primary kidney endpoint 41.1% vs. 45.4%, P = 0.79). Cardiovascular death was more common (10 vs. 3) in the olmesartan-treated group, which was attributed to an imbalanced randomization: 21.3% of those randomized to olmesartan had cardiovascular disease at baseline, compared to only 11.6% given placebo.

The simple message may be that combining two inhibitors of the renin-angiotensin system increases the risk of hypotension, hyperkalemia, and acute kidney injury and does not improve kidney outcomes in type 2 diabetes.

Only one trial has compared the long-term kidney effects of an ARB vs. an ACE inhibitor in hypertensive subjects with type 2 diabetes; it enrolled only 250 subjects and was designed as a non-inferiority study [68]. Although the dropout rate was a concern (see Chap. 11), the change in isotopically measured glomerular filtration rate was not significantly different after 5 years of treatment with either enalapril or telmisartan. Whether this "proves" that an ARB and an ACE inhibitor are "equivalent" for diabetic kidney disease is debatable.

Blood Pressure Lowering

Although often overlooked in the vigorous debate about the importance of having an inhibitor of the renin-angiotensin system in the treatment regimen of many (if not all) patients with type 1 and all patients with type 2 diabetes, simply lowering blood pressure both reduces albuminuria (particularly with greater severity of albuminuria) and delays the loss of kidney function. During the last millennium, this was hotly debated and frequently cited as "the reason" that early trials of ACE inhibitors showed benefits in diabetic kidney disease. The clearest early demonstration of the role of strict blood pressure control was a series of 11 subjects with type 1 diabetes and a baseline blood pressure of 143/96 mm Hg, albumin excretion rate of 1038 μg/min, and decline in glomerular filtration rate of 0.89 mL/min/month [69]. After 72 months of intensive antihypertensive treatment (usually with a diuretic, beta-blocker, and hydralazine), blood pressure fell to 129/84 mm Hg, albumin excretion

rate was only 504 μg/min, and the decline in kidney function was 0.22 mL/min/month. These observations have been validated by subsequent sophisticated analyses of on-treatment blood pressures in both IDNT [44] and RENAAL [45].

Calcium antagonists appear to be heterogeneous with respect to reducing urinary albumin excretion in diabetic subjects, particularly in short-term trials. Dihydropyridine compounds, notably nifedipine, have been associated with increases in urinary protein excretion, whereas the non-dihydropyridine compounds, verapamil and diltiazem, tend to reduce it [70]. These effects were more easily discerned in patients who were not treated with an inhibitor of the renin-angiotensin system (which is now commonly recommended). It appears that combining even a dihydropyridine calcium antagonist with an inhibitor of the renin-angiotensin system reduces not only albuminuria but also the longer-term risk of deterioration in kidney function, as demonstrated in RENAAL [45, 53]. Verapamil did not reduce the long-term risk of severely increased albuminuria, either as monotherapy (compared to placebo) or when added to trandolapril (compared to trandolapril monotherapy) [71].

Dietary Protein Restriction

There is currently much less enthusiasm for dietary protein restriction as a means of preventing the progression of diabetic kidney disease, although two trials done in the last millennium were positive. These two trials enrolled 19 and 35 subjects with type 1 diabetes and showed that daily consumption of only 0.6 gm of protein per kg of ideal body weight reduced the rate of decline in glomerular filtration rate by 60–75% and urinary albumin excretion [72, 73]. A subsequent trial in Denmark, however, showed no differences in the decline in kidney function, but instead a higher risk of both end-stage kidney disease or death and mortality alone [74]. While some would argue that these trials were done in patients with late diabetic kidney disease, there are general concerns about the wisdom of restricting dietary protein in diabetic patients with kidney disease, who are already at risk for protein-calorie malnutrition, and must follow strict dietary regimens that limit carbohydrate, fat, and potassium consumption. The 2020 KDIGO guideline on diabetes management in chronic kidney disease recommends a middle ground of 0.8 gm of protein intake per kg of body weight per day for diabetic patients who are not on dialysis [3].

Dietary Sodium Restriction

Dietary sodium intake (or diuretic therapy) has a direct effect on proteinuria in patients with non-diabetic chronic kidney disease who are treated with inhibitors of the renin-angiotensin system. Several small studies in patients with diabetic kidney disease suggest a similar antiproteinuric effect of low-sodium diets [75–77], but it is

not clear whether this phenomenon is mediated or otherwise influenced by concomitant blood pressure changes. Furthermore, the effects of dietary sodium restriction have not been linked to kidney endpoints; most of the "long-term" studies of the intervention were limited to about 5 weeks' duration [3]. A recent report from the US National Academy of Sciences concluded that low sodium intake was "insufficient and inconsistent" with regard to any harmful effects on type 2 diabetes, glucose tolerance, and insulin sensitivity, and limiting sodium intake to 1.5–2.3 gm/d was not linked to any harm. It is likely that a low-sodium diet will lower blood pressure and reduce the need for diuretic therapy; both outcomes would presumably be beneficial for early or late diabetic kidney disease. The 2020 KDIGO guideline again recommends a middle ground of <2 gm (< 90 mmol)/d of sodium or < 5 gm/day of sodium chloride intake for people with diabetes and chronic kidney disease [3].

Sodium-Glucose Linked Transporter-2 (SGLT-2) Inhibitors

In 2008, the US FDA decreed that it would require, as a condition of marketing approval, that all new hypoglycemic medications be subjected to one or more "cardiovascular outcome trials," because long-term follow-up of some older agents indicated that they *increased* the risk of cardiovascular events in diabetic subjects. The FDA published guidance to industry that each new agent should not increase cardiovascular risk by more than 30%, compared to placebo in a large, multicenter, randomized clinical trial, and recommended that the primary endpoint should be a composite of cardiovascular death, stroke, or myocardial infarction, with a strict hierarchical system for the analysis and reporting of such trials. The stakes for such trials were very high: if the P-value for non-inferiority of the new agent was < 0.05, the medication could still be marketed. If this hurdle was met, *and* the P-value for superiority was < 0.05, the FDA would consider a Supplemental New Drug Application for a claim of protection from the event. This gave birth to an entire new generation of clinical trialists, with new insights into how the results of such expensive, long-term trials should be done.

Eventually, all four sodium-glucose linked transporter-2 (SGLT-2) inhibitors reported successful non-inferiority studies, and two showed superiority for preventing cardiovascular events. In addition, all four trials eventually reported, usually as a low secondary or "exploratory" outcome, an endpoint that included progressive diabetic kidney disease [78–81]. When the results of the first three trials and those from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE, discussed in detail below) [82] were meta-analyzed (see Fig. 23.5), there was not only a significant prevention of the composite of dialysis, kidney death, or transplantation and prevention of "substantial" loss of kidney function (defined as either > 50% or > 40% decline in *e*GFR, as defined in each trial) but also a significant prevention of acute kidney injury in subjects randomized to the SGLT-2 inhibitor [83]. The FDA had previously warned in 2016 that it had received case reports of acute kidney injury with these drugs [84], but the

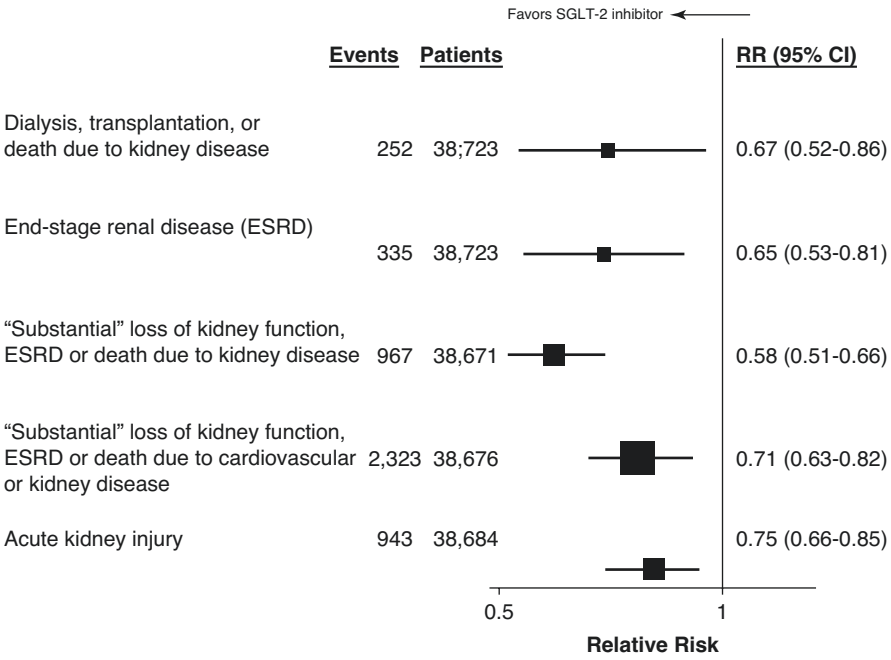

Fig. 23.5 Summary of meta-analyses of various composite kidney endpoints from four large randomized clinical trials [78–80, 82] of sodium-glucose linked transporter-2 inhibitors performed in patients with type 2 diabetes mellitus. SGLT-2, sodium-glucose linked transporter-2; RR, relative risk; 95% CI, 95% confidence interval; "substantial," either 50% or 40% reduction in kidney function, depending on the individual study's predetermined kidney endpoint; ESKD, end-stage kidney disease. (Adapted from [83])

meta-analytic result suggested that this association was exactly the opposite in randomized clinical trials!

Because the FDA traditionally considers new indications for drugs that have demonstrated safety and efficacy in clinical trials using a primary endpoint directly pertinent to the application, two SGLT-2 inhibitors have been tested in large clinical trials, specifically for their effects on preventing the progression of diabetic kidney disease.

The first was CREDENCE, which randomized 4401 type 2 diabetic subjects treated with RAAS blockade and older than 30 years with an *e*GFR between 30–90 mL/min/1.73 m^2 and 300–5000 mg of albumin/gram of creatinine to canagliflozin 100 mg/d or placebo [82]. The primary endpoint was doubling of serum creatinine, ESKD, or death from kidney or CV causes, but the first secondary endpoint omitted the CV death. The trial was stopped early, after 2.6 years, because the canagliflozin group enjoyed a 30% lower risk of the primary endpoint. Essentially all the kidney outcomes were better prevented with canagliflozin, compared to placebo. Study limitations included the following: (1) Because it was stopped early, secondary endpoints may have been underpowered to see a significant difference.

(2) It didn't measure *e*GFR after stopping canagliflozin, so differences at trial end are probably underestimated. (3) It excluded patients with stages 4–5 of CKD, non-albuminuric or "microalbuminuria," and CKD due to disorders other than diabetes, so its findings may not be generalizable to everyone. Nonetheless, the CREDENCE data were submitted to the FDA, which, on 30 SEP 19, granted canagliflozin an indication "to reduce the risk of end-stage kidney disease, worsening of kidney function, cardiovascular death, and heart failure hospitalization, in adults with type 2 diabetes and diabetic kidney disease."

The second such study randomized 4304 subjects with an *e*GFR between 25 and 75 mL/min/1.73 m^2 and an albumin/creatinine ratio of 200–5000 mg/gm (more than two-thirds of whom had diabetes) to dapagliflozin 10 mg or placebo. The study was terminated after only 2.4 years of follow-up, because the dapagliflozin group saw a 39% reduction in the primary outcome, a composite of a sustained decline in eGFR >50%, end-stage kidney disease, or death from kidney or cardiovascular causes [85]. There were also important reductions in the first secondary endpoint (which excluded cardiovascular death, 44%) and all-cause mortality (31%). Subgroup analyses of the primary endpoint (including those restricted to diabetic subjects) were entirely consistent with the overall conclusion. It is likely that these data, along with similar positive results in preserving renal function in patients with heart failure [86, 87], were reviewed by the FDA, which on 30 APR 21, granted dapagliflozin a new indication to prevent progressive decline in kidney function. These and other emerging data allowed the 2020 KDIGO guideline to recommend an SGLT-2 inhibitor for people with type 2 diabetes and stages 3–5 of chronic kidney disease [3].

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

As with the SGLT-2 inhibitors, cardiovascular outcome trials were required by the FDA for all GLP-1 agonists. Eight such trials have been reported; all succeeded in demonstrating non-inferiority, and four showed significant cardiovascular benefits. Different kidney outcomes were included as secondary or lower endpoints in six trials, the most common of which was the incidence of "severely elevated albuminuria." A meta-analysis of seven of these trials examined kidney outcomes, using a broad composite endpoint: incident severely increased albuminuria, decline in *e*GFR (or rise in serum creatinine), incident end-stage kidney disease, or death from kidney causes [88]. Although the relative risk for this endpoint was reduced to 0.83 (95% CI, 0.78–0.89) for subjects receiving a GLP-1 agonist compared to placebo, this was primarily driven by the reduction in severely increased albuminuria. In sensitivity analyses, excluding this component of the composite endpoint resulted in a non-significant relative risk reduction (13%; 95% CI, 27% to –3%). Results of a trial with a primary kidney endpoint comparing a GLP-1 agonist with placebo in diabetic patients treated with a RAS blocker, who have baseline *e*GFRs between 25 and 50 mL/min/1.73 m^2 and/or albumin/creatinine ratios >300 mg/gm, are eagerly awaited.

Summary

Commonly recommended interventions for diabetic subjects with early stages of kidney disease include strict glycemic control, one inhibitor (but *not* two inhibitors) of the renin-angiotensin system to prevent progression (and possibly enhance the chance of regression) of albuminuria, adequate (but maybe not intensive) lowering of blood pressure, dietary sodium (and maybe protein) restriction, a sodium-glucose linked transporter-2 antagonist, and maybe a glucagon-like peptide-1 agonist. The exception seems to be normotensive diabetic patients with normal to mildly elevated albuminuria, in which trials of inhibitors of the renin-angiotensin system have generally not shown significant benefit. Otherwise, these recommendations hold for all stages of diabetic kidney disease, although outcome data are more extensive in stages 3–5 of chronic kidney disease.

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Chapter 24
Diabetes and Kidney disease: metformin

Luigi Gnudi and Carlo Alberto Ricciardi

Metformin: Mechanisms of Action (Fig. 24.1)

Metformin, of the class of biguanides, is the undisputed first-line oral hypoglycaemic agent for the treatment of patients with type 2 diabetes in the absence of contraindications such as severe renal or hepatic impairment [1, 2].

The biguanides derive from a natural plant, *Galega officinalis*, a herbal medicine used in diabetes treatment for centuries since medieval times [3]. The risk of lactic acidosis seen mainly with biguanides such as phenformin and buformin resulted in their withdrawal from the market [4]. In contrast, the prevalence of lactic acidosis has not been so pronounced with metformin. Metformin is safe, effective, cheap and, most importantly, well tolerated by most patients [5].

Metformin, unlike other hypoglycaemic agents such as sulfonylureas or other secretagogues, does not affect insulin secretion and therefore does not cause hypoglycaemia. It is widely utilised as an insulin sensitiser in patients with type 2 diabetes (and at times in patients with type 1 diabetes in conjunction with insulin).

Metformin promotes a reduction in plasma glucose concentrations, increased insulin-mediated glucose uptake in insulin-sensitive tissues, while, in the liver, it inhibits lipogenesis and hepatic glucose production (gluconeogenesis).

Metformin-mediated effects on hepatic glucose production occur via activation of adenosine monophosphate-activated protein kinase (AMPK), lowering cyclic adenosine monophosphate (cAMP) and secondary reduction of the expression of gluconeogenic enzymes [6].

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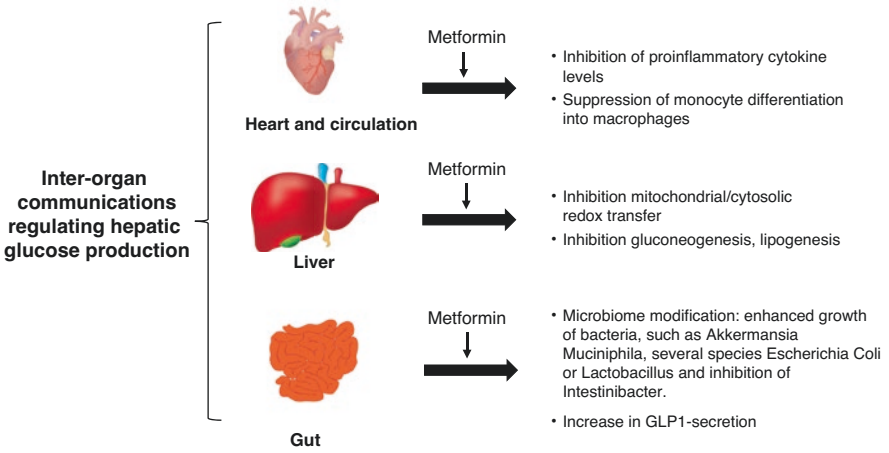

Fig. 24.1 Schematic representation of the action of metformin in different organs
Metformin's main action is to suppress hepatic glucose production. Metformin has different various non-glucose metabolism-related effects: (a) lowers proinflammatory cytokines and inhibits monocyte differentiation into macrophages, (b) modifies the gut microbiome and (c) activates the incretin axis with an increase in GLP1 secretion

The mechanism of metformin action on the regulation of mitochondrial activity and the potential involvement of AMPK in the inhibition of gluconeogenesis is quite controversial.

Metformin, a positively charged molecule, accumulates within the mitochondria where it inhibits mitochondrial complex I resulting in an uncoupling effect on oxidative phosphorylation [7] paralleled by a disruption of energy metabolisms [8–10].

Reports also suggest that pharmacological concentration of metformin stimulates mitochondrial respiration by increasing mitochondrial fission through AMPK-mediated mitochondrial fission factor signalling; conversely, when metformin accumulates to supra-pharmacological concentrations, it can reduce mitochondrial respiration through decreasing adenine nucleotide levels [11]. The inhibition of hepatic gluconeogenesis by metformin seems a consequence of an AMPK-independent disruption of energy metabolism driven by a decrease in hepatic ATP levels [8, 9, 12]. Conversely, studies suggest a potential metformin AMPK-dependent inhibition of the rate-limiting enzyme for gluconeogenesis phosphoenolpyruvate carboxykinase [13, 14], though this remains debated [12].

Other studies have described a metformin-mediated role in stimulation of hepatic insulin sensitivity also occurring via AMPK activation of acetyl-CoA carboxylase resulting in inhibition of lipid synthesis and increase in lipid oxidation [15].

The glycaemia-independent effects of metformin are weight loss [6, 8, 9], anti-inflammatory action with suppression of monocyte differentiation into macrophages via inhibition of nuclear factor kappa B [6, 16], promotion of glucagon-like peptide-1 (GLP-1) secretion in the gut [17–19] and modification of the gut microbiome [20].

The use of metformin is associated with a reduction in cardiovascular morbidity and mortality [21, 22], though this evidence is still debated [23]. A recent systematic review of 65 studies on metformin in patients with mild to moderate chronic kidney disease suggests a potential favourable effect of metformin on macrovascular outcomes [24–26].

Metformin-Positive Effects in the Diabetic Kidney

Experimental Work

The diabetic kidney is characterised by a progressive deposition of extracellular matrix both in the glomeruli and tubular interstitium leading to kidney fibrosis and a relentless renal function decline and end-stage renal disease (ESRD) [27, 28].

Studies suggest a protective effect of metformin on kidney fibrosis; this has been observed in experimental models (cell culture, animal studies) [29–32] and in humans [33, 34]; importantly, prospective randomised clinical trials are required to support these initial observations.

The proposed mechanism for the metformin-mediated antifibrotic effect and inhibition of epithelial mesenchymal transition appears to be driven by the activation of AMPK, downregulation of transforming growth factor-β1 and inhibition of angiotensin-2 [35]. Further, in kidney cells, AMPK activation by metformin has been implicated in inhibition of fatty acid oxidation, inflammation, oxidative stress and reactive oxygen species and in bone cells with downregulation of fibroblast growth factor 23 (known predictors of kidney disease) [36], which have been implicated in the pathophysiology of acute and chronic kidney disease [37, 38].

Metformin has been found to also ameliorate podocyte loss, an event described in diabetic kidney disease in both experimental models and humans [39]. In experimental animal models, metformin protects podocytes from apoptosis/detachment from the glomerular basement membrane via AMPK activation and inhibition of mammalian target of rapamycin (mTOR) signalling [40].

Importantly, metformin also retains a direct protective action on the vascular endothelium [41].

Because of its mechanism of action, metformin could be beneficial both in the classical presentation of diabetic kidney disease phenotype characterised by albuminuria and progressive kidney function decline and in the less classical non-albuminuric diabetic kidney disease associated with atypical vascular and tubulo-interstitial lesions with arteriolosclerosis instead of the typical glomerular lesions [42, 43].

Initial experimental work has also demonstrated a beneficial blood pressure and/or glucose-independent direct metformin effects on the kidney with the beneficial effect of metformin driven by AMPK activation and secondary improvement of mitochondrial biogenesis [44].

Clinical Studies

In an open retrospective study in approximately half a million patients with type 2 diabetes in a primary care database setting, the use of metformin was associated with a reduced risk for vascular chronic diabetic complications including kidney failure [45]. Importantly metformin use also associates with a reduced risk of renal function decline when compared to sulfonylureas independently of glycaemic and blood pressure control and body mass index [34].

In another retrospective study, in patients with diabetes and advanced chronic kidney disease (stage CKD 3B), metformin usage decreased the risk of all-cause mortality and incident ESRD [46].

Further in kidney transplant recipients, the use of metformin has been associated with a lower hazard ratio for allograft loss at 3 years post-transplant and with lower mortality [47].

Metformin and Lactic Acidosis in Patients with Diabetes: The Role of Kidney Function

As detailed above, biguanides cause a shift toward anaerobic metabolism (where lactate is a by-product) and less energy for gluconeogenesis. The spectrum of increased lactate accumulation in the blood resulting in lactic acidosis has been very common with phenformin (later withdrawn from the market) possibly because of its more powerful inhibitory effect on the mitochondrial respiratory chain when compared to metformin [48, 49]; this has been shadowing the glycaemic and glycaemic-independent beneficial properties of metformin.

Lactic acidosis is an anion gap metabolic acidosis with a plasma lactate level higher than 5 mmol/L and a pH less than 7.35. Severe lactic acidosis associates with multi-organ and system dysfunction with mainly neurological (e.g. coma, seizures) and cardiovascular (e.g. hypotension, ventricular arrhythmias) presentations paralleled by a high mortality [50].

Metformin is metabolised by the liver and excreted by the kidney in the urine [51]; indeed, lactic acidosis seems to occur more in patients on metformin treatment who had an episode of acute kidney injury (AKI) [52, 53].

In mild to moderate chronic kidney disease (CKD stage 1–2), there is a reduction in metformin renal clearance of approximately 20–30% that is further reduced, around 70%, as renal function declines (CKD stage 3) [54]; despite reduction in renal function, the circulating metformin levels remain within a putative safe therapeutic range, although this still needs to be defined [55]. Similarly, circulating lactate levels remain mostly within the normal range in metformin-treated patients with or without renal function impairment (CKD stages 1–3) [56].

One of the first studies, aimed at dissecting the potential concerns about the safety of metformin, was a randomised trial, the Comparative Outcomes Study of

Metformin Intervention versus Conventional (COSMIC) Approach Study that compared 1 year of treatment with metformin to other antidiabetic agents. The incidence of serious adverse events (including lactic acidosis) was similar between the two groups [57, 58]. Other studies followed providing reassurance on the use of metformin in prediabetes and newly diagnosed patients with diabetes [59, 60]. A recent systematic review has suggested a safe use of metformin with no risk for lactic acidosis in a total of 36,000 patients studied [61].

Despite significant reassurance from clinical trials, reports of cases of lactic acidosis in patients with diabetes treated with metformin have been reported extensively [62, 63].

A recent report highlights the occurrence of severe lactic acidosis in patients treated with metformin, without any other underlying conditions, that per se could have triggered the increase in lactate [64].

Of major importance, the risk of metformin-induced lactic acidosis remains a very rare event [61]. Most cases of lactic acidosis in patients treated with metformin occur in patients with underlying conditions (sepsis, kidney and liver impairment, severe cardiovascular disease/heart failure) rather than to metformin per se, as often a lack of correlation between lactate and metformin levels is observed [62, 65, 66].

It is often difficult, if not impossible, to determine the role, if any, of metformin in contributing to lactic acidosis [67].

In patients with type 2 diabetes, the incidence of lactic acidosis is similar to patients not taking metformin [58].

A recent study highlighted a potential increase in lactic acidosis in patients with impaired renal function. Specifically the risk of lactic acidosis or raised lactate concentrations was associated with metformin use in patients with GFR < 60 ml/min consistent with the recommendations that in metformin users renal function should be carefully monitored and metformin dose adjusted [68]. Nevertheless, parallel studies in the same population highlighted that lactic acidosis in metformin users is a rare event with only a trend for increasing lactic acidosis with GFRs less than 60 ml/min [69].

Guidelines on the Use of Metformin in Patients with Kidney Disease (Fig. 24.2)

Recent Clinical Practice Guideline by the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) on management of patients with diabetes and CKD stage 3b or higher (eGFR <45 ml/min) [70] recommends metformin treatment at a dose adapted to renal function as a first-line agent when lifestyle measures alone are insufficient to get to the target HbA1c [70].

The use of metformin clearly has the advantage of not causing hypoglycaemia, an important risk in patient with diabetes and CKD [71].

Of major importance is the sick day rule whereby patients are advised to temporarily stop metformin in conditions of dehydration (e.g. vomiting, diarrhoea), in

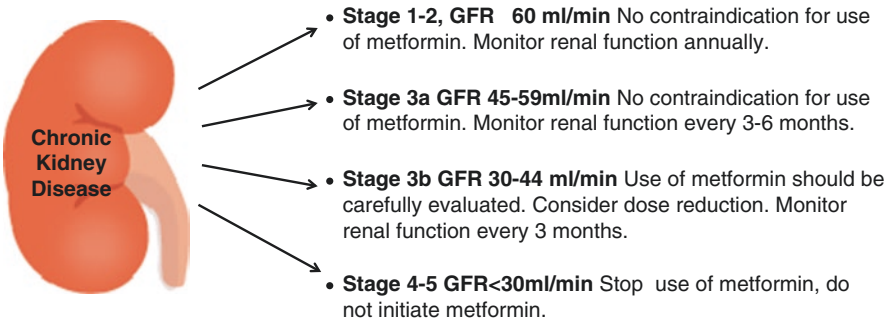

Fig. 24.2 Use of metformin in CKD stages
Schematic representation of safe use of metformin in patient affected by CKD. Use of metformin is not contraindicated in CKD stages 1–3; however, renal function needs to be monitored annually (CKD stages 1–2) or 6 monthly (CKD stage 3) to assess renal function decline. Reduction of metformin doses is required as GFR approaches 30 ml/min. Metformin should not be continued or initiated in patients with CKD stages 4–5

situations with an increased risk for AKI or when undergoing contrast media investigations. Specifically, in patient undergoing contrast media investigations, metformin continuation in diabetic patients with normal GFR (more than 60 ml/min) appears not to enhance the risk of metformin-associated lactic acidosis [72]. It is worth remembering that, as the probability of contrast media-mediated acute renal impairment in individual with normal renal function is around 2% or lower [73], we should still acknowledged the potential (low) risk of metformin-induced lactic acidosis in this population. In the interest of safety, a brief (few days) transient interruption of metformin treatment in patient, with normal renal function, undergoing contrast media investigations would be advisable.

The most recent Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines [74] propose a dose adjustment (reduction) for metformin with declining GFR. GFR should be monitored for patients treated with metformin; metformin dose should be reduced when the eGFR is less than 45 ml/min (and for some patients with eGFR 45–59 ml/min at high risk of acute kidney injury).

Metformin should be discontinued (and not initiated) in patients with eGFR less than 30 ml/min or kidney failure.

Conclusions

Evidence-based medicine on metformin use in patients with diabetes and CKD is clearly lacking, and no randomised clinical trials have, to date, tested the hypothesis on metformin safety in CKD patients with diabetes.

Lactic acidosis is a very rare event, and clinical studies addressing this specific issue will need hundreds of thousands of patients to be enrolled, studies that will likely never happen.

We should support the advice of the ERA-EDTA and KDIGO on metformin use in patients with diabetes and CKD in parallel with a careful monitoring of kidney function.

Any use of metformin in patients with GFR less than 44 ml/ min will have to carefully be reviewed and metformin dose adjusted. Metformin use at GFR less than 30 ml/min is today not advised.

In the past we had a limited number of oral hypoglycaemic agents, and insulin therapy was the only therapeutic option in patients with impaired renal function. Conversely, today we have more space for manoeuvres with new molecules that can help the diabetologist in achieving the desired glycaemic targets (e.g. incretins) [75]; further the described renoprotective effects of SGLT2 inhibitors will allow the use of metformin for longer periods in the natural evolution of diabetes and its vascular chronic complications [76, 77].

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Chapter 25
Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

Ashish Kataria and Christos Argyropoulos

Introduction

Roughly 9.4% of the US population has diabetes mellitus (DM) [1]. Diabetic kidney disease (DKD) is the single largest cause of chronic kidney disease (CKD), and over 38% of maintenance hemodialysis (HD) patients in the USA in 2017 had End-Stage Kidney Disease (ESKD) secondary to DM [2]. In addition, medical care of patients who have both DM and CKD adds a significant burden to the US healthcare system. In 2017, it contributed to 7.5% of the net Medicare fee for service expenditure and nearly 45 deaths per 1000 patient-years at risk [2]. Reducing the incidence of DKD will thus have a significantly beneficial impact on patient outcomes and healthcare costs. After the landmark trials [3, 4] showing benefit of renin-angiotensin system inhibition (RASi) in DKD in the early 2000s, there was a period of stagnation with no new approvals of medications that can protect the kidneys from the damaging effects of diabetes. However, in the last 5 years, sodium-glucose cotransporter-2 inhibitors (SGLT2is) have demonstrated a promising action in stabilizing and even reversing the effects of DKD, in addition to their cardiovascular (CV) benefits [5]. This chapter focuses on their mechanisms of action, current evidence, and clinical applications in DKD.

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Basic Pharmacology of SGLT2i

Glucose Transport in the Kidney and the SGLT2 Protein Kidneys can filter large amounts of glucose daily, and the exact amount filtered varies with blood glucose level and the prevailing glomerular filtration rate. Integrated over 24 hours, the filtered load is roughly between 150 and 180 gm in individuals without diabetes. In the absence of specific mechanisms for glucose reabsorption, the loss of this large amount of glucose would put the organism at a major caloric deficit, while also causing fluid and electrolyte losses that would obligatorily accompany glucose in the urine. Since glucose cannot enter the cell membranes freely, sodium-glucose cotransporters evolved to reabsorb filtered glucose in the nephron. Two members of the solute carrier 5 family are present in the proximal tubule and account for the reabsorption of glucose in the kidney: the low affinity, high capacity SGLT2 that is responsible for reabsorbing up to 90% of the filtered glucose in the S1 segment of the proximal tubule, effectively accounting for the bulk of total reabsorption in the kidney [6], and the high affinity, but low-capacity SGLT1 which accounts for approximately 10% of reabsorption in the S3 segment (SGLT1 is also responsible for the absorption of glucose in the small intestine). In humans, SGLT2 is a 14 helical transmembrane (TM) protein with a stoichiometric coupling ratio of Na/glucose of 1:1 [7]. The cotransporter action is driven by the basolateral sodium potassium-ATPase (Na^+/K^+-ATPase), which creates an intracellular negative Na gradient. This is a typical example of facilitated diffusion [8]: the Na/K-ATPase expels 3 Na^+ and transports 2 K^+ inside the cell, thus generating a net-negative gradient which is used by the SGLT2 to cotransport one glucose and one Na^+ inside the cell *from the tubular lumen*. Glucose then diffuses across the basolateral membrane into the interstitial space via the GLUT2 facilitative transporter.

A rather complex six-state rapid-equilibrium, alternative access model has been proposed to explain the cotransport of sodium and glucose [9]. The unloaded (state 1) has low affinity for sugar until a charged ion binds to the protein (state 2), opening thus an outer gate, and increasing the affinity of the SGLT2 for glucose which then binds to the transporter (state 3). This leads to a conformational change that presents both sodium and glucose to the intracellular space and the opening of an inner gate (state 4), followed by unloading of the glucose, the sodium (stage 5), and the generation of an unloaded protein with its binding site facing the cytoplasm (state 6). The latter undergoes a final conformational change that returns its orientation to the original state 1. The conformational changes that account for the transition from stage 3 to 4 have been crystallographically solved for the vibrio sodium/galactose cotransporter [9, 10]. Along with Na, once the substrate is sandwiched within the center pocket of the cotransporter with hydrogen bonds, a rearrangement of amino acid residues in the second TM segment (TM2) leads to the conformational change from inward-occluded to inward-open and opening of a tyrosine gate [10]. It is thought that similar gating mechanisms play a role in SGLT2, a channel that has been much less extensively studied than SGLT1 or its bacterial homologues.

Inhibition of Glucose Transport and the Anti-glycemic Effect of SGLT2i The naturally occurring O-glucoside compound, phlorizin [9, 11], has been known since the nineteenth century to cause glucosuria; however O-glucosides are metabolically unstable, due to their cleavage by beta glucosidases in the gastrointestinal tract, thus requiring large doses for the achievement of a pharmacologically relevant effect. This limitation reduced the potential for whole animal studies, until the development of C-glycosides, which are the basis of the commercially available SGLT2i. All small molecular inhibitors of the SGLT2 protein, irrespective of their chemical structure, inhibit the SGLT2 by acting on the luminal side of the first segment of the proximal collecting tubule [6]. To understand the effects of SGLT2i on glucose metabolism, we will consider the kinetics of glucose handling by the proximal tubule (Fig. 25.1). The net urinary glucose excretion (UGE, i.e., the amount of the glucose appearing in the urine) is the difference between the filtered load (the product of the concentration of the plasma glucose and glomerular filtration rate) and the reabsorption rate. The latter is subject to saturation kinetics: as long as the filtered glucose load is less than the maximum rate of reabsorption (Tm ~ 375 mg/min), SGLT2 can reabsorb the entire load, and no sugar is detected in the urine. When the filtered load becomes equal to the maximum reabsorption rate, glucose starts to appear in the urine. Plasma glucose concentration above which the SGLT2 transporters become saturated and glucosuria develops is known as the renal threshold for glucose excretion (RT_G). The latter under normal conditions is between 180 and 200 mg/dL (10 and 11 mmol/L), and thus no glucosuria is detected in individuals without diabetes or patients whose diabetes is well controlled.

In the presence of persistent hyperglycemia, as occurs in poorly controlled diabetes, the transport maximum increases, thus shifting the RT_G by about 40 mg/dl (2.2 mmol/L) higher [8]. Therefore, the kidneys reabsorb an additional 50–70 mg/min of glucose compared to the situation when RT_G is not increased. The precise

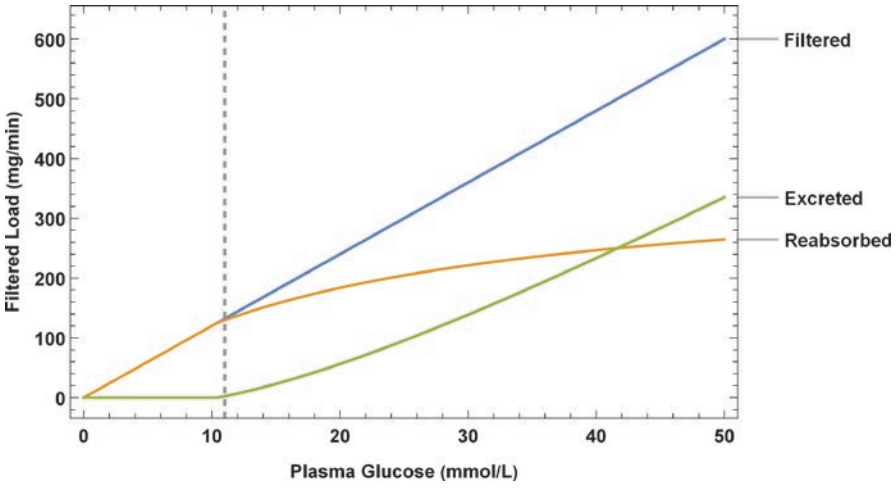

Fig. 25.1 Quantitative aspects of glucose handling in the proximal tubule. Dashed line: renal threshold for glucose excretion RT_G

mechanisms that this occurs has only been evaluated in animal models and is linked to the enhanced expression of the SGLT2 protein [12, 13]. Under these circumstances the kidneys become an important contributor to hyperglycemia. It thus follows that inhibiting glucose transport in the kidney would be a rational way to improve glycemic control. Since SGLT2 is responsible for resorption of ~90% of filtered glucose, its inhibition would result in renal glucosuria, a consequent loss of 70–80 gram of glucose daily, and an anticipated average reduction in glycosylated hemoglobin (HbA1c) of 0.5–0.8% [14]. The anti-glycemic effect of SGLT2i is accompanied by a low propensity for hypoglycemia, which can be explained by the drug's ceiling effect on glucose absorption at around 50% of the net-filtered glucose [15]. The effects of SGLT2i on UGE and thus A1c would diminish as the glomerular filtration rate declines because the ability of the kidney to *lose* glucose in the urine will decline. In pharmacodynamic studies, as summarized by Scheen [16], the UGE was reduced by 40–50% in the presence of CKD. The generally modest effect of SGLT2i on A1c (−0.81 to −1.02% in treatment-naive patients and − 0.57 to −0.63% on a metformin background) [17] was reduced to ~0.25% in the CREDENCE kidney outcome trial of canagliflozin. Similarly, an analysis of the 24-week Ph3 RCTs of empagliflozin [18] showed eGFR-dependent diminution of the placebo-corrected changes in A1c of 0.88%, 0.67%, 0.38%, and 0.04% as the eGFR declined from >90 ml/min/1.73 m^2 to <30 ml/min/1.73 m^2 in decrements of 30. Finally an analysis of 11 pooled Ph3 studies with dapagliflozin showed an insignificant dose-independent placebo-corrected change of 0.03% in patients with baseline eGFR between 12 and 45 ml/min/1.73 m^2 [19]. Collectively, these data show that SGLT2is are unlikely to exert a substantial anti-glycemic effect in patients with reduced kidney function, despite the higher *systemic* exposure (plasma concentration) [16]. This loss of efficiency limits the utility of these drugs as anti-glycemics in patients with reduced kidney function.

Effects of SGLT2i on the Mechanisms of Diabetic Kidney Disease According to the Brenner hypothesis, chronic kidney disease progresses as a result of the compensatory induction of hyperfiltration in the undamaged nephrons after an initial kidney injury in order to maintain total kidney function. This process is maladaptive because the increase in the single-nephron GFR eventually damages the hyperfiltering units, leading to more hyperfiltration in the remaining nephrons and further injury until global glomerulosclerosis and kidney failure occur. The Brenner hypothesis has been the basis of the successful application of RASi across the entire spectrum of CKD. However, the actual mechanisms of hyperfiltration in (diabetic) kidney disease remained poorly understood until it was experimentally demonstrated that phlorizin inhibits glomerular hyperfiltration in the diabetic rat [20]. It is instructive to review the findings of this seminal, yet underappreciated paper, since it underlines the success of SGLT2i in clinical applications. In these experiments, the investigators demonstrated a 25% decrease in the delivery of sodium, chloride, and potassium in the superficial nephrons from hyperfiltering kidneys of rats with streptozocin-induced diabetes mellitus. Such hyperfiltration could only result from

a more proximal enhancement in the reabsorption of those electrolytes. Phlorizin, delivered in the Bowman capsule, normalized the concentration of these electrolytes in the macula densa and the single-nephron GFR. This paper not only provided a mechanistic basis for hyperfiltration in the Brenner hypothesis, i.e., activation of tubuloglomerular feedback due to SGLT2-mediated proximal sodium reabsorption, but also highlighted the luminal site of the action of SGLT2i. These renal hemodynamic observations were later recapitulated in studies using the C-glycoside SGLT2i dapagliflozin [21] and genetic lesions (knockout) of the SGLT2i protein [22]. In another study in rats, it was experimentally shown that empagliflozin reduces both kidney damage (albuminuria) and hyperfiltration [23], thus preventing the initiation of diabetic kidney disease. In contrast to the anti-glycemic effects, the renal hemodynamic effects would be expected to manifest across the entire range of renal filtration since according to the Brenner hypothesis [24], hyperfiltration of *some* units will always be present until the kidney function declines to zero. Hence, to the extent that reduction of hyperfiltration *delays* the total loss of kidney function, SGLT2i may be a useful strategy at all levels of preserved kidney function.

Additional potential benefits of SGLT2i include reduced glucose toxicity on kidneys, leading to reduced inflammation and hypoxia injury by increased expression of hypoxia-inducible factor (HIF) [25] or even reduced oxygen consumption (which in turn may explain the apparent protection conferred by SGLT2i against acute kidney injury). Other potential effects include improved oxygenation of the renal cortex from reduced tubular workload, improved tubular cell integrity, and reduced oxidative stress, inflammation, and fibrosis [26–28]. Studies have shown a reduction in urinary levels of inflammatory cytokine interleukin-6 and monocyte chemoattractant protein-1 after treatment with SGLT2i [29, 30]. The "tubular hypothesis" [23] has been put forward as a unifying mechanism of the beneficial effects of SGLT2 inhibition on kidney disease and the "salt" paradox in diabetes [31]. The latter is the experimental observation that a low-salt diet induces renal vasodilation, hyperfiltration, and renal hypertrophy, whereas salt loading leads to renal vasoconstriction in the streptozocin model of diabetes. This inverse relationship between dietary salt and GFR, which is unique in diabetic kidney disease, is counterintuitive because the kidneys increase filtration under conditions, e.g. salt depletion, in which the GFR must be reduced to maintain homeostasis and vice versa. The unifying mechanism is that of tubular growth and the development of a senescent phenotype in tubular cells that make them more likely to secrete proinflammatory and fibrotic factors and more sensitive to changes in dietary salt. It has been demonstrated that enhanced glucose sensing in diabetes triggers tubular growth and that empagliflozin may partially but not completely attenuate tubular growth [23].

All SGLT2is cause a dose-dependent natriuresis and volume contraction of about 7% of plasma volume and a drop in blood pressure by 2–4 mmHg [32]. The combined effect of natriuresis and glucosuria is a modest weight loss of up to 3 kg which stabilizes after 6 months of continued use [33–35]. Interestingly enough, the effects

on blood pressure, body weight, and renal hemodynamics appear to be preserved at even lower eGFR levels, at which the anti-glycemic effect of SGLT2i is attenuated [16]. The mechanisms behind the beneficial effects on renal hemodynamics in patients with DKD are manifold. Most important is the restoration of the tubuloglomerular feedback [36] as a result of the increased distal sodium delivery from natriuresis, activation of the macula densa, which leads to constriction of afferent arteriole, and a consequent reduction in hyperfiltration. Inhibiting hyperfiltration reverses a key step in the pathophysiology of DKD and is accompanied by reductions in albuminuria by 30–40% [37, 38]. A universal and early reduction in estimated glomerular filtration rate (eGFR) of roughly 4–6 mL/min/1.73 m^2 is a class effect of SGLT2i and is reversible upon stopping the medication [39, 40]. While one may expect the hemodynamic effects of SGLT2i in humans to be a manifestation of vasodilatory effect on the afferent arteriole, as shown in type 2 diabetes [41], efferent vasoconstriction has been shown in patients with type 1 diabetes [36]. A unifying explanation for these divergent results may be provided by the effects of adenosine on vascular tone in the glomerulus. Adenosine is considered to play a key role in mediating the afferent arteriolar vasoconstriction in the tubuloglomerular feedback [13], through the adenosine A1 receptor (A1R), and in fact, pharmacologic inhibition of A1R blocks the effects of empagliflozin in experimental diabetic kidney disease [42]. However, adenosine may also affect tubuloglomerular feedback through the A2R which induces efferent vasodilatation [13, 43]. Since both efferent and afferent mechanisms contribute to the tubuloglomerular feedback through the increased production of adenosine by the macula densa, modulation of the feedback mechanism by SGLT2i may act to decrease renal hyperfiltration through either vascular effect. The prevailing mechanisms in a particular patient is likely to depend on a complex interplay of factors, including glycemia and/or hyperinsulinism, as well as the background level of RASi signaling, indicating that further work is required to clarify the relevant physiology and the downstream molecular mechanisms of SGLT2i.

In summary, SGLT2is exert pleotropic effects on kidney physiology and pathophysiology that are mainly, but not completely, explained by their effects on tubuloglomerular feedback enhancement of renal hyperfiltration in accordance with the Brenner hypothesis.

Cardiorenal Benefits of SGLT2i in Patients with Type 2 Diabetes

The renal benefits of SGLT2i were initially established not as primary outcomes in RCTs but as secondary or exploratory outcomes in trials designed to study their effects on cardiovascular outcomes (CVOT). Drug manufacturers are required to comply with the Food and Drug Administration (FDA)‘s mandate of proving CV safety of any new antidiabetic agent. In the EMPA-REG OUTCOME trial [44], 7020 patients with type 2 DM, established CV disease, and eGFR > 30 mL/

min/1.73 m^2 BSA were randomized to placebo or either 10 or 25 mg of empagliflozin and followed for mean 3.1 years. CV benefit was documented for the primary (MACE-3: a composite of cardiovascular death, non-fatal myocardial infarction, or stroke) outcome: hazard ratio (HR) of 0.86, 95% CI of 0.74–0.99, and p = 0.04 for superiority. In addition to the lower primary CVOT, composite renal endpoint (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease) was lower in the empagliflozin groups (12.7 versus 18.8%, hazard ratio (HR) in the empagliflozin group, 0.61; P < 0.001) [45]. The second trial on CVOT was the integrated CANVAS program in which 10,142 patients with type 2 DM and high CV risk were randomized to canagliflozin or placebo. After a median follow-up of 2.4 weeks, canagliflozin was associated with a statistically significant reduction in the primary MACE-3 outcome (HR, 0.86; 95% CI, 0.75–0.97, p = 0.02 for superiority). A benefit was also noted for canagliflozin in a prespecified composite renal outcome of 40% decrease in GFR, the need for RRT, or death from renal causes (HR, 0.60; 95% CI, 0.47 to 0.77) [46]. Dapagliflozin's CVOT trial, DECLARE-TIMI-58, randomized 17,160 participants to either 10 mg of the drug or placebo. After a median follow-up of 4.2 years, dapagliflozin [47] did not result in a lower rate of MACE-3 (HR, 0.93; 95% CI, 0.84–1.03; p = 0.17 for superiority), but was associated with a 24% reduction (HR, 0.76; 95% CI, 0.67–0.97) in the composite renal endpoint of >40% reduction in eGFR to <60 ml/min/1.73 m^2, new ESKD, or death from renal or cardiovascular causes. VERTIS-CV randomized 8246 patients in 1:1:1 ratio to placebo and 5 and 15 mg of ertugliflozin [48]; after a median follow-up of 3 years, the study showed that ertugliflozin was non-inferior, but not superior to placebo for the primary, MACE-3 outcome (HR, 0.97; 95% CI, 0.85–1.11). While the renal composite endpoint of doubling of the serum creatinine/need for dialysis or transplant or renal death did not achieve statistical significance (p = 0.08), it was also in the same direction of benefit as seen in the other CVOT (HR, 0.81; 95% CI, 0.63–1.04). All four SGLT2i safety trials reported consistent reductions in hospitalizations for congestive heart failure, with HR falling in the very narrow range of 0.65–0.73, obtaining the same benefit against this outcome that was seen in dapagliflozin's heart failure trial DAPA-HF. The latter trial included 4744 patients with heart failure, with or without diabetes, and showed that dapagliflozin reduced hospitalizations by 30% (95% CI, 17%–41%). While not statistically significant, dapagliflozin was associated with a 29% reduction in worsening kidney function during DAPA-HF.

The CREDENCE trial [49] was specifically designed to assess the effects of canagliflozin on kidney outcomes in patients with type 2 diabetes and albuminuric chronic kidney disease [50]. Patients with type 2 DM and albuminuric CKD (eGFR 30 to <90 mL/min/1.73 m^2 BSA and albumin (mg): creatinine (g) ratio > 300 to 5000) were treated with maximally tolerated RASi and were randomized to canagliflozin 100 mg daily or placebo. The primary outcome was a composite of ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes. After a median follow-up of 2.62 years, the trial was stopped. The relative risk of the primary outcome was 30% lower in the canagliflozin group (event rates of 43.2 versus

61.2 per 1000 patient-years in the placebo group: HR, 0.70; 95% CI, 0.59–0.82; p < 0.001) [49]. Canagliflozin reduced numerous kidney-relevant outcomes during CREDENCE: the relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lowered by 34% (HR, 0.66; 95% CI, 0.53–0.81; p < 0.001), and that of ESKD was lowered by 32% (HR, 0.68; 95% CI, 0.54–0.86; p = 0.002). Cardiovascular outcomes were also improved by canagliflozin: the HR for MACE-3 was 0.80; 95% CI, 0.67–0.95; p = 0.01, while that for hospitalization for heart failure was 0.61; 95% CI, 0.47–0.80; p < 0.001. In accordance with the Brenner hypothesis, canagliflozin exhibited a biphasic effect on eGFR: a reduction of 3.17 ml/min/1.73 m^2 relative to placebo during the first 3 weeks, which was followed by a slower rate of loss of eGFR over the long term. The placebo-corrected eGFR slope was 2.74 ml/min/1.73 m^2/year in the canagliflozin arm (95% CI, 2.37–3.11). Similarly, albuminuria was reduced by 31% (95% CI, 26–35). As mentioned previously, the reduction in A1c of 0.25% in CREDENCE was too small to account for the impressive improvement in kidney outcomes. Similarly, the systolic and diastolic blood pressures were reduced by 3.3 and 0.95 mmHg, which were also too small effects to account for the clinical benefit.

DAPA-CKD [51] randomized 4304 participants with an eGFR of between 25 and 75 ml/min/1.73m^2, with residual proteinuria (200–5000 mg of urinary albumin/gm of urinary creatinine) on maximally tolerated doses of inhibitors of the renin-angiotensin system to receive either 10 mg of dapagliflozin or placebo. Participants could have either diabetic or non-diabetic forms of CKD. Dapagliflozin reduced the primary endpoint of a sustained >50% eGFR decline, ESKD, renal, or cardiovascular death by 39% (HR, 0.61; 95% CI, 0.51–0.72; p < 0.001), with no evidence of statistical interaction between diabetes status at baseline. Death occurred in 4.7% of the dapagliflozin group and 6.8% in the placebo group (hazard ratio, 0.68; 95% CI, 0.53–0.88; p = 0.004). The hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55–0.92; p = 0.009). Hence, DAPA-CKD provided the first concrete evidence that the cardiorenal effects of SGLT2i extend to patients with CKD without diabetes. Furthermore, prespecified subgroup analyses showed that the benefits of dapagliflozin are observed independent of age (younger than 65 vs older than 65), gender, race, geographic region, level of eGFR (above or below 45 ml/min/1.73 m^2), and level of albuminuria (less or more than 1000 mg).

A high-level summary of the cardiorenal outcomes of SGLT2i in trials of patients with type 2 diabetes, patients with diabetic and non-diabetic kidney disease and heart failure is shown in Table 25.1. Other completed or currently ongoing studies to investigate the role of SGLT2i in renoprotection across the spectrum of CKD are listed in Table 25.2. At the time of the writing of this chapter, there is a large ongoing SGLT2 studies assessing the impact of SGLT2 across the spectrum of kidney disease that also includes patients with reduced eGFR but without albuminuria: EMPA-KIDNEY [52] that contrasts empagliflozin, respectively.

Table 25.1 Cardiorenal outcomes of SGLT2i studies to date in patients with type 2 diabetes

Angiotensin Receptor blockers		SGLT2 inhibitors								
Irbesartan	Losartan	Canagliflozin		Dapagliflozin			Empagliflozin		Ertugliflozin	Meta-analysis estimate
IDNT	RENAAL	CREDENCE	CANVAS program	DECLARE-TIMI-58	DAPA-HF	DAPA-CKD	EMPA-REG OUTCOME	EMPEROR-REDUCED	VERTIS-CV	
		ESKD or worsening renal function or death from all causes								
0.80	0.84	0.71 ¶	0.80¶	0.81¶	NR	0.61¶	0.64¶	0.84¶	NR	0.73
(0.66–0.97)	(0.72–0.98)	(0.62–0.80)	(0.70–0.91)	(0.73–0.90)		(0.51–0.70)	(0.55–0.75)	(0.72–1.00)		(0.66–0.81)
		Composite cardiorenal outcome ¦								
		0.70	0.76¶	0.76	0.78¶	0.61	0.59¶	0.84¶	0.88¶	0.74
		(0.59–0.82)	(0.65–0.88)	(0.67–0.87)	(0.68–0.89)	(0.51–0.72)	(0.49–0.71)	(0.72–1.00)	(0.76–1.02)	(0.67–0.81)
		Composite renal outcome ǂ								
		0.66	0.60	0.41	0.71	0.56	0.54	NR	0.81	0.61
		(0.53–0.81)	(0.47–0.77)	(0.20–0.82)	(0.44–1.16)	(0.45–0.68)	(0.40–0.75)		(0.63–1.04)	(0.54–0.68)

(continued)

Table 25.1 (continued)

Angiotensin Receptor blockers		SGLT2 inhibitors								
Irbesartan	Losartan	Canagliflozin		Dapagliflozin			Empagliflozin		Ertugliflozin	Meta-analysis estimate
IDNT	RENAAL	CREDENCE	CANVAS program	DECLARE-TIMI-58	DAPA-HF	DAPA-CKD	EMPA-REG OUTCOME	EMPEROR-REDUCED	VERTIS-CV	
		End-stage renal disease/need for renal replacement therapy (RRT)/worsening renal function (DSC or sustained eGFR reduction)								
All ARB [53]	**All ACEi** [53]									
0.78	0.60	0.64¶	0.63×	0.52¶	0.71	0.58¶	0.54¶	0.50	0.65†,*	0.59
(0.67–0.91)	(0.39–0.93)	(0.54–0.75)	(0.49–0.81)	(0.42–0.65)	0.44–1.16	(0.49–0.69)	(0.39–0.74)	(0.32–0.78)	(0.41–1.02)	(0.54–0.65)

Footnote: The definitions of the prespecified composite renal outcomes differed among trials: IDNT and RENAAL (development of end-stage renal disease (ESKD), doubling of serum creatinine (DSC) or death from any cause), CREDENCE (ESKD, DSC, sustained eGFR<15 ml/min/1.73 m^2, or death from renal or cardiovascular causes), CANVAS (40% reduction in eGFR, need for renal replacement therapy (RRT), or death from renal causes), EMPAREG (progression to macroalbuminuria, DSC, RRT, renal death, and incident albuminuria; in this table we calculated a composite cardiorenal outcome that includes DSC/RRR-ESKD or death from renal or cardiovascular causes to make comparisons more uniform against the other studies); DECLARE-TIMI-58 (40% reduction in eGFR, ESKD, or death from renal or cardiovascular causes), DAPA-HF (sustained reduction in the eGFR by 50% or more, ESKD, or death from renal causes), and VERTIS-CV (doubling of serum creatinine/need for renal replacement or renal death). Data in ACEi/ARB are from studies in patients with both type 1 diabetes and type 2 diabetes, while all SGLT2i studies enrolled patients with type 2 diabetes. ¦ composite cardiorenal outcome: ESKD/RRT/DSC or death from cardiac or renal causes ǂ ESKD/RRT/DSC and renal death † since there were no renal deaths in VERTIS CV, the outcome of ESKD/RRT/DSC is identical to the composite renal outcome × calculated from the event rate provided by the investigators after excluding the three renal deaths in the placebo arm of the study with the aid of a relative risk (Poisson) regression model. *The primary kidney outcome in VERTIS-CV included patients with any doubling of serum creatinine (HR, 0.81; 95% CI, 0.63–1.04); a subsequent analysis by the investigators looked at sustained doubling of serum creatinine [54], chronic dialysis/transplant, and kidney death, and this is the value reported herein ¶ calculated using a random effects meta-analysis of the hazard ratios of the components of the outcome as reported by the study investigators. NR: Not reported. The meta-analysis estimate is derived from all SGLT2i studies using a random effects model

Table 25.2 Summary of selected trials on SGLT2i with kidney disease endpoints

Study information: Acronym/Title/ Clinicaltrials.gov identifier/ Sample size	Methodology	Primary outcomes studied	Specific kidney disease endpoints
EMPA-REG OUTCOME Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients NCT01131676 N = 7064	Phase III, multicenter, international, randomized, parallel group, double-blind CV safety study empagliflozin (10 mg and 25 mg administered orally once daily) compared to the usual care in type 2 DM patients with increased CV risk (all patients had eGFR >30 mL/min/1.73 m^2 BSA)	Time to the first occurrence of the components of the MACE-3	1. Percentage of participants with new-onset albuminuria 2. Percentage of participants with new-onset macroalbuminuria 3. New or worsening nephropathy defined as: New onset of macroalbuminuria Doubling of the serum creatinine level accompanied by an eGFR ≤45 mL/min/1.73 m^2 Initiation of continuous renal replacement therapy. Death due to renal disease
EMPEROR-reduced EMpagliflozin outcomE tRial in patients with chrOnic heaRt failure with reduced ejection fraction NCT03057977 N = 3730	Phase III, randomized, double-blind trial to evaluate efficacy and safety of once-daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with reduced ejection fraction (HFrEF)	Composite primary endpoint of time to the first event of: 1. Adjudicated CV death 2. HHF in patients with HFrEF	1. eGFR slope from baseline 2. Time to the first occurrence of chronic dialysis or kidney transplant or sustained reduction of eGFR 3. Time to the first occurrence of one of: Chronic dialysis Kidney transplant Sustained reduction of > = 40% eGFR (CKD-EPI) Sustained eGFR <15 mL/min/1.73 m^2 for patients with baseline eGFR > = 30 mL/min/1.73 m^2 Sustained eGFR (CKD-EPI) cr <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2

(continued)

Table 25.2 (continued)

Study information: Acronym/Title/ Clinicaltrials.gov identifier/ Sample size	Methodology	Primary outcomes studied	Specific renal endpoints
Study information: Acronym/Title/ Clinicaltrials.gov identifier/ Sample size	Methodology	Primary outcomes studied	Specific kidney disease endpoints
EMPEROR-preserved EMpagliflozin outcomE tRial in patients with chrOnic heaRt failure with preserved ejection fraction NCT03057951 N = 5988	Phase III, randomized, double-blind trial to evaluate efficacy and safety of once-daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF)	Composite primary endpoint of time to the first event of the following: 1. Adjudicated CV death 2. HHF in patients with HFpEF	1. eGFR slope from baseline 2. Time to the first occurrence of chronic dialysis or kidney transplant or sustained reduction of eGFR 3. Time to the first occurrence of one of the following: Chronic dialysis Kidney transplant Sustained reduction of > = 40% eGFR (CKD-EPI) Sustained eGFR <15 mL/min/1.73 m^2 for patients with baseline eGFR > = 30 mL/min/1.73 m^2 Sustained eGFR (CKD-EPI) cr <10 mL/ min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2
EMPA-KIDNEY (the study of heart and kidney protection with Empagliflozin) NCT03594110 N = 6000 Participants may or may not have diabetes	Multicenter, international, randomized, parallel group, double-blind placebo-controlled clinical trial of empagliflozin once daily to assess cardiorenal outcomes in patients with chronic kidney disease	Composite primary outcome is time to the first occurrence of the following: 1. Kidney disease progression: Defined as: ESKD A sustained decline in eGFR to <10 mL/ min/1.73 m^2 Renal death A sustained decline of ≥40% in eGFR from randomization 2. CV death	Kidney outcomes are primary endpoints

Study information: Acronym/Title/ Clinicaltrials.gov identifier/ Sample size	Methodology	Primary outcomes studied	Specific kidney disease endpoints
CANVAS Canagliflozin cardiovascular assessment study NCT01032629 N = 4330	Randomized, multicenter, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on CV outcomes in adult subjects with type 2 DM	Time to the first occurrence of MACE-3	1. Percentage of participants with progression of albuminuria at the end of treatment 2. Change from baseline in UACR 3. Change from baseline in eGFR
CREDENCE Evaluation of the effects of Canagliflozin on kidney and cardiovascular outcomes in participants with diabetic nephropathy NCT02065791 N = 4401	Randomized, double-blind, event-driven, placebo-controlled, multicenter study of the effects of canagliflozin on kidney and cardiovascular outcomes in subjects with type 2 diabetes mellitus and diabetic nephropathy (albuminuric CKD (eGFR 30 to <90 mL/min/1.73 m^2 BSA and albumin (mg): Creatinine (g) ratio > 300 to 5000)	Composite primary outcome of: 1. ESKD 2. A doubling of the serum creatinine level 3. Death from renal or CV causes	Renal outcomes are primary endpoints
DAPA-HF A study to evaluate the effect of Dapagliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic heart failure NCT03036124 N = 4744	International, multicenter, parallel group, event-driven, randomized, double-blind, placebo-controlled study in patients with HFrEF, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to background regional standard of care therapy, for the prevention of CV death or reduction of HF events	Time to the first occurrence of any of the components of the composite: 1. CV death 2. HHF 3. Urgent HF visit	Composite of worsening kidney function, defined as: 1. A sustained decline in the eGFR of 50% or greater 2. ESKD 3. Renal death

(continued)

Table 25.2 (continued)

Study information: Acronym/Title/ Clinicaltrials.gov identifier/ Sample size	Methodology	Primary outcomes studied	Specific renal endpoints
Study information: Acronym/Title/ Clinicaltrials.gov identifier/ Sample size	Methodology	Primary outcomes studied	Specific kidney disease endpoints
DAPA-CKD A study to evaluate the effect of Dapagliflozin on kidney outcomes and cardiovascular mortality in patients with chronic kidney disease NCT03036150 N = 4304	International, multicenter, event-driven, randomized, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to standard of care, to prevent the progression of CKD or CV/renal death	Time to the first occurrence of any of the components of the composite outcome of: 1. ≥50% sustained decline in eGFR 2. Reaching 3. CV death 4. Renal death	Kidney outcomes are primary end counts
The VERTIS CV study cardiovascular outcomes following Ertugliflozin treatment in type 2 diabetes mellitus participants with vascular disease NCT01986881 N = 8246	Randomized, double-blind, placebo-controlled, parallel-group study to assess cardiovascular outcomes following treatment with ertugliflozin in subjects with type 2 diabetes mellitus and established vascular disease	Time to the first occurrence of MACE-3	Time to the first occurrence of the composite: 1. ESKD (dialysis or transplant) 2. Doubling of serum creatinine 3. Renal death

Footnote: *CKD* chronic kidney disease, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *HHF* hospitalization for heart failure, *HFrEF* heart failure with reduced ejection failure, *MACE* (major adverse cardiovascular event)-3 composite of cardiovascular death non-fatal myocardial infarction or non-fatal stroke, *UACR* urinary albumin-to-creatinine ratio

The results of the SGLT2i must be put in the context of the pivotal trials of angiotensin receptor blockers (ARBs) in diabetic kidney disease: IDNT (irbesartan) and RENAAL (losartan) and meta-analyses involving ACE inhibitors and ARBs from the late 1990s and early 2000s. The clinical trial evidence clearly shows that SGLT2i reduces the need for dialysis, worsening kidney function or composite outcomes of worsening kidney function, and death from cardiac or renal causes to a degree that is equivalent, if not superior, to the protection seen in the angiotensin receptor blocker (ARB) trials nearly 20 years ago [3, 4]. Hence the journey that started nearly two decades ago with an underappreciated micropuncture study [20] of a compound discovered in the nineteenth century led to the transformation of nephrology therapeutics and a major win for nephrology and public health in the twenty-first century.

Adverse Effects

The CV safety of SGLT2i was proven in four large RCTs: CANVAS, EMPA-REG OUTCOME, DECLARE-TIMI 58, and VERTIS-CV trials [44, 46, 47, 55]. Despite their multiple beneficial effects on CV and kidney physiology, patients taking SGLT2i are at risk of developing several adverse effects (AEs). Most AEs of SGLT2i are a class effect with no evidence of heterogeneity among members of the class and are directly driven by their mechanisms of action. We will briefly review the most frequent and the more fearful AEs likely to be encountered in clinical practice or even invoked to justify the non-use of SGLT2i. To aid comparison among the commercially available SGLT2is, we will resort to meta-analysis of the odds ratios of these complications against placebo in the major cardiovascular and kidney outcome trials in patients with diabetes.

Urogenital Infections

Urogenital infections such as urinary tract infections and mycotic genital infections are important complications of SGLT2i. RCTs [44] and meta-analyses [56] have consistently shown a higher incidence of urogenital infections in both males and females using SGLT2i [57]. Analyses of these infectious events in the major cardiovascular and kidney outcome SGLT2i trials are shown in Fig. 25.2 for urinary tract infections and Fig. 25.3 for mycotic infections for men and women. The incidence of urogenital infections thus differs according to the type of infection: mycotic infections are consistently higher in the users of SGLT2i (odds ratio, OR > 4) in both men and women. The incidence of these infections may be reduced substantially through personal hygiene advice that involves washing the urogenital area with water after each void and before going to bed [58]. On the other hand, bladder infections and pyelonephritis may not differ substantially in users versus non-users of SGLT2i (a non-statistically significant OR of 1.09). The lack of association

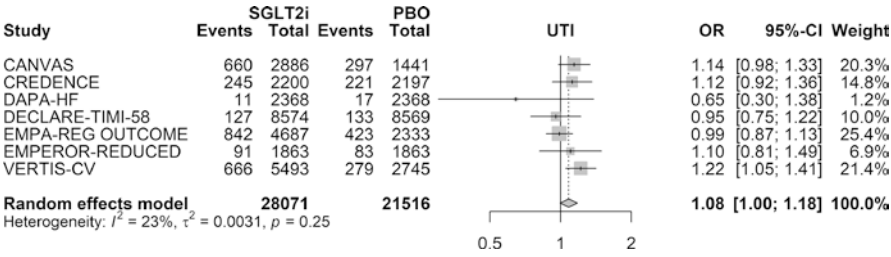

Fig. 25.2 Odds ratio of urinary tract infections (UTIs) between users and non-users of SGLT2i in the large CVOT safety and kidney outcome trials for canagliflozin (CANVAS and CREDENCE), empagliflozin (EMPAREG), dapagliflozin (DECLARE-TIMI-58, DAPA-HF, DAPA-CKD), and ertugliflozin (VERTIS-CV)

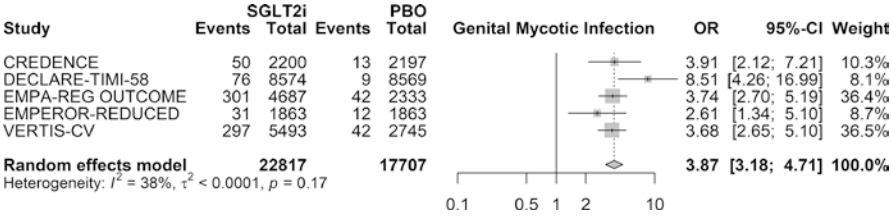

Fig. 25.3 Odds ratio of genital mycotic infections between users and non-users of SGLT2i in the large CVOT safety and kidney outcome trials for canagliflozin (CANVAS and CREDENCE), empagliflozin (EMPA-REG OUTCOME and EMPEROR-REDUCED), dapagliflozin (DECLARE-TIMI-58), and ertugliflozin (VERTIS-CV)

between SGLT2i and UTIs was also noted in previous meta-analyses of RCTs from the entire phase III development programs of these agents [59]. Fournier's gangrene – a rare but life-threatening infection – has been reported in patients taking SGLT2i in individual reports and FDA AE surveillance studies [60]. In the CREDENCE trial, the number of Fournier gangrene episodes was equally distributed in the canagliflozin and the placebo arms (two in each arm). A high index of suspicion is necessary to diagnose this condition because it may progress rapidly to multi-system organ failure and death. It cannot be stressed enough that one cannot attribute all cases of Fournier's gangrene that develop in patients receiving SGLT2i to the SGLT2i, as diabetes per se is the most common predisposing factor of this condition, accounting for 20–70% of cases even during the pre-SGLT2i era [61, 62].

Diabetic Ketoacidosis (DKA)

Despite early reports and an analysis of insurance claims database showing an increased risk of euglycemic DKA in patients taking SGLT2i [63], two different meta-analyses [57, 64], one powered to detect CV and non-CV safety of SGLT2i

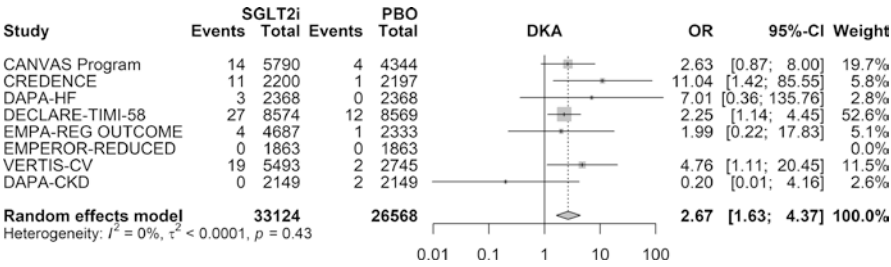

Fig. 25.4 Odds ratio of diabetic ketoacidosis (DKA) between users and non-users of SGLT2i in the large CVOT safety and renal outcome trials for canagliflozin (CANVAS/CANVAS-R and CREDENCE), empagliflozin (EMPA-REG OUTCOME, EMPEROR-REDUCED), dapagliflozin (DECLARE-TIMI-58, DAPA-HF, DAPA-CKD), and ertugliflozin (VERTIS-CV)

and the other designed specifically for DKA, have not shown an increased risk of DKA in patients taking SGLT2i. However the likelihood of DKA was consistently higher (OR, 2.79) in participants assigned to SGLT2i versus those of placebo in the large cardiovascular safety and kidney outcome trials (Fig. 25.4). Notably, the risk for DKA was numerically increased among patients with T2D, but not in those who did not have diabetes (e.g. the participants in EMPEROR-REDUCED and patients without T2D in DAPA-CKD) but there was no statistical heterogeneity in DKA among trials. Notwithstanding these high odd ratios, it should be emphasized that the absolute risk for DKA remains low even among patients with T2D: in the CREDENCE trial, the rate of this complication was 2.2 episodes for every 1000 patient-years in the canagliflozin arm. However, prescribing physicians are advised to be cautious in patients at higher risk due to this rare but severe complication [65]. Potential risk factors for DKA include pancreatic insulin deficiency, caloric restriction, and alcohol abuse. Physicians should consider temporarily discontinuing SGLT2i in clinical situations that predispose to ketoacidosis, e.g., prolonged fasting, post-surgery, or an acute illness. Alternatively, such patients may be provided urinary or capillary ketone strips for early detection [65]. This strategy, however, has not been subjected to a controlled clinical investigation. As the incidence of euglycemic ketoacidosis appears to be higher in patients with type 1 diabetes, the use of SGLT2i is not currently indicated for such patients in the USA (though two SGLT2i are approved as antiglycemics for patients with type 1 diabetes in the European Union).

Acute Kidney Injury (AKI) and Volume Depletion

All SGLT2is cause an immediate 4–6 mL/min/1.73 m^2 drop in GFR after initiation [18, 19]. The drop is reversible, and GFR increases upon their cessation, even after a prolonged use. This results from vasoconstriction of afferent arteriole and the natriuresis causing slight volume depletion. Volume depletion was numerically

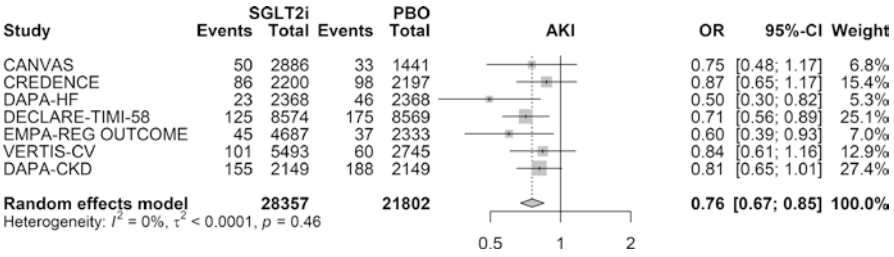

Fig. 25.5 Odds ratio of acute kidney injury (AKI) between users and non-users of SGLT2i in the large CVOT safety and kidney outcome trials for canagliflozin (CANVAS/CANVAS-R and CREDENCE), empagliflozin (EMPA-REG OUTCOME and EMPEROR-REDUCED), dapagliflozin (DECLARE-TIMI-58, DAPA-HF, DAPA-CKD), and ertugliflozin (VERTIS-CV)

higher in the large cardiovascular and kidney outcome trials with odds ratios ranging from 1.03 (DECLARE-TIMI-58) to 1.53 (CANVAS), with an estimated odds ratio of 1.17 (95% CI, 1.03–1.33) using random effects meta-analysis. Patients with precarious volume status, gastrointestinal losses, and reduced oral intake are at risk of developing frank pre-renal AKI with SGLT2i, similar to other medications that impact volume status. Despite these warnings, examination of the odds of volume depletion and AKI in real-world clinical datasets suggests a different narrative. In a prospective cohort from Israel with ~12,000 patients, the odds for AKI was 0.47 (05% 0.27–0.80) in patients initiating SGLT2i relative to DPP4 inhibitors [66]. Similar results were obtained in US cohorts from two large health care systems using propensity score analysis: SGLT2i users had a highly statistically significant 40–50% reduction in the hazard ratio for AKI relative to non-SGLT2i users [67]. Finally, an examination of the AKI events in the major outcomes trials (Fig. 25.5) also shows reduced odds of AKI with SGLT2i, by ~25%. These data provide some reassurance that the prevalence of AKI is *not* increased among the population of patients receiving SGLT2i, even though SGLT2i may be implicated in AKI episodes related to volume depletion in specific patients. As more data accumulate, it is likely that the prescriber information will carry warnings about AKI related only to volume depletion, e.g., as was done for canagliflozin in early 2020.

The pathophysiology of AKI that develops while receiving SGLT2i may differ from the conventional drug- related AKI. This hypothesis was explored in a prospective cohort of patients receiving SGLT2i who were hospitalized with an acute illness [68]. Patients with AKI, while receiving SGLT2i, had elevated serum and urinary NGAL, consistent with distal tubular injury. On the other hand, the same patients had unaltered levels of KIM-1 (a proximal tubule injury biomarker), suggesting that in those patients who develop AKI, the mechanism may be related to outer medullary hypoxia but with relatively preserved or even possibly improved cortical oxygenation. In line with this hypothesis, an examination of several urinary biomarkers in new users of dapagliflozin found that after a period of 6 weeks, the drug reduced urinary KIM-1 by 22.6% and IL-6 by 23.5% with no changes in NGAL [19].

So how does one put these data together to come up with a rational clinical approach to AKI in SGLT2i users? In our practice, we decrease the dose of other

diuretics by 25–50% when initiating SGLT2i to avoid precipitating frank pre-renal AKI. Subsequently, we titrate the diuretics upward as needed to meet blood pressure and volume overload goals. We also check kidney function within 4 weeks of initiating SGLT2i to establish the patient's new baseline after the expected hemodynamic drop in the eGFR. Patients who develop AKI while on SGLT2i usually have additional causes for this event, e.g., an intercurrent illness or surgery, and therefore we do not hesitate to restart these agents once the acute event has resolved.

Dosage recommendations vary according to eGFR for the various SGLT2is (see "Approved Uses" later in this chapter). This represents a major change from the late 2010s when all SGLT2is were contraindicated in patients with severe CKD (eGFR<30) ESKD. This relative contraindication stems from the early trials of SGLT2i as anti-glycemic agents: as the eGFR declines, SGLT2is lose their A1c lowering efficacy. However, improvements in cardiorenal outcomes may be maintained at lower levels of eGFR as shown in CREDENCE and the DAPA-CKD trials and thus individual SGLT2i may be used to very low eGFR, or even until the patients start dialysis for cardiorenal protection.

Amputations

The absolute risk of amputations was found to be higher in patients taking canagliflozin in the CANVAS program [69]. It is not, however, clear if this risk was a chance finding as it was not reproduced in analyses of FDA AE reporting system analysis [70] or insurance claims [71, 72]. Reassuringly, this signal was not seen in the CREDENCE trial for canagliflozin or the subsequent trials with other SGLT2i, e.g. the VERTIS-CV trial for ertugliflozin or DAPA-CKD of dapagliflozin. A meta-analysis of the amputation events in the major cardiovascular safety and kidney outcome trials is shown in Fig. 25.6. The statistical heterogeneity (p = 0.02) is

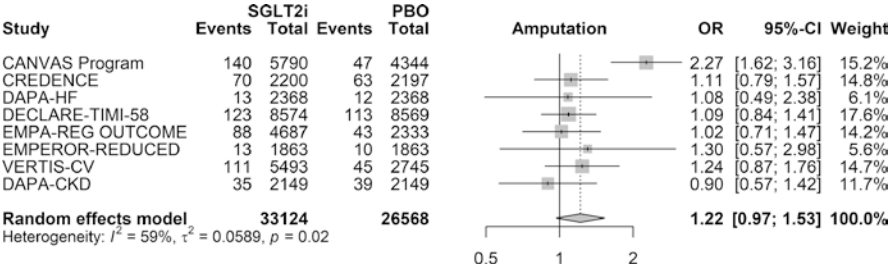

Fig. 25.6 Odds ratio of amputations between users and non-users of SGLT2i in the large CVOT safety and kidney outcome trials for canagliflozin (CANVAS/CANVAS-R and CREDENCE), empagliflozin (EMPA-REG OUTCOME and EMPEROR-REDUCED), dapagliflozin (DECLARE-TIMI-58, DAPA-HF, DAPA-CKD), and ertugliflozin (VERTIS-CV)

driven by the results in the CANVAS program, and all other studies showed a relative risk that was numerically close to one. While the numerical estimate of the risk is different from one, the 95% confidence interval includes one. It should be remembered that peripheral vascular (arterial) disease is a form of atherosclerotic disease, and in that regard, not using SGLT2i in patients with peripheral vascular disease may exclude a large number of patients who will potentially benefit from these therapies (e.g., 20–24% of participants in EMPA-REG OUTCOME and CREDENCE trials had peripheral vascular disease). Until more data from the ongoing trials becomes available, it is reasonable to avoid SGLT2i in patients with active peripheral vascular disease (e.g., critical ischemia, non-healing ulcers) and discuss the potential for this complication in all other patients initiated on SGLT2i and follow them clinically for signs of incident or worsening of peripheral arterial disease.

Use in Kidney Transplant Recipients

Up to one-third of kidney transplant recipients (KTR) suffer from post-transplant diabetes mellitus (PTDM) [73, 74]. The presence of preexisting DM or its development after transplantation negatively impacts both short- and long-term patient survival from the added CV mortality [75–77]. PTDM also lowers graft survival [78, 79], and there are signals to suggest that recurrence of DN in transplanted kidney adds to graft losses [80]. SGLT2is thus have a unique role post-transplant by providing added CV benefit and renoprotection along with diabetes control. Empagliflozin and canagliflozin have been used safely in KTR with PTDM in both unrandomized and randomized studies [81–83]. Reductions in HbA1c were modest (0.2–0.8%), no major interactions were noted with immunosuppressives, and there were no significant declines in eGFR in KTR [82, 84, 85]. Their use as monotherapy aimed to replace insulin has shown suboptimal glycemic control in a prospective trial [83]. Most studies in KTR did not report a significantly increased risk of UTIs over the short term, and this needs to be confirmed in studies with longer observation periods. It is, thus, recommended to use SGLT2i as add-on therapy to insulin or other oral agents and using extreme caution in patients who are prone to recurrent UTIs. While these studies were not powered to investigate the long-term CV benefits or effects on graft or patient survival among KTR, extrapolation from the non-transplant literature strongly supports their use even in KTR. The optimal timing for the initiation of SGLT2i after KTR remains to be determined. At our institution, we start SGLT2i 6 months after the surgery in patients who are deemed to be of high residual cardiac risk. Histopathologic findings of diabetic kidney disease in allograft biopsies would also be a valid indication to initiate SGLT2i. There are no studies that have examined whether early initiation of SGLT2i in recipients of organs from donors with diabetics will allow the prolongation of the function of the allograft.

Approved Uses and Pharmacological Properties of Individual SGLT2i

There are currently four SGLT2i approved for clinical use in the USA (Table 25.3): empagliflozin (Jardiance [86]), canagliflozin (Invokana [87]), dapagliflozin (Farxiga [88]), and ertugliflozin (Steglatro [89]). SGLT2is are also coformulated with sustained release metformin, and such combination products aim to provide two American Diabetes Association guidelines that indicated therapies in a single pill to improve compliance and patient convenience. All SGLT2is are currently indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes, and to date this is the only approved indication for ertugliflozin. In addition, empagliflozin is also indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. Dapagliflozin has two cardiovascular indications: (i) to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes and established cardiovascular disease or multiple risk factors and (ii) to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure and reduced ejection fraction (NYHA II–IV), irrespective of the presence of diabetes. Canagliflozin's cardiovascular indication is to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. At the time of the writing of this text, canagliflozin is approved to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic kidney disease with albuminuria. In early 2021, dapagliflozin was approved by the FDA to reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression. The approved indications of the SGLT2is follow from their effects on the prespecified outcomes in their large clinical outcomes and are likely to change as more studies are completed.

Practical Considerations

Currently, the American Diabetes Association (ADA) recommends using SGLT2i as an add-on therapy with metformin or other antidiabetic agents in patients with type 2 DM and CHF or elevated risk for CV disease or presence of CKD, independent of the HbA1c level or individual HbA1c target [90]. The lowering of HbA1c with SGLT2i is modest. However, they have an overarching role beyond achieving euglycemia in the form of cardioprotection, renoprotection, and reduction in heart failure exacerbations. As a result of the CREDENCE trial, we have solidly established that the standard of care for patients with T2D and CKD is not just RASi, but RASi *and* SGLT2i, while DAPA-CKD confirmed the validity of this paradigm

Table 25.3 Overview of currently available SGLT2i in the USA

Drug	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Common dosages	100 mg, 300 mg	5 mg, 10 mg	10 mg, 25 mg	5, 15 mg
US brand names	Invokana	Farxiga	Jardiance	Steglatro
Dosage in renal impairment	eGFR ≥60 mL/minute/1.73 m^2: No dose adjustment necessary eGFR 30 to <60 mL/minute/1.73 m^2: 100 mg once daily eGFR <30 mL/minute/1.73 m^2: Initiation is not recommended, but patients with albuminuria >300 mg/day may continue 100 mg daily to reduce the risk of ESKD, doubling of creatinine, cardiovascular death, or heart failure hospitalization ESKD, HD: Use contraindicated	eGFR ≥45 mL/minute/1.73 m^2: start at 5 mg and may increase to 10 mg for additional glycemic control eGFR 25 to <45 mL/minute/1.73 m^2: 10 mg once a day <25 mL/minute/1.73 m^2: initiation is not recommened, but patients may continue 10 mg daily to reduce the risk of eGFR decline, End Stage Kidney Disease, Cardiovascular Death and hospitalization for heart failure. ESKD or HD: Use contraindicated	eGFR ≥30 mL/minute/1.73 m^2: No dose adjustment necessary for glycemic control eGFR <30 mL/minute/1.73 m^2: use not recommended for glycemic control, insufficient data for patients who have T2D and established cardiovascular disease eGFR <20 mL/minute/1.73 m^2: insufficient data to make a dosing recommentation for those patients with heart failure with reduced ejection fraction ESKD or dialysis: contraindicated	eGFR ≥45 mL/minute/1.73 m^2: No dose adjustment necessary eGFR <45 mL/minute/1.73 m^2: use not recommended ESKD or dialysis: Use contraindicated
Dosage in hepatic impairment	Mild or moderate impairment: No dose adjustment necessary Severe impairment: Not studied, use not recommended	No dosage adjustment necessary, has not been studied	No dosage adjustment necessary	Mild or moderate impairment: No dose adjustment necessary Severe impairment: Not studied, use not recommended

(continued)

Table 25.3 (continued)

Bioavailability	65%	72%	78%	~100%
Peak plasma time	1–2 hour	2 hour (fasting)–3 hr. (fatty meal)	1.5 hour	1 hour (fasting)–2 hr. (after meal)
Protein binding	99%	91%	86.2%	93.6%
Volume of distribution	119 L	118 L	73.8 L	85 L
Elimination half-life	100 mg dose, 10.6 hours; 300 mg dose, 13.1 hours	12.9 hours	12.4 hours	16.6 hours
Elimination	Urine, 33%; feces, 41.5%	Urine, 75%; feces, 21%	Urine, 54.4%; feces, 41.2%	Urine, 50.2%; feces, 40.9%
Renal recovery of parent drug	<1%	< 2%	~20%	1.5%
Selectivity for SGLT2 over SGLT1	1:414	1:1200	1:2500	1:2000

shift and extended it to patients with CKD but without T2D. From a nephrology perspective, all patients with DKD and eGFR >30 mL/min/1.73m^2 are candidates for SGLT2i initiation. For an optimal effect, these agents should be added on a background of maximally tolerated RASi. The choice of SGLT2i depends upon several factors: cost, dose adjustments with eGFR, presence of active PVD, and availability in the institutional or insurance formularies. Such factors may result in the use of specific SGLT2s off their approved labels. Prescribing information should be consulted for individual agent's dosing, and adjustments should be made for most recent eGFR. As these cutoffs are likely to change in the near future, prescribers should consult the most recent version of the drug package insert. Patients should be warned about the potential AE, especially DKA and urogenital infections. The evidence behind the increased risk of amputations is weak; however, a thorough discussion of the risk-benefit ratio should be undertaken in patients with active PAD. The absolute increase in the risk of amputations in the canagliflozin arm of CREDENCE over placebo was a non-statistically significant 0.9 episodes per 1000 patient-years. However, the use of canagliflozin also resulted in absolute rate reduction of ESKD by 13.4 events per 1000 patient-years. For most patients, this would represent a highly acceptable trade-off to avoid dialysis and at the same time avoid a cardiovascular event or a symptomatic heart failure episode. Like RASi, kidney function should be rechecked after initiation (recommend 3–4 weeks after initiation, except in patients on concomitant diuretics, in whom one may check sooner) and should be monitored regularly. An expected drop in eGFR by 4–6 mL/min/1.73m^2 should not lead to automatic discontinuation, especially if it is observed in the first 3–4 weeks of treatment and is not progressive. More pronounced changes in eGFR, should prompt reconsideration of the entire regimen (not just the SGLT2i!), especially the types and doses of concomitant diuretic agents. In general, all SGLT2is lower albuminuria by approximately 30 to 40% [38, 91, 92]; the concomitant drop in albuminuria and eGFR suggests that the drug is reducing hyperfiltration. The beneficial effect on blood pressure and weight reduction is modest yet may be an important element to discuss with the patient under a shared decision-making paradigm. SGLT2i-induced natriuresis may be detrimental in patients with precarious fluid balance or inadequate oral intake and may predispose them to AKI or DKA. It is thus important to be mindful of conditions that impair the patient's ability to ingest fluid or defend their intravascular volume, and thus it is prudent to temporarily discontinue these agents during acute illnesses or surgeries. All SGLT2is are contraindicated in patients with ESKD. In summary, SGLT2i can be used in combination with insulin, other oral hypoglycemics (RASi), and other antihypertensives to achieve first and foremost cardiorenal protection and secondarily to improve glycemic control in patients with type 2 diabetes.

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Chapter 26
Glucagon-like Peptide-1 Receptor Agonists (GLP1-RA)

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Introduction

The number of patients with diabetic kidney disease has been progressively increasing over the past two decades with a dearth of therapeutic development. As a result, until recently, the treatment of diabetic kidney disease (DKD) was based on management of modifiable risk factors such as hyperglycemia and hypertension by renin-angiotensin system inhibitors. However, management of DKD has been altered by the results of recently published large cardiovascular outcome trials of glucagon-like peptide-1 receptor agonists (GLP1-RAs), which demonstrated unexpected mitigation of kidney disease, cardiovascular death, and atherosclerotic events [1–4].

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GLP1-RAs were initially developed as glucose-lowering therapies for the treatment of type 2 diabetes mellitus (T2DM) based on the physiological mechanisms by which endogenous incretin hormones regulate glucose homeostasis. However, secondary outcomes for kidney disease from the GLP1-RA trials have shown prevention of new-onset albuminuria, progression to macroalbuminuria, and slowing of glomerular filtration rate (GFR) decline in early- to late-stage chronic kidney disease (CKD). These effects are independent of the glucose-lowering effects of these agents [1, 3–5]. Therefore, there has been a considerable interest in the non-glycemic mechanisms of action of GLP1-RAs. Evidence to date suggests that the central mechanisms involve direct immune system modulation and inflammatory signaling, which are both important contributors to mechanisms of kidney damage in DKD [6–8]. Clinical trials assessing the impact of GLP1-RA on primary outcomes for kidney disease in patients with DKD are underway [9]. This chapter will focus on current recommendations for the use of GLP1-RA therapies in patients with DKD, emerging results from clinical trials, and proposed biological mechanisms for kidney protection beyond glucose homeostasis.

Glucagon-like Peptide-1 Physiology and Natural Functions

GLP1-RAs are referred to as "incretins" as they are used therapeutically to augment incretin-like effects. The term incretin effect (*in*testinal se*cret*ion of *in*sulin) describes the increased insulin response that occurs after oral versus intravenous glucose administration [10]. Discovery of the incretin effect prompted the search for glucoregulatory gut peptides known as incretin hormones. Gastric inhibitory peptide (GIP) was the first incretin hormone, identified in the 1970s [11, 12]. Glucagon-like peptide-1 (GLP-1) was later discovered in the early 1980s following the cloning and sequencing of the mammalian proglucagon gene [13, 14]. GLP-1 and GIP have since proven to be important mediators of post-meal insulin release.

GLP-1 is one of the products of proglucagon, a peptide that is cleaved into several different hormones in the human pancreas, gut, and brain [15]. Differential expression of these cleavage products is controlled by tissue-specific expression of cleavage enzymes [15]. Different nutrients, neuroendocrine factors, products of bacterial metabolism (e.g., bacterial endotoxin), and inflammatory mediators (e.g., interleukin-6) promote GLP-1 release from enteroendocrine L cells. These cells are most densely located in the terminal ileum and colon [16–21].

In humans, basal GLP-1 concentrations are maintained at low circulating levels, but secretion peaks quickly after meals as part of the response to eating [15]. The kinetics of postprandial GLP-1 release is rapid and biphasic. Plasma concentrations peak 10–30 minutes after eating and again about 1–2 hours later [15, 21, 22]. Because the initial peak occurs before food reaches the distal intestine, the stimulus for the initial GLP-1 secretion is thought to be via vagal nerve stimulation, while the stimulus for the second peak is probably intestinal nutrient absorption [19, 23]. Elimination of GLP-1 once released is extremely rapid and is primarily mediated by breakdown of GLP-1 by the enzyme dipeptidyl peptidase 4 (DPP-4 or DPP-IV).

Thus, the plasma half-life of GLP-1 is less than 5 minutes [24]. Because GLP-1 is so rapidly degraded by DPP-4, glucose-lowering therapies that inhibit DPP-4 have also been developed.

Natural Roles of GLP-1

GLP-1 is classically known as an insulin secretagogue [25]. Additionally, GLP-1 has multiple actions beyond glucose homeostasis, including roles as a central nervous system neurotransmitter and a modulator of immunity and inflammation [26]. Actions of GLP-1 are mediated primarily by GLP-1 receptors. These receptors abound in the human pancreas and duodenum, stomach, and kidney, with lower expression observed in the heart, lung, and distal intestine [27–30]. Kidney expression of the GLP-1 receptor is still under investigation. In various models (e.g., primates, mice, rats, human tissues), the receptors have been observed in the endothelium of arterioles and glomeruli and less consistently in interstitial macrophages and proximal tubular epithelial cells [27, 31–34].

Glucose Homeostasis

GLP-1 is a key mediator of postprandial insulin release. GLP-1 receptor activation lowers glycemia via several mechanisms: [1] stimulation of glucose-dependent insulin release, [2] decreased glucagon secretion from pancreatic α-cells, and [3] delayed gastric emptying contributing to reduced postprandial hyperglycemia and reduced appetite and food intake.

Pancreatic islets express GLP-1 receptors, and binding of GLP-1 to these receptors is the classic mechanism by which GLP-1 prompts release of insulin-containing secretory granules from pancreatic β cells [35]. The effect of GLP-1 on the stomach also promotes a sensation of satiety, which intersects with its third role related to digestion and metabolism to act as an appetite suppressant [36]. The role of GLP-1 in gastric emptying and gastrointestinal motility is likely related to activation of vagus nerve afferent fibers [23, 37]. Notably, vagus nerve afferent neurons express the GLP-1 receptor, and gene knock-out of this receptor causes increased blood glucose excursions after eating [38]. Nerve fibers that express GLP-1 innervate multiple areas of the brain, particularly the hypothalamus [39]. The exact roles of GLP-1 as a receptor ligand or a neurotransmitter in the gastrointestinal and central nervous systems remain to be fully elucidated.

Immunity

GLP-1 has important effects on the immune system. Development and clinical testing of GLP1-RAs have been instrumental in the improved understanding of a close relationship between nutrient signaling and the immunity. The GLP-1 receptor has

been detected on natural killer cells isolated from peripheral blood in humans, and treatment of these cells with either GLP-1 or liraglutide reduces release of interferon-γ and interleukin-4 [7]. Conversely, T-cells regulate local GLP-1 concentrations in the intestinal epithelium. A population of T-cells are targeted to the gut by the β7-integrin protein, and once in the gut, these T-cells capture GLP-1 by binding to the GLP-1 receptor on the cell surface [40]. By this mechanism, β7-integrin targeting of T-cells to the intestinal epithelium provides a means of modulating local GLP-1 concentrations [40, 41]. GLP-1 binding to the GLP-1 receptor on immune cells may also reduce the inflammation in the gut as evidenced by downregulated intracellular inflammatory signaling [25, 42, 43].

Currently Available GLP-1 Receptor Agonist Therapies

GLP1-RAs demonstrate high receptor affinity and resistance to inactivation by the DPP-4 enzyme, thus circumventing the limitations of using native GLP-1 due to its extremely short half-life [44]. Currently available GLP-1 receptor agonists can be functionally divided into short- and long-acting agents. Twice-daily exenatide and lixisenatide are both considered short-acting agents (Table 26.1). These agents have short half-lives, thus resulting in fluctuations in plasma drug levels throughout the day depending on administration time [45]. Short-acting agents demonstrate strong effects on gastric emptying and are associated with strong postprandial glucose-lowering effects [46]. Treatment with longer-acting agents, in contrast, results in more consistent activation of GLP-1 receptors [46]. Longer-acting GLP-1 receptor agonists have less pronounced effects on postprandial glucose and greater effects on fasting glucose [47]. Table 26.1 provides a summary of GLP1-RAs currently marketed in the USA and current recommended dosing.

Kidney Disease Outcome Data

Clinical trials with primary outcomes of kidney disease endpoints have yet to be completed with agents from the GLP1-RA class. However, encouraging data from other clinical trials with secondary outcomes of kidney disease endpoints are available from the cardiovascular outcome trials (CVOTs) and a glycemic control study, the AWARD-7 trial, with dulaglutide (Table 26.2).

Lixisenatide

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial included participants with type 2 diabetes with a recent history of myocardial infarction (MI) or hospitalization for unstable angina [1]. ELIXA was designed to test a primary

Table 26.1 GLP-1 receptor agonist general dosing and recommended adjustments in CKD

Agent	Route/dosing frequency	General recommended dosing	Recommended adjustment in CKD
Short-acting agents			
Exenatide [77]	Subcutaneous/ twice daily	• Initially, 5 mcg twice daily within the 60-minute period before the morning and evening meals. • Based on clinical response, can increase to 10 mcg twice daily after 1 month of therapy.	• Not recommended with CrCl <30 mL/min. • Caution recommended with initiating or escalating the dose with CrCl 30–50 mL/min. • Caution in patients with renal transplantation.
Lixisenatide [78]	Subcutaneous/ once daily	• Initially, 10 mcg once daily within the 60-minute period before the first meal of the day. • On day 15, can increase to 20 mcg once daily.	• Not recommended with eGFR <15 mL/ min/1.73m^2. • Limited experience in patients with eGFR <30 mL/min/1.73m^2.
Long-acting agents			
Liraglutide [49]	Subcutaneous/ once daily	• Initially, 0.6 mg once daily at any time of day. • After 1 week of the 0.6 mg dose, increase to 1.2 mg once daily. • If additional glycemic control is required, can increase to 1.8 mg once daily after ≥1 week of treatment with the 1.2 mg dose.	• No dosage adjustments recommended. • Limited experience in ESKD.
Semaglutide [79]	Oral/once daily	• Initially, 3 mg once daily at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. • After 30 days on the 3 mg dose, increase to 7 mg once daily. • If additional glycemic control is required, can increase to 14 mg once daily after ≥30 days of treatment with the 7 mg dose.	• No dosage adjustments recommended.
Dulaglutide [80]	Subcutaneous/ once weekly	• Initially, 0.75 mg once weekly at any time of day. • If additional glycemic control is required, can increase to 1.5 mg once weekly.	• No dosage adjustments recommended. • Use with caution in ESKD.
Exenatide XR [81]	Subcutaneous/ once weekly	• 2 mg once weekly at any time of day	• Not recommended with eGFR <45 mL/ min/1.73m^2 or ESKD.

(continued)

Table 26.1 (continued)

Agent	Route/dosing frequency	General recommended dosing	Recommended adjustment in CKD
Semaglutide	Subcutaneous/ once weekly	• Initially, 0.25 mg once weekly at any time of day. • After 4 weeks on the 0.25 mg dose, increase to 0.5 mg once weekly. • If additional glycemic control is required, can increase to 1 mg once weekly after ≥4 weeks of treatment with the 0.5 mg dose.	• No dosage adjustments recommended.

Abbreviations: *CrCl* creatinine clearance, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *XR* extended release

composite cardiovascular outcome that included cardiovascular death, MI, stroke, or hospitalization for unstable angina. After a median follow-up of 2.1 years, lixisenatide was found to be non-inferior to placebo for the primary outcome (HR, 1.02; 95% CI, 0.89–1.17; $P < 0.001$), which met criteria for cardiovascular safety. An exploratory analysis of the ELIXA trial included 4441 participants with normoalbuminuria, 1148 participants with microalbuminuria, and 389 participants with macroalbuminuria. It examined the percentage change in mean urinary albumin-to-creatinine ratio (UACR) and eGFR according to baseline albuminuria levels. Following a median follow-up of 108 weeks, lixisenatide was associated with a reduced risk of new-onset severely increased albuminuria [48], with no significant difference between the lixisenatide and placebo groups for eGFR decline or serum creatinine doubling.

Liraglutide

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial enrolled 9340 participants with type 2 diabetes and high cardiovascular risk [3]. LEADER primarily evaluated a composite cardiovascular outcome that included death from cardiovascular causes, nonfatal MI, or nonfatal stroke. While mean eGFR of LEADER participants was 76 ml/min/1.73 m^2, approximately 36% had albuminuria. Urine albumin-to-creatinine ratio (UACR) was 30–300 mg/g in 26% and ≥ 300 mg/g in 10% of participants. The primary outcome occurred in fewer patients receiving liraglutide than in those receiving placebo (13.0% versus 14.9%; HR, 0.87; 95% CI, 0.78–0.97; $P < 0.001$). In addition to meeting criteria for cardiovascular safety, liraglutide demonstrated superiority to placebo for the primary cardiovascular outcome leading to a US label indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease [49]. LEADER additionally included a secondary outcome with kidney disease endpoints, the composite of new-onset severely increased albuminuria, persistent doubling of serum creatinine, kidney failure, or

Table 26.2 Kidney outcomes with GLP-1 receptor agonists

Drug	Lixisenatide	Liraglutide	Semaglutide	Dulaglutide		Exenatide
Study	ELIXA [1, 48] (n = 6068)	LEADER [3, 5] (n = 9340)	SUSTAIN-6 (2) (n = 3297)	REWIND [50, 51] (n = 9901)	AWARD-7 (4) (n = 577)	EXSCEL [53] (n = 14,752)
Trial type	CVOT	CVOT	CVOT	CVOT	Clinical trial	CVOT
Median duration of follow-up	2.1 years	3.8 years	2.1 years	5.4 years	52 weeks	3.2 years
Mean baseline eGFR	76	80	75	77	38	76
Severely increased albuminuria at baseline (%)	7%	10%	N/R	7.9%	44%	3.5%
Secondary kidney outcome(s)	1. New-onset severely increased albuminuria. 2. Doubling of SCr.	New-onset severely increased albuminuria, persistent doubling of SCr, ESKD, or death due to kidney disease	Persistent severely increased albuminuria, persistent doubling of SCr, a CrCl of <45, or need for KRT	New-onset severely increased albuminuria, sustained fall in eGFR of ≥30% from baseline, or need for KRT	1. Change in eGFR. 2. Change in ACR.	1. 40% eGFR decline, kidney replacement, or renal death 2. 40% eGFR decline, kidney replacement, renal death, or severely increased albuminuria.

(continued)

Table 26.2 (continued)

Drug	Lixisenatide	Liraglutide	Semaglutide	Dulaglutide		Exenatide
Kidney outcome results	1. Adjusted HR, 0.81 (0.66–0.99). 2. Adjusted HR, 1.16 (0.74–1.83).	HR, 0.78 (0.67–0.92)	HR, 0.64 (0.46–0.88)	HR, 0.85 (0.77–0.93)	1. Decline of eGFR of 0.7 mL/min/1.73m^2 in both dulaglutide groups, decline of 3.3 mL/min/1.73m^2 in glargine group ($p < 0.05$). 2. No significant differences between dulaglutide and insulin glargine on UACR reduction of 52 weeks.	1. Adjusted HR, 0.87 (0.73–1.04). 2. Adjusted HR, 0.85 (0.74–0.98)

Abbreviations: *ACR* albumin-to-creatinine ratio, *AWARD-7* A Study Comparing Dulaglutide With Insulin Glargine on Glycemic Control in Participants With Type 2 Diabetes (T2D) and Moderate or Severe Chronic Kidney Disease (CKD), *CrCl* creatinine clearance (mL/min), *eGFR* estimated glomerular filtration rate (mL/min/1.73m^2), *CVOT* cardiovascular outcome trial, *ELIXA* Evaluation of Lixisenatide in Acute Coronary Syndrome, *ESKD* end-stage kidney disease, *EXSCEL* Exenatide Study of Cardiovascular Event Lowering, *HR* hazard ratio, *LEADER* Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results, *N/R* not reported, *REWIND* Researching Cardiovascular Events with a Weekly Incretin in Diabetes, *SCr* serum creatinine, *SUSTAIN-6* Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

death due to kidney disease. Liraglutide treatment was associated with a lower rate of this secondary outcome compared to placebo (HR, 0.78; CI, 0.67–0.92; P = 0.003) [2].

Semaglutide

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was designed to assess the cardiovascular safety of injectable semaglutide [2]. SUSTAIN-6 included 3297 participants with type 2 diabetes and established cardiovascular disease, CKD (30% had eGFR <60 ml/min/1.73m^2), or both. After a median follow-up of 2.1 years, semaglutide proved superior to placebo for the primary composite outcome of the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke (HR, 0.74; 95% CI, 0.58–0.95; P < 0.001 for non-inferiority; P = 0.02 for superiority). SUSTAIN-6 included a secondary outcome with kidney disease endpoints defined as persistent severely increased albuminuria, doubling of serum creatinine, creatinine clearance (CrCl) of <45 ml/min, or kidney replacement therapy. Kidney disease risk was significantly reduced in the group receiving semaglutide compared to placebo (HR, 0.64; 95% CI, 0.46–0.88; P = 0.005) [2]. The risk reduction was primarily driven by prevention of severely increased albuminuria.

A phase 3 clinical trial of injectable semaglutide is underway with a primary outcome of kidney disease endpoints in patients with type 2 diabetes and CKD. The Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial is expected to complete in 2024 [9].

Dulaglutide

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial enrolled 9901 participants and followed them for a median duration of 5.4 years [50, 51]. The primary cardiovascular composite outcome included nonfatal MI, nonfatal stroke, or death from cardiovascular causes. At the baseline 27% participants had eGFR <60 ml/min/1.73m^2, 27% had UACR 30–300 mg/g, and 8% had UACR ≥300 m/g. Treatment with dulaglutide significantly reduced the risk for the primary outcome (HR, 0.88; 95% CI, 0.79–0.99; P = 0.026). REWIND additionally included a secondary outcome of kidney disease endpoints that included new-onset severely increased albuminuria, a sustained fall in eGFR of ≥30%, or kidney replacement therapy. Fewer participants receiving dulaglutide experienced this secondary outcome compared to placebo (17.1 versus 19.6%; HR, 0.85; 95% CI, 0.77–0.93; *P* = 0.0004) [51].

The AWARD-7 clinical trial enrolled patients with moderate-to-severe CKD [4]. A total of 577 participants with type 2 diabetes were randomized evenly to receive either dulaglutide 1.5 mg once weekly, dulaglutide 0.75 mg once weekly, or insulin

glargine for 52 weeks. All participants were managed with insulin lispro for prandial glucose control. Mean eGFR at baseline was 38 ml/min/1,73 m^2, and 31% of participants had eGFR <30 ml/min/1.73 m^2. At baseline, three quarters of participants had albuminuria: 29% with UACR >30 mg/g and 46% with UACR >300 mg/g. Following the 52-week intervention, both dulaglutide treatment groups experienced less eGFR decline when compared to treatment with insulin glargine. Importantly, eGFR decline was markedly reduced in the participants with UACR >300 mg/g, a group at high risk for rapid progression to kidney failure (GFR decline: −5.5 ml/min/1.73 m^2 with daily insulin glargine, −0.7 ml/min/1.73 m^2 with dulaglutide 0.75 mg weekly, −0.5 ml/min/1.73 m2 with dulaglutide 1.5 mg weekly; $P < 0.05$ for either dulaglutide group or insulin glargine). The abrogated eGFR decline with dulaglutide with insulin glargine was not related to weight loss (Fig. 26.1) [52].

Exenatide

The cardiovascular safety of once-weekly exenatide was tested in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial [53]. EXSCEL enrolled 14,752 participants with type 2 diabetes with or without a history of cardiovascular disease. At baseline, 22% of participants had an eGFR <60 ml/min/1.73 m, while 17% and 4% had UACR 30–299 mg/g or UACR ≥300 mg/g, respectively. The primary cardiovascular composite outcome included death from cardiovascular causes, nonfatal MI, and nonfatal stroke. Following a median follow-up period of 3.2 years, exenatide met the criteria for cardiovascular safety (HR, 0.91; 95% CI, 0.83–1.00; $P < 0.001$ for non-inferiority). In a post-hoc analysis of EXSCEL, the mean change in eGFR from baseline was similar in the once-weekly exenatide and placebo groups. Of the 14,269 participants without albuminuria at baseline, new-onset severely increased albuminuria was noted in 2.2% and 2.5% of participants in the exenatide and placebo groups, respectively (HR, 0.87; 95% CI, 0.70–1.07; $P = 0.19$) [54].

Putative Mechanisms of Kidney Protection by GLP-1 Receptor Agonists

Inflammation, apoptosis, and fibrosis are central mechanisms in DKD pathogenesis [28, 29]. The kidney contains a resident network of mononuclear phagocytes co-expressing markers for macrophages and dendritic cells, with macrophages being recognized as the most frequent cell type [55]. Metabolic abnormalities associated with diabetes (e.g., hyperglycemia, advanced glycation end products) activate mononuclear cells and cause a shift to a pro-inflammatory phenotype that precipitates recruitment of additional inflammatory cells and release of pro-inflammatory cytokines, chemokines, and adhesion molecules [56]. The extent of structural changes (e.g., glomerulosclerosis) and rate of eGFR decline directly correlates with the magnitude of macrophage infiltration (Fig. 26.2) [57].

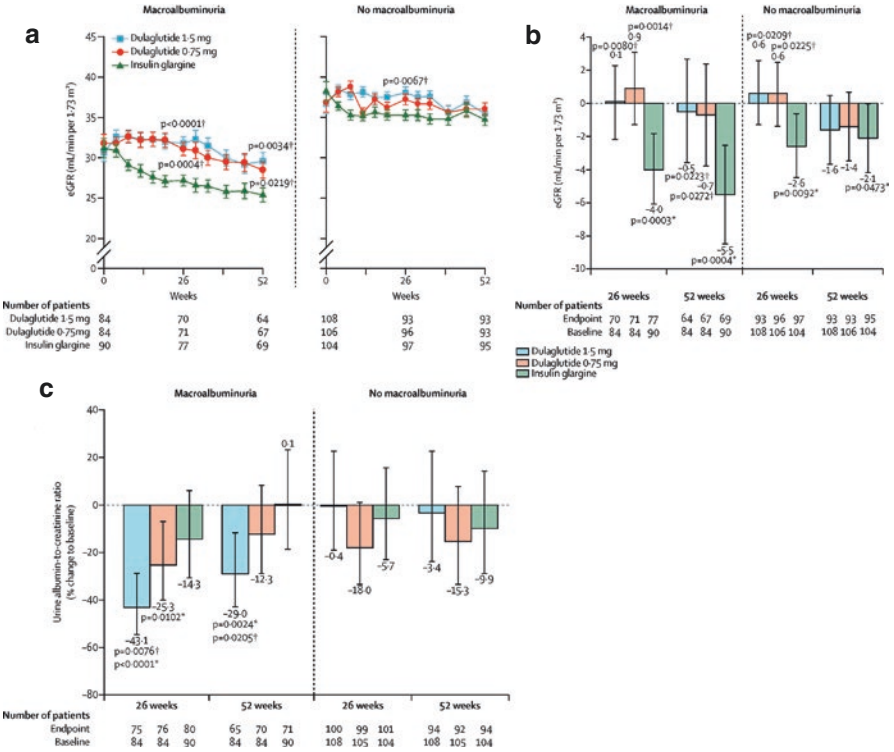

Fig. 26.1 Changes in estimated glomerular filtration rate and albuminuria by macroalbuminuria status at baseline

Reused with permission from [4]. (**a**) Estimated glomerular filtration rate (eGFR; calculated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation by cystatin C) by macroalbuminuria status at baseline, presented as geometric least squares mean (LSM, SE) from log-transformed analysis; statistical significance was only tested for between-group differences versus insulin glargine. (**b**) Actual untransformed change from baseline in eGFR (calculated by CDK-EPI equation by cystatin C) by macroalbuminuria status at baseline, with values presented as LSM (95% CI), with p-values reported for statistical significance versus baseline (within-group) and versus insulin glargine; values shown above or below the bars are LSM. (**c**) Urine albumin-to-creatinine ratio (UACR) by macroalbuminuria status at baseline, presented as LSM (95% CI) for percentage change from baseline, with p-values reported for statistical significance versus baseline (within-group) and versus insulin glargine. Data presented for safety population, by use of a mixed-effects repeated measures model analysis. p-Values are reported for statistical significance at the 26- and 52-week prespecified analysis points. A number of patients analyzed at baseline and endpoints are shown under the x-axis. *Versus baseline. †Versus insulin glargine

In addition to reducing hyperglycemia, GLP-1 receptor agonists appear to have direct anti-inflammatory effects. Anti-inflammatory effects are manifested by:

(1) Reduction in systemic inflammation as reflected in circulating inflammatory biomarkers and modulating of immune cell function.
(2) Fewer immune cells, pro-inflammatory cytokines, chemokines, adhesion molecules, and pro-fibrotic mediators in the kidney.

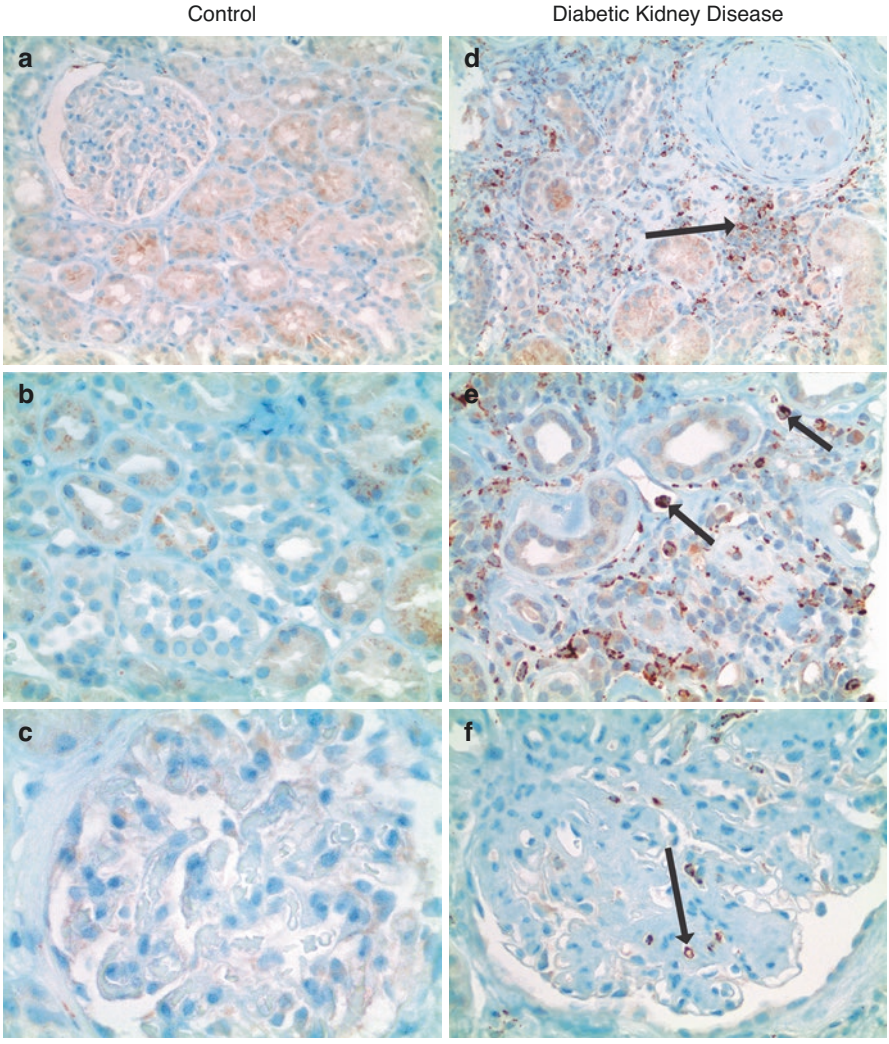

Fig. 26.2 Histological images of inflammatory cell infiltration of diabetic kidney with evidence of diabetic kidney disease

Adapted with permission from [83]. Anti-CD68 (KP-1) immunohistochemistry of kidney biopsies from diabetic patients without and with histological features of diabetic kidney disease. CD68 antibodies highlight influx of macrophage lineage cells (marked with arrows) in different kidney structures. Immunohistochemistry with anti-CD68 (KP-1) antibody (Roche Diagnostics, Indianapolis, IN) used at a concentration of 0.4 mg/mL. (**a–c**) Human kidney from diabetic patient without histological features of diabetic kidney disease (control); magnification: 2003 (**a**), 4003 (**b**), and 6003 (**c**). (**d**) Interstitial macrophage lineage cells infiltrate in diabetic kidney disease (magnification, 2003). (**e**) Macrophage lineage cells in peritubular capillaries (magnification, 4003). (**f**) Macrophage lineage cells in glomerular capillary (magnification, 6003)

Meta-analysis of GLP-1 receptor agonist trials in patients with type 2 diabetes demonstrated reduction of ~2 mg/L in serum CRP [58]. Exposure of cultured human peripheral blood mononuclear cells (PBMCs) to exendin-4 (a GLP-1 analogue) attenuated pro-inflammatory responses by reduction of the pro-inflammatory cytokines [tumor necrosis factor (TNF), interleukin-1 β (IL-1β), interleukin-6 (IL-6)], chemokines [regulated on activation normal T-cell expressed and secreted (CCL5/RANTES), interferon-γ-induced protein 10 (CXCL10)], and decreased oxidative stress as measured by decreased superoxide production [59]. Treatment of human and mice PBMc with liraglutide, GLP-1, and exenatide modulated macrophage function resulting in a decrease in pro-inflammatory macrophages and an increase in anti-inflammatory macrophages [60, 61].

Direct evidence for a kidney-specific anti-inflammatory effect of GLP1-RA treatment comes from pre-clinical studies. In mouse and rat models of DKD, treatment with liraglutide or exedin-4 reduces expression and protein production of markers of oxidative stress (NOX4, NADPH), inflammation and fibrosis (transforming growth factor beta [TGF-β1], fibronectin, type IV collagen, ICAM1, CCL2, TNF, IL-1β, transcription factor NF-κB activation), macrophage infiltration, and the number of pro-inflammatory macrophages. These changes correlate with corresponding amelioration of structural (reduction of kidney hypertrophy, mesangial matrix expansion, loss of podocytes, and glomerular basement membrane thickness) and functional changes (reduction in albuminuria) [33, 62–65] (Fig. 26.3).

Guideline Recommendations on GLP-1 Receptor Agonist Use in DKD

In consideration of the growing body of evidence supporting the use of GLP-1 receptor agonists in the setting of DKD, major guideline development groups have recently published recommendations for the use of GLP-1 receptor agonists in patients with DKD [66–72]. As summarized in Table 26.3, current recommendations for the use of SGLT2 inhibitors and GLP1-RAs in patients with type 2 diabetes and DKD are consistent, with some nuance in recommendations provided from one organization to the next. Overall, major guideline development groups, largely based on findings from the CREDENCE and DAPA-CKD trials [73, 74], preferably recommend the use of a SGLT2 inhibitor in patients with adequate kidney function (eGFR >30 mL/min/1.73m^2), with GLP1-RAs recommended as an alternative option for use in patients who are not good candidates for SGLT2 inhibitor use. While many of the major guidelines highlighted in Table 26.3 touch within their recommendations on the use of glucose-lowering agents to slow the progression of DKD, the 2020 KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease specifically addresses management of patients with DKD [66]. Overall, the 2020 KDIGO recommendations state that glycemic management for patients with type 2 diabetes and CKD should include lifestyle therapy, first-line

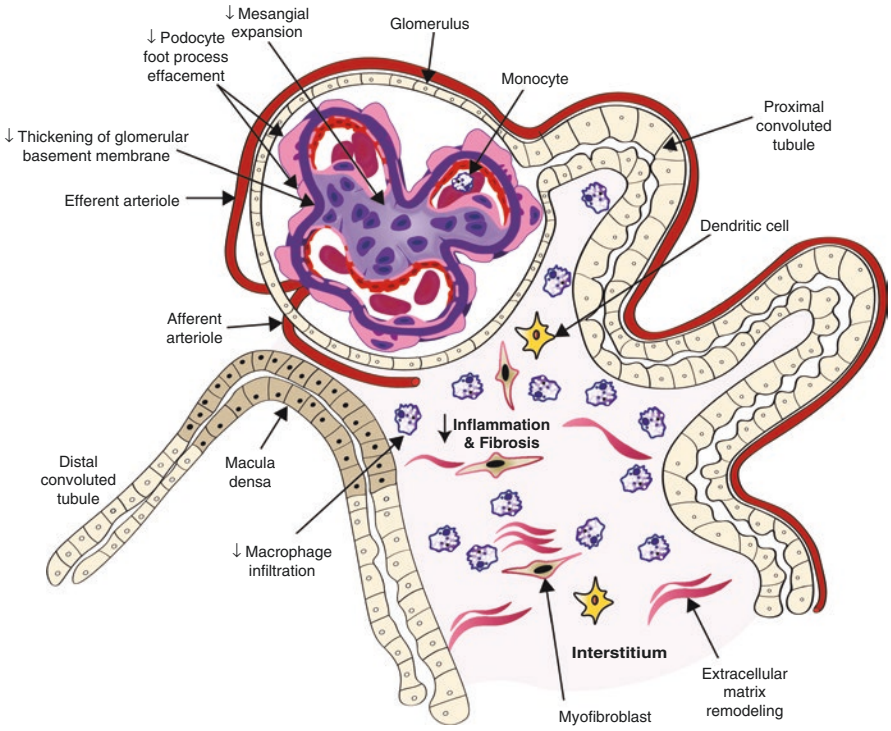

Fig. 26.3 Inflammatory changes in diabetic kidney disease ameliorated with glucagon peptide-1 receptor agonists
Adapted with permission from [83]. Conceptual model of immunity and inflammation in diabetic kidney disease ameliorated with glucagon-like peptide-1 agonists. Metabolic and hemodynamic abnormalities induced by diabetes instigate cytokine production and activate resident macrophages and dendritic cells. This leads to the recruitment of the additional immune cells and further cytokine release. Biological effects of the inflammatory process include podocyte foot process effacement, thickening of the glomerular basement membrane, mesangial expansion, and extracellular matrix remodeling. These biological processes are ameliorated with treatment with glucagon-like peptide-1 agonists

drug therapy with metformin *and* a SGLT2 inhibitor (provided the patient has an eGFR >30 mL/min/1.73m^2 and no other contraindications to therapy), and additional drug therapy as needed for glycemic [66]. For those patients requiring additional drug therapy to meet individualized glycemic targets, the recommended selection of glucose-lowering therapy is guided by patient preferences, comorbidities, eGFR, and cost. Notably, KDIGO gives preference to the addition of a GLP1-RA in patients who do not meet goals despite treatment with metformin plus a SGLT2 inhibitor. Because of the high risk of hypoglycemia in patients with CKD, GLP-1 receptor agonists offer a safe and effective alternative to insulin, especially in patients with CKD categories 4–5. In AWARD-7, dulaglutide produced significantly lower rates of clinically significant hypoglycemia (blood glucose ≤70 mg/dl)

Table 26.3 Summary of key professional society recommendations for GLP-1 receptor agonist use in patients with DKD

Organization(s)	Key recommendations for GLP-1 receptor agonist use in patients with DKD
AACE/ACE [72]	• Independent of glycemic control, if established atherosclerotic cardiovascular disease or high-risk, CKD 3 or heart failure with reduced ejection fraction, start long-acting GLP1-RA or SGLT2 inhibitor with proven efficacy.
ACC [71]	• Opportunities for the initiation of a SGLT2 inhibitor or GLP1-RA with demonstrated cardiovascular or renal benefit in patients with type 2 diabetes include: – In a patient with type 2 diabetes and atherosclerotic cardiovascular disease (SGLT2 inhibitor or GLP1-RA). – In a patient with type 2 diabetes and DKD (SGLT2 inhibitor, alternatively a GLP1-RA for eGFR <30 mL/min/1.73m^2).
ADA [70]	• Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high-risk, established kidney disease or heart failure, a SGLT2 inhibitor or GLP1-RA with demonstrated cardiovascular benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors. • For patients with type 2 diabetes and DKD, consider the use of a SGLT2 inhibitor in patients with an eGFR ≥30 mL/min/1.73m^2 and urinary albumin >30 mg/g creatinine, particularly in those with urinary albumin >300 mg/g creatinine, to reduce the risk of CKD progression, cardiovascular events, or both. In patients with CKD who are at increased risk for cardiovascular events, use of a GLP1-RA may reduce the risk of progression of albuminuria, cardiovascular events, or both.
ADA/EASD [69, 82]	• Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, SGLT2 inhibitors or GLP1-RAs with proven cardiovascular benefit are recommended as part of glycemic management. • To reduce the risk of major adverse cardiovascular events, GLP1-RAs can be considered in patients with type 2 diabetes without established cardiovascular disease with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid, or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 mL/min/1.73m^2, or albuminuria.
ESC/EASD [67]	• Liraglutide, semaglutide, or dulaglutide is recommended in patients with type 2 diabetes and cardiovascular disease, or at very high/high cardiovascular risk, to reduce cardiovascular events. • Liraglutide is recommended in patients with type 2 diabetes and cardiovascular disease, or at very high/high cardiovascular risk, to reduce the risk of death.
KDIGO [66]	• In patients with type 2 diabetes and CKD who have not achieved individualized glycemic targets despite the use of metformin and SGLT2 inhibitor, or who are unable to use those medications, we recommend a long-acting GLP1-RA.

Abbreviations: *A1C* glycated hemoglobin A1c, *AACE/ACE* American Association of Clinical Endocrinologists/American College of Endocrinology, *ACC* American College of Cardiology, *ADA* American Diabetes Association, *ADA/EASD* American Diabetes Association/European Association for the Study of Diabetes, *CKD* chronic kidney disease, *DKD* diabetic kidney disease, *eGFR* estimated glomerular filtration rate, *ESC/EASD* European Society of Cardiology/European Association for the Study of Diabetes, *GLP1-RA* glucagon-like peptide-1 receptor agonist, *KDIGO* Kidney Disease: Improving Global Outcomes, *SGLT2* sodium-glucose cotransporter-2

compared to insulin glargine [4], and liraglutide, semaglutide, and dulaglutide do not require dose adjustment for low eGFR. Although experience in patients treated by hemodialysis is limited, pharmacokinetic studies among individuals on peritoneal dialysis showed no relationship between creatinine clearance, pharmacokinetics, and gastrointestinal side effects [4, 75, 76].

Conclusion

DKD develops in the setting of multiple metabolic abnormalities and a high burden of comorbidities including obesity, hypertension, and atherosclerotic cardiovascular disease. GLP-1 receptor agonists may be used as safe and effective glucose-lowering agents in patients with type 2 diabetes and CKD. Importantly, GLP-1 receptor agonists also reduce the risk of major cardiovascular events, and emerging data suggest the possibility of kidney protective effects as well. The ongoing FLOW trial with injectable semaglutide in patients with type 2 diabetes and CKD will provide important insight into the role of GLP-1 receptor agonists for reducing the risk of kidney disease endpoints as the primary outcome.

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Chapter 27
Dipeptidyl Peptidase-4 (DPP4) Inhibitors

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Introduction

In 2014, the World Health Organization (WHO) estimated that there were 422 million adults living with diabetes, with its prevalence having doubled since 1980 [1]. Diabetic kidney disease (DKD), defined as the presence of increased urinary albumin excretion (UAE) ratio of urinary albumin to creatinine (30 mg/g more), decreased glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2, or both. DKD occurs in 20% to 40% of patients with diabetes mellitus and is one of the major microvascular complications of type 2 diabetes mellitus (T2DM) [2–4]. It is the leading cause of end-stage kidney disease (ESKD), accounting for one-third of all patients initiating renal replacement therapy (RRT) worldwide [1]. A vital part of reducing the risk of DKD and preserving the kidney requires targeting glycated hemoglobin (HbA1C) levels to less than 7% [5]. Unfortunately, therapeutic options for patients with T2DM and DKD are limited as kidney function declines and the potential for toxicities is increased due to reduced renal clearance of endogenous insulin and the decline in renal gluconeogenesis. The dipeptidyl peptidase-4 inhibitors (DPP-4is) are oral, weight-neutral hypoglycemic drugs used to treat patients with T2DM by preventing the breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), two incretins pivotal for glucose regulation. There are currently four DPP-4 inhibitors (Table 27.1) that are approved by the Food and Drug Administration (FDA)

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Table 27.1 Overview of currently available DPP-4i in the USA

Drug	Sitagliptin [9]	Saxagliptin [8]	Linagliptin [7]	Alogliptin [6]
Common dosages	25 mg, 50 mg, 100 mg	2.5 mg, 5 mg	5 mg	6.25 mg, 12.5 mg, 25 mg
US brand names	Januvia	Onglyza	Trajenta	Nesina
Dosage in renal impairment	eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary eGFR ≥30 to <45 mL/minute/1.73 m^2: 50 mg once daily eGFR <30 mL/minute/1.73 m^2: 25 mg once daily Hemodialysis, intermittent (thrice weekly): Not significantly dialyzable (13.5% removed during 3- to 4-h hemodialysis session) 25 mg once daily; may administer without regard to timing of dialysis Peritoneal dialysis: 25 mg once daily	eGFR ≥45 mL/minute/1.73 m^2: No dosage adjustment necessary eGFR <45 mL/minute/1.73 m^2: 2.5 mg once daily ESRD requiring hemodialysis: 2.5 mg once daily; administer post-dialysis Peritoneal dialysis: Has not been studied	Altered kidney function: Mild to severe impairment: No dosage adjustment necessary Hemodialysis, intermittent (thrice weekly): Unlikely to be dialyzed: No supplemental dose or dosage adjustment necessary Peritoneal dialysis: Unlikely to be dialyzed (manufacturer labeling): No dosage adjustment necessary	CrCl ≥60 mL/minute: No dosage adjustment necessary CrCl ≥30 to <60 mL/minute: 12.5 mg once daily CrCl ≥15 to <30 mL/minute: 6.25 mg once daily ESRD (CrCl <15 mL/minute or requiring hemodialysis): 6.25 mg once daily; administered without regard to timing of hemodialysis Peritoneal dialysis: Has not been studied
Dosage in hepatic impairment	Mild to moderate: No dose adjustment necessary Severe impairment: Has not been studied	Mild to moderate: No dose adjustment necessary Severe impairment: Has not been studied	No dose adjustment necessary	Mild or moderate impairment (child-Pugh class A or B): No dose adjustment necessary. Use with caution Severe impairment (child-Pugh class C): Has not been studied

Table 27.1 (continued)

Drug	Sitagliptin [9]	Saxagliptin [8]	Linagliptin [7]	Alogliptin [6]
Elimination half-life	12.4 h	Saxagliptin, 2.5 h; 5-hydroxy saxagliptin, 3.1 h	Half-life elimination: ~11 h; terminal (DPP-4 saturable binding), ~200 h	~21 h
Elimination	Urine 87% (~79% as unchanged drug, 16% as metabolites); feces 13%	Urine (75%, 24% of the total dose as saxagliptin, 36% of the total dose as 5-hydroxy saxagliptin); feces (22%)	80% feces unchanged; 5% urine unchanged	Urine 76% (60% to 71% as unchanged drug); feces 13%

for the treatment of T2DM in the USA: alogliptin (Nesina) [6], linagliptin (Tradjenta) [7], saxagliptin (Onglyza) [8], and sitagliptin (Januvia) [9]. DPP-4 inhibitors have potential beneficial effects on the kidneys, e.g. by reducing the risk of development or progression of albuminuria compared with placebo or other antidiabetic agents [10–14]. This chapter discusses their mechanism of action, current evidence, as well as clinical applications in DKD in the field of nephrology.

Mechanism of Action

DPP-4 Enzyme

DPP-4 is an aminopeptidase that functions as a binding protein, a ligand for a variety of extracellular molecules, and exhibits catalytic activity [15, 16]. This multifunctional protein is made up of an extracellular domain, anchored in the cell membrane by a flexible segment coupled to a trans-membrane sequence, with a short intracellular trail at the N-terminus [17]. DPP-4 is both a membrane-bound and a soluble protein in the plasma and has widespread distribution, expressed on the intestinal and renal brush-border membranes, vascular endothelium, the liver, the pancreas, the kidneys, glandular epithelial cells, and by cells of the immune system [15–17]. Both membrane-bound and solution DPP-4 can exert catalytic activity, preferentially cleaving proteins containing alanine or proline in the penultimate position at the N-terminal position [15, 17]. Beyond its role as a proteolytic enzyme, it has also been implicated in various pathological processes such as metabolic control, inflammation, immune-mediated disease, and tumor biology [18–22].

Antiglycemic Effects of DPP-4 Inhibitors (DPP-4i)

The link between DPP-4 and glucose homeostasis was not identified until after the intestinal hormone, GLP-1, was discovered to be a DPP-4 substrate. Subsequent pharmacological studies demonstrated an increase in circulation of GLP-1 components as a result of DPP-4 catalytic activity [23, 24]. These studies led to the hypothesis of a novel approach for the treatment of T2DM through the inhibition of the DPP-4 catalytic pathway [25, 26]. As oral antidiabetic therapies, DPP-4is are reversible competitive inhibitors of the catalytic protein, DPP-4, which is responsible for breaking down the incretin hormones, GLP-1 and GIP [27, 28]. At appropriate doses, DPP-4is have been associated with at least 70% inhibition of the plasma DPP-4 activity [29]. DPP-4is do not possess inherent glucose-lowering activity, but by prolonging the half-life of endogenous DPP-4 substrates, they prolong the antihyperglycemic effects of incretin hormones [15]. This leads to a two- to threefold elevation of the endogenous GLP-1, which lowers postprandial hyperglycemia by lowering glucagon secretion from pancreatic alpha cells and by causing insulin release from the pancreatic beta cells in a glucose-dependent manner [30]. Unlike GLP-1 agonists, DPP-4is do not alter gastric emptying; therefore they have a neutral impact on weight. As monotherapy, DPP-4is have an average reduction of glycosylated hemoglobin (HbA1c) of 0.6–0.8% [31–33].

Potential Effects of DPP-4i on the Mechanisms of Diabetic Kidney Disease

Among the various tissues in the body, DPP-4 is predominantly expressed in the kidney and concentrated primarily in the cortex, brush-border, and microvillus fractions [16]. It can also be found on glomeruli and podocytes in the region of the glomerular basement membrane and on the proximal convoluted tubules [16]. Several studies have explored renoprotective mechanisms of DPP-4i independent of the glucose-lowering mechanisms. The effects of the DPP-4 activity in kidney cells were evaluated with the administration of DPP-4i to hypersensitive salt-sensitive (Dahl-S) rats and found DPP-4 activity in kidney tissue extracts, and glomerular and tubular cells were suppressed without affecting blood pressure and glucose levels [34, 35]. The inhibition of DPP-4 activity was associated with improvement in albuminuria and suppression of inflammation and fibrosis-related genes [34, 35]. Other preclinical studies found DPP-4i promotes a distal tubular natriuresis; however, the inhibition did not affect the tubuloglomerular feedback or impair renal hemodynamic function [36]. Furthermore, kidney fibrosis and DPP-4 activity were suppressed resulting in reduced kidney fibrosis after the administration of linagliptin in patients with T2DM [36].

Benefits of DPP-4i in Patients with Type 2 Diabetes Mellitus

Based on their pharmacokinetics, DPP-4is can be utilized in patients with chronic kidney disease when dosed appropriately according to eGFR, with the exception of linagliptin, which can be used at any eGFR because it is predominately eliminated through the liver [37]. The potential kidney specific benefits (Table 27.2) of DPP-4i in patients with T2DM and CKD were examined primarily as secondary endpoints or post-hoc analyses in the DPP-4is cardiovascular outcome trials (CVOT).

In the SAVOR-TIMI trial, 16,492 patients with T2DM who had a history of, or were at risk for, cardiovascular events were randomized to receive either 2.5 mg or 5 mg saxagliptin (dose adjusted based on eGFR) or placebo [11]. After a median follow-up of 2.1 years, saxagliptin did not impact the rate of 3-point MACE (composite cardiovascular death, myocardial infarction, or ischemic stroke) with an HR of 1.00, 95% CI of 0.89 to 1.12, and P = 0.99 for superiority and P < 0.001 for noninferiority [11]. At baseline, participants had a mean eGFR of 72 ± 22 mL/min/1.73 m^2 with 84.4% greater than 50 mL/min/1.73 m^2 [11]. A total of 58.8% of participants had normoalbuminuria, while 26.8% had microalbuminuria, and 9.9% had macroalbuminuria [38]. Patients receiving saxagliptin in addition to usual care were more likely to demonstrate improvements in UACR compared with those receiving placebo (11% versus 9%, $P < 0.01$), with significant improvement occurring among those with microalbuminuria at baseline without affecting eGFR [38]. There were no meaningful differences in any of the kidney specific safety outcomes (doubling of serum creatinine, initiation of chronic dialysis, kidney transplant, or serum creating >6.0 mg/dL) between saxagliptin and placebo [38] (Table 27.1).

The EXAMINE trial studied the CV safety of alogliptin in patients with T2DM who recently had a recent acute coronary syndrome (either acute MI or unstable angina requiring hospitalization within the previous 15–90 days) [10]. A total of 5380 patients underwent randomization to receive alogliptin 12.5 mg or 25 mg (adjusted based on eGFR) or placebo and followed up for a median follow-up day of 533 days [10]. The study was stopped early after the interim analysis indicated noninferiority between alogliptin for the primary composite 3-point MACE outcome (HR, 0.96; 95% CI, 1.16; p < 0.001 for noninferiority) [10]. Baseline median eGFR was 71 mL/min/1.73 m^2 between both groups with ≥70% of participants having an eGFR of ≥60 mL/min/1.73 m^2 [10]. Kidney specific outcomes examined included the changes in estimated eGFR according to baseline kidney function and incidence of initiation of dialysis, and these were found to be similar in the two study groups [10].

In the third CVOT trial, TECOS, 14,671 patients with T2DM, history of cardiovascular disease, and eGFR >30 mL/min/1.73 m^2 received sitagliptin 50 mg or 100 mg (adjusted based on eGFR) and followed for a median of 3 years [13]. The primary outcome was composite cardiovascular outcome (MACE-4: composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) (HR, 0.98; 95% CI, 0.88 to 1.09; p < 0.001 for noninferiority) [13]. The study population had a mean eGFR at baseline of 74.9 ± 21 mL/min/1.73 m^2, and 9.5% of participants had eGFR of <50 ml/min/1.73 m^2 at baseline [13]. In post-hoc analysis of CV and CKD outcomes from the TECOS trial, mean eGFR reduction over 4 years from baseline was greater in the sitagliptin group compared to placebo

Table 27.2 Summary of selected trials on DPP-4i with kidney specific endpoints

Study information: Acronym/Title/ClinicalTrials.gov identifiers/sample size	Methodology	Primary outcomes studied	Kidney specific endpoints
EXAMINE [10] trial Alogliptin after acute coronary syndrome in patients with type 2 diabetes N = 5380 NCT 00968708	Multicenter, randomized, double-blind Patients were randomly assigned to receive alogliptin or placebo, administered in a double-blind fashion, in addition to standard-of-care treatment for type 2 diabetes mellitus. 25 mg in patients with an estimated glomerular filtration rate (GFR), calculated with the use of the modification of diet in renal disease (MDRD) formula, of at least 60 ml per minute per 1.73 m^2 of body surface area, 12.5 mg in patients with an estimated GFR of 30 to less than 60 ml per minute per 1.73 m^2, and 6.25 mg in patients with an estimated GFR of less than 30 ml per minute per 1.73 m^2	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Changes in eGFR over the study Need for dialysis
SAVOR-TIMI [11] Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus N = 16,492 NCT 01107886	Phase 4 trial, multicenter, randomized, double-blind, placebo-control Eligible patients receive saxagliptin at a dose of 5 m daily (or 2.5 mg daily in patients with an eGFR of <50 ml per minute) or matching placebo on 1:1 ratio	Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke	Doubling of serum creatinine or ESKD Categorical change in urinary ACR from baseline Doubling of serum creatinine Need for dialysis, transplant, or serum creatinine >530 umol/L

Study information: Acronym/Title/ClinicalTrials.gov identifiers/sample size	Methodology	Primary outcomes studied	Kidney specific endpoints
TECOS [13] Effect of Sitagliptin on cardiovascular outcomes in type 2 diabetes N = 14,671 NCT 00790205	Randomized, double-blind, placebo-controlled, event-driven trial Patients receive either sitagliptin at a dose of 100 mg daily (or 50 mg daily if the baseline eGFR was ≥30 and < 50 ml per minute per 1.73 m^2) or matching placebo on a randomly assigned 1:1 ratio	The first confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina	Comparison of urinary ACR versus placebo Changes in eGFR over the study
CARMELINA [12] Effect of Linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and kidney disease risk N = 6979 NCT 01897532	Randomized, double blind, placebo-controlled Eligible individuals were randomized 1:1 to receive once-daily double-blind oral linagliptin, 5 mg, or matching placebo	The time to the first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke (3-point major adverse CV event [MACE])	Sustained ≥40% decrease in eGFR and eGFR ≤60 ml/min/1.73 m^2, ESKD, renal death microalbuminuria (ACR 30–300 mg/g) Need for dialysis ≥30 days or kidney transplant

(−4.0 ± 18.4 vs −2.8 ± 18.3 ml/min.1.73m^2) [39]. When the effect on the urine albumin-to-creatinine ratio (UACR) was examined, the median value was lower in the sitagliptin group compared to placebo with an overall mean difference of −0.18 mg/g (95% CI, −0.35 to −0.02; p = 0.031) [39]. The primary MACE-4 outcome rate was higher in participants with lower eGFR levels and increased UACR [39].

Lastly, the CARMELINA trial evaluated the effects of linagliptin on the risk of major CV events and kidney outcomes in patients with T2DM [12]. A total of 6991 participants with high CV risk (history of vascular disease and urine albumin-to-creatinine ratio [UACR] (>200 mg/g) and high risk for kidney disease progression (reduced eGFR and micro- or macroalbuminuria) were randomized to receive linagliptin 5 mg or placebo and followed for a median of 2.2 years [12]. Results concluded that linagliptin was noninferior to placebo in the primary composite 3-point MACE outcome, with an absolute incidence difference of 0.13 (95% CI, −0.63–0.90) [12]. At baseline, 57% of participants had established CV disease, 74% of participants with prevalent kidney disease (defined as eGFR <60 mL/min/1.73 m^2 and/or UACR >300 mg/g creatinine), 33% had both CV and kidney disease, and 15.2% had an eGFR less than 30 mL/min/1.73 m^2 [12]. Secondary kidney outcomes (ESKD, death due to kidney failure, or sustained decrease of ≥40% in eGFR from baseline) were not significant between the two groups [12]. Similar results were seen with exploratory kidney endpoints (ESRD, death due to kidney failure, or sustained decrease of 50% or more in eGFR) [12]. Additionally, Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With Linagliptin (MARLINA-T2D), a prospective, 24-week trial, assessed the effects of linagliptin on albuminuria in patients with T2DM [40]. A total of 360 participants with an eGFR ≥30 mL/min/1.73 m^2 and ACR 30–3000 mg/g on agent renin-angiotensin-aldosterone system (RAAS) blockade were randomized to receive linagliptin for 24 weeks [40]. Participants had a mean eGFR of 75.4 ± 23.9 and 72.4 ± 24.4 and mean UACR of 120.8 ± 152.9 and 131.9 ± 166.6 mg/g in the linagliptin and placebo group, respectively [40]. At 24 weeks, linagliptin demonstrated improved glycemic control and demonstrated improved glycemic control non-significant reduction in albuminuria with no change in eGFR and no evidence of renal adverse effects in a high-risk population of patients with T2DM and early DKD [40].

In addition to the analyses of the kidney specific outcomes from the four large CVOT trials, meta-analysis exploring the efficacy and safety of DPP-4i in T2DM with CKD have demonstrated the effectiveness of DPP-4i in glycemic control for patients with diabetes with CKD without significant adverse effects [41–43] but with results on outcomes that were too uncertain to draw any definitive conclusions.

Adverse Events (AEs)

The four CV safety trials conducted ((TECOS [13], EXAMINE [10], CARMELINA [12], and SAVOR-TIMI [11]) suggested that DPP-4is neither increased nor reduced cardiovascular mortality or morbidity in patients with T2DM. As a class, DPP-4i appeared well tolerated with a relatively benign side effect profile. Most of the AEs

associated with DPP-4is appear to be a class effect with the exception of hospitalization for heart failure. We will review the evidence regarding the safety profile of the available DPP-4is. To aid comparison among the commercially available DPP-4is, we will resort to meta-analysis of the odds ratios of these complications against placebo in the major cardiovascular outcome trials.

Pancreatitis

Post-marketing events of acute pancreatitis including hemorrhagic or necrotizing pancreatitis have been reported in patients receiving sitagliptin and saxagliptin [8, 9]. Analysis of the US FDA Adverse Event Reporting System (FAERS) between 2004 and 2009 showed the use of sitagliptin increased the odds ratio reported pancreatitis sixfold compared to other therapies [44]. The analysis also identified patients who took sitagliptin were more likely to have pancreatic cancer [44]. Additionally, other studies have shown an increased risk of pancreatitis with the use of DPP-4i [44–46]. Though the four CV trials did not individually find an significant increase in pancreatitis in the treatment group receiving DPP-4i compared to placebo [10–13], a meta-analysis of their results (Fig. 27.1) suggest an increased risk. More recently, an updated meta-analysis of randomized controlled trials that included more recent trials concluded that DPP-4is were not associated with an increased risk of pancreatitis or pancreatic cancer when compared against other classes of antiglycemic agents, with no significant differences across individual molecules of the class [47]. However, even in that meta-analysis, there was a higher risk of acute pancreatitis when these agents were compared against placebo (OR, 1.42; 95% CI, 1.02–1.97).

Hospitalization for Heart Failure (hHF)

In 2016, the FDA issued a warning about an increased risk for heart failure events for saxagliptin and alogliptin following the results of SAVOR-TIMI 53 and EXAMINE (Fig. 27.2) [48]. In the SAVOR-TIMI 53 trial, more patients in the saxagliptin group compared to placebo had hHF (3.5% vs 2.8%; HR, 1.27 [95% CI, 1.07–1.51] p = 0.007),

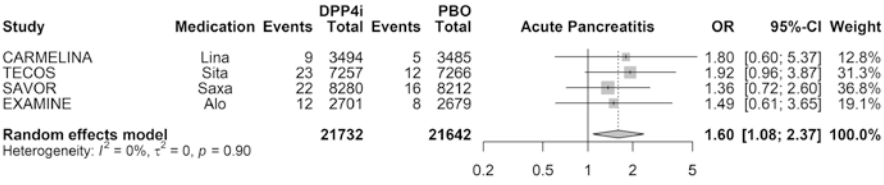

Fig. 27.1 Odds ratio of pancreatitis between users and non-users of DPP-4i in the large CVOT safety trials for lina(gliptin), sita(gliptin), saxa(gliptin), and alo(gliptin)

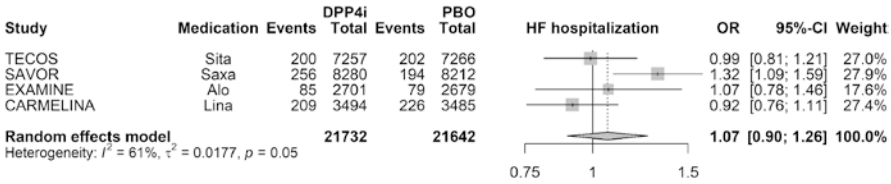

Fig. 27.2 Odds ratio of heart failure hospitalizations between users and non-users of DPP-4i in the large CVOT safety trials for lina(gliptin), sita(gliptin), saxa(gliptin), and alo(gliptin)

particularly in patients with the highest concentration of brain natriuretic peptide (BNP) at baseline [11]. These results did not translate to an increase in heart failure-related deaths in patients taking saxagliptin compared to placebo (44 vs 40 cases) [11]. Further observations from the SAVOR-TIMI 53 suggest that eGFR <60 mL/min/1.73 m^2, previous history of heart failure, elevated BNP, and albumin-to-creatinine ratio were strong risk predictors for hHF failure [49]. In the EXAMINE trial, both groups had 28% of congestive heart failure at randomization; however, hHF was not initially reported in the study results [10]. In a post-hoc analysis of EXAMINE, those receiving alogliptin had more frequent hHF compared to placebo (3.1% vs 2.9%; HR, 1.07; 95% CI, 0.79–1.46) [50]. The composite endpoint of cardiovascular death and hHF was similar for alogliptin and placebo in post-hoc analysis, despite the higher event rate in patients with a history of heart failure [50]. In the TECOS trial, sitagliptin had identical rate for hHF compared to placebo (3.1% vs 3.1%; HR, 1:00 [95% CI, 0.83–1.20] p = 0.98) [13]. Such results were further strengthened with a sub-group analysis of TECOS revealing identical results (HR, 1.00; 95% CI, 0.84–1.20, and HR, 1.02; 95% CI, 0.83–1.26) [51]. Lastly, in CARMELINA, linagliptin had lower rates (2.77% vs 3.04%; HR, 0.90 [95% CI, 0.74–1.08]) compared to placebo for hHF [12]. However, a pooled analysis suggested an increase in adverse heart failure events with linagliptin [52]. In a nationwide cohort study in patients with T2DM non-CKD and CKD, DPP-4is were associated with a 25% increase risk of hHF in the CKD cohort compared to the no-CKD cohort [53]. Further meta-analyses of DPP-4is did not find an increase in hHF, the heterogeneity of this effect may reflect differences in trial designs or even differences among the members of the DPP-4i [54–56]. Until further data emerge, one should follow the American Diabetes Association (ADA) standard of care document which suggest DPP-4i except saxagliptin can be used in the setting of heart failure if patients are not receiving a GLP1-RA. The evidence for this guidance is shown below:

Arthralgias

DPP-4is were also implicated in another FDA-issued guidance warning relating to severe and disabling joint pain associated with DPP-4i after several cases of joint pain were reported on the FDA Adverse Event Reporting System (FAERS) in 2015 [48]. Observational studies have demonstrated a strong association of joint

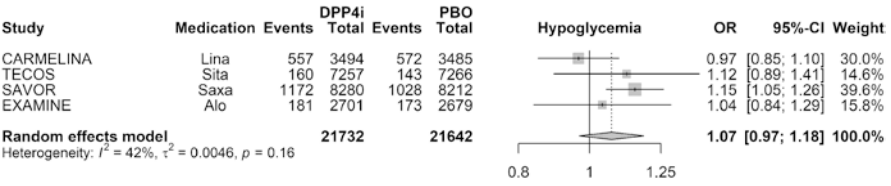

Fig. 27.3 Odds ratio of hypoglycemias between users and non-users of DPP-4i in the large CVOT safety trials for lina(gliptin), sita(gliptin), saxa(gliptin), and alo(gliptin)

pain with DPP-4i use despite the non-significance of arthralgias reported in the clinical trials of DPP-4i [57]. In a review of the arthralgia clinical cases, proposed mechanisms of DPP-4i-induced arthralgias include increase in cytokines, chemokines, matrix metalloproteinases, or genetic factors [58]. Among population-based cohort and nested case-control studies observed an increased risk of arthralgia during the first year after initiation of DPP-4i but declined with cumulative use [59]. Meta-analysis of randomized controlled trials and retrospective cohort study has also suggested DPP-4 inhibitors were associated with a slightly but significantly increased risk of overall arthralgia (RR, 1.13; 95% CI, 1.04–1.22; P = 0.003) and a non-significant increased risk of serious arthralgia (RR, 1.44; 95% CI, 0.83–2.51; P = 0.20) [60, 61].

Hypoglycemia In general, the DPP-4i augments insulin secretion in a glucose-dependent manner, thus preventing hypoglycemia [17]. In the four CV trials, hypoglycemia risk was similar between DPP-4i and placebo (Fig. 27.3) [10–13]. Furthermore, in long-term safety, systematic review and meta-analysis of DPP-4i have shown a low risk of hypoglycemia when compared to placebo (RR, 0.92 [95% CI, 0.74–1.15]) or sulfonylureas (RR, 0.20 [95% CI, 0.74–1.15]) [62]. However, there is an increased risk for hypoglycemia when DPP-4is are combined with sulfonylurea or insulin. The hypoglycemia data from the large CVOT trials are shown below and indicate no major increased risk:

Application of DPP-4i in Special Populations

Kidney Transplant Recipients

Post-transplant diabetes mellitus (PTDM), previously known as new-onset diabetes after transplant, is a serious and common complication after solid organ transplantation. An incidence of PTDM in kidney transplant recipients at 1- and 2-years post-transplant is 16% and 24%, respectively [63]. Both modifiable and nonmodifiable risk factors have been implicated in the pathogenesis of PTDM. Management of PTDM is essential as it can not only impact graft function and survival but also cardiovascular morbidity and mortality [63–65]. PTDM impact on survival showed that 1-year survival was 98% in those without PTDM versus 83% in those with PTDM

[66]. The annual risk of a CVD death is 3.5% to 5% in kidney transplant recipients, which is 50-fold higher than the general population [67, 68]. In the non-transplant setting, the advantages of DPP-4i include their low incidence of hypoglycemia, neutral weight, and their excellent safety profile in patients who have only mild reductions in kidney function or if the dose is adjusted appropriately with more significant chronic kidney disease. In the post-transplant setting, retrospective and small controlled trials have demonstrated the safe use of several DPP-4i in post-transplant recipients [69–71]. In addition to HbA1c improvement, studies have also demonstrated no alteration in immunosuppression levels or reduction in eGFR [72, 73].

Dialysis

Patients with kidney disease have been described as an insulin-resistant state [74]. Patients with diabetes having hemodialysis (HD) are more vulnerable to hypoglycemia as a result from a combination of impaired insulin clearance, changes in glucose metabolism, as well as the dialysis process [75]. The risk of hypoglycemic episodes is often more difficult to predict and associated with mortality rates reported at 30%, especially when drug clearance is variable as eGFR declines and is particularly relevant to those receiving dialysis [74, 75]. DPP-4 inhibitors are FDA approved for use as monotherapy and in combination with other diabetes medicines such as metformin [76]. Alogliptin, saxagliptin, and sitagliptin share renal elimination pathways and require dose adjustment in patients with moderate-to-severe kidney functional impairment; hence, all three are administered once daily with dose adjustment in those with ESKD that require dialysis [6, 8, 9]. Linagliptin [7] is primarily excreted via the bile and gut and does not require dose adjustment for any level of kidney function. However, if adding DPP-4 inhibitors to sulfonylurea/insulin therapy, consider decreasing the sulfonylurea/insulin dose, to reduce hypoglycemia risk [75, 77]. Studies have shown that treating HD patients with DPP-4 inhibitors does not result in an increased incidence of adverse events such as hypoglycemia or liver dysfunction [78, 79]. Effectiveness of DPP-4 inhibitors in HD patients was reviewed and showed that treatment decreases HbA1c and glycated albumin levels by 0.3% to 1.3% and 1.7% to 4.9%, respectively [79]. Although the anti-inflammatory effects of linagliptin monotherapy have already been reported in HD patients, it will be beneficial to further investigate the anti-inflammatory or anti-atherosclerosis efficacies of DPP-4 inhibitors in HD patients in addition to HbA1c improvement [78–81].

Practice Considerations

Overall, DPP-4is are effective oral agents to control blood glucose in patients with T2DM and kidney functional impairment. Currently, the American Diabetes Association (ADA) recommends the utilization of DPP-4is as the second line if there is a compelling need to reduce hypoglycemia in patients who are not at high risk of

ASCVD or have established ASCVD, in the absence of CKD or HF [82]. While they differ in their pharmacokinetics properties, they all exhibit reversible inhibition of the DPP-4 enzyme and have similar HbA1c-lowering effects. From a nephrology perspective, DPP-4is should be considered a treatment option in CKD patients if there is a concern for hypoglycemia or if there is an injection aversion that prohibits the use of an GLP-1 agonist. It is important to consult the packaging insert for individual agents to ensure patients are appropriately dosed based on their eGFR. In general, the DPP-4i are well tolerated with a relatively benign side effect profile. These agents have been proven to have a neutral effect for cardiovascular disease in patients with diabetes and demonstrated conservative kidney benefits in post-hoc analysis on markers of kidney damage (albuminuria). Additionally, they are available in fixed dose combination with metformin and can be administered in triple combination with metformin and SGLT-2 inhibitors, which may help reduce pill burden for some patients. Nonetheless, patients should be counseled on the potential AEs of arthralgias and risk of pancreatitis. Given the mixed results surrounding DPP-4is and hospitalization for heart failure, it may be prudent to select a DPP-4i that has not been implicated in having an increased risk for heart failure in patients with a history or risk factor for heart failure. Kidney function should be regularly monitored prior to and during therapy.

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Chapter 28
Novel Treatments and the Future of DKD: What Is on the Horizon?

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Introduction

Since the emergence of diabetic kidney disease as a major public health issue in the 1970s, the scope and the extent of the problem have continued to grow. Worldwide intense research continues. There has been much new insight gained in the last quarter century but still somehow short of a cure. In this chapter, we will briefly review the future frontiers of diabetes research focused mainly with regard to diabetic kidney disease.

During the past decade, new types of medications that counter glucose dysregulation through different mechanisms have been introduced to clinical practice in type 2 diabetes (T2D) treatment. Their influences on diabetes complications such as cardiovascular diseases and diabetic kidney disease have also been evaluated in clinical studies. These new drugs are discussed in detail in other chapters of this book and elsewhere in the published literature [1–11]. Included among these newer therapeutics are the following: (1) the dipeptidyl peptidase-4 (DPP4) inhibitors that reduce the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1), including sitagliptin (Januvia), linagliptin (Tradjenta), saxagliptin (Onglyza), and vildagliptin (Galvus); (2) the GLP-1 receptor (GLP-1R) agonists that mimic GLP-1 action but are resistant to DPP4 degradation, such as exenatide (Byetta/Bydureon), liraglutide (Victoza), lixisenatide (Lyxumia/Adlyxin), dulaglutide (Trulicity), and semaglutide (Ozempic); and (3) the sodium-glucose co-transporter 2 (SGLT2) inhibitors that reduce glucose reabsorption in the proximal tubules of the kidney, which include canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance).

These new drugs have opened new frontiers in diabetes treatment, contributing to the substantial improvement in T2D management and complication prevention

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during the past decade [7, 8, 11]. Development of once-weekly GLP-1R agonists such as semaglutide and dulaglutide further increases the durability of effects and ease of use [12, 13]. Both DPP4 inhibitors and GLP-1R agonists target on the incretin system, particularly GLP-1 and its receptor. GLP-1 exerts its glucose-lowering effects by stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner [14, 15]. GLP-1 also slows gastric emptying, suppresses appetite, and reduces food intake [2, 16], all of which are beneficial for the management of diabetes. Indeed, clinical studies consistently show DPP4 inhibitors and GLP-1R agonists improve glycemic control with very low risk of hypoglycemia, and cause sustainable weight loss. GLP-1R agonists often significantly reduce adverse cardiovascular events, while DPP4 inhibitors appear to have a neutral effect on cardiovascular outcome [5, 17–20]. Protective effects of DPP4 inhibitors and GLP-1R agonists on kidney function have also been observed, which may result from a direct GLP-1/GLP-1R effect on kidney physiology and an indirect metabolic and hemodynamic action that reduces kidney risk in T2D [4, 7, 21].

Another new class of anti-diabetic drugs is SGLT2 inhibitors. SGLT2 inhibitors lower blood glucose by blocking kidney tubular reabsorption of glucose, which results in glucosuria and natriuresis and also leads to a caloric deficit and weight loss. Increased sodium excretion in the kidney may have blood pressure-lowering effects and is uniquely helpful in preventing diabetic kidney disease [22–24]. The cardiovascular outcome trials for empagliflozin (EMPA-REG), canagliflozin (CANVAS), and dapagliflozin (DECLARE) have been completed recently, and the results show significant reduction in major advanced cardiovascular events despite variations among trials due to differences in patient recruitment [25–29]. A meta-analysis of these trials revealed substantial risk reduction in hospitalization for heart failure, and the effect was even greater in patients with diabetic kidney disease [30]. Further analysis suggests the SGLT2 inhibitors slow albuminuria progression, reduce glomerular injury, and decrease the occurrence of end-stage kidney disease [1, 3]. The beneficial effects of SGLT2 inhibitors on cardiovascular and kidney function are further confirmed by a recently completed trial, EMPEROR-Reduced (NCT03057977), which is designed to examine empagliflozin effects on cardiovascular and kidney outcome on a broad spectrum of patients with heart failure, regardless of diabetes status [31]. These striking benefits make SGLT2 inhibitors a new class of anti-diabetic drugs that offer significant cardiovascular and kidney protection. Currently, dedicated kidney outcome trials, including DAPA-CKD, Empa-Kidney, and CREDENCE (for canagliflozin), are being conducted to examine renoprotection effects of these SGLT2 inhibitors on a broader range of patients with chronic kidney diseases [32–35]. The results from CREDENCE trial have been reported recently, which shows canagliflozin substantially reduces risks (>30% reduction) of end-stage kidney disease or death from kidney causes compared to the placebo group, after a median follow-up of 2.62 years, and the results are consistent across different eGFR subgroups [36, 37].

Despite the recent progresses, there are needs for further groundbreaking research to reduce the burden of the disease and organ damage caused by diabetes. In this chapter, we will review the recent endeavors in diabetes research and the future

implications of this rapidly expanding knowledge on the lives of patients with diabetes and diabetic kidney disease.

The Role of Immune System and Prospects of Immunotherapy in Type 1 Diabetes

The immune system, including both adaptive and innate immunity, plays critical roles in the pathogenesis of type 1 diabetes (T1D). Since the first demonstration in 1974 of islet cell antibodies [38], T1D was believed to be autoimmune in nature. Although initially these antibodies were believed to be responsible for β cell destruction, later research has shown that these antibodies (representing the humoral arm of the immune system) are not necessarily responsible for the β cell destruction, but are markers of autoimmunity against β cells, and that the cellular arm of the immune system, specifically T lymphocytes, mediates the β cell destruction [39–41]. Studies have further shown that the T lymphocytes do not act alone. They initiate the response after interaction with antigen-presenting cells such as dendritic cells and macrophages and appear to receive help from a complex array of interactions between the innate and adaptive immunity systems. The initial immune response triggers and propagates secondary and tertiary responses that result in impairment of β cell function, progressive β cell death, and consequent development of T1D. The details are depicted in Fig. 28.1.

One critical component in T1D etiology is regulatory T cells (Tregs), which are $CD4^+$ T cells expressing a high level of Foxp3 and CD25 (the IL-2 receptor α chain) [42, 43]. Tregs play essential roles in immunological tolerance of self-antigens/self-molecules. In general, autoreactive T cells against self-molecules are eliminated in thymus, but some autoreactive T cells may leak out of the thymus. In normal immune system, these autoreactive T cells are suppressed in the periphery by Tregs; therefore, they do not cause autoimmune diseases. In T1D-predisposed patients, their immunological self-tolerance to islet autoantigens such as insulin, IA-2 (tyrosine phosphatase-like protein insulinoma antigen 2), glutamic acid decarboxylase (GAD), and the zinc transporter ZnT8 is impaired [40, 44]. Islet-autoreactive $CD4^+$ and $CD8^+$ T cells are able to escape from thymic negative selection and acquire effector functions upon encounter of target autoantigens. Indeed, islet-autoreactive $CD8^+$ T cells specific for a single antigen or multiple antigens have been detected in human pancreatic tissues from T1D donors [45]. Tregs, the gatekeeper of self-tolerance, appear to have multiple functional defects in T1D patients and are unable to effectively suppress these autoreactive effector T cells [46–48]. The defects are attributable to increased Treg apoptosis, decreased Foxp3 expression, decreased IL-2R signaling, and an increase in the frequency of Tregs that produce proinflammatory cytokines such as IFN-γ and IL-17 [42, 49–54]. A recent study has also demonstrated that frequency of activated $Foxp3^+$ Tregs decreases in T1D patients compared to non-diabetic subjects [55].

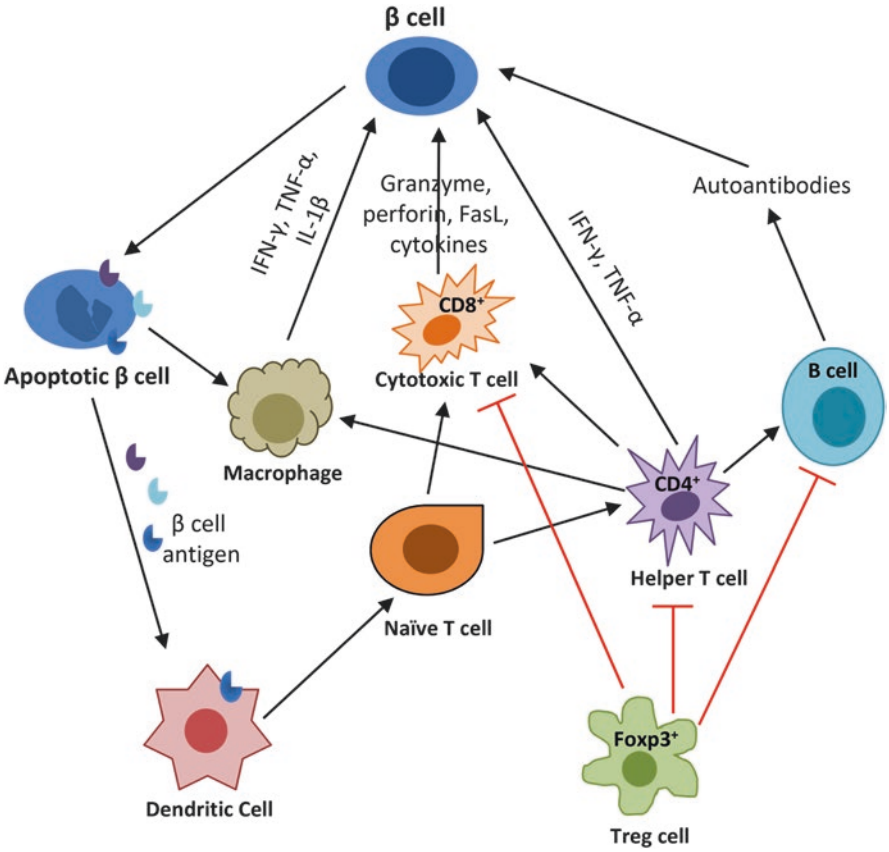

Fig. 28.1 The role of the immune system in β cell destruction and T1D development. Spontaneous β cell death can occur physiologically or be induced by infections. The cell debris is normally cleared up by macrophages, and β cell antigens can be taken up by dendritic cells. In T1D-predisposed patients, the dendritic cells, acting as antigen-presenting cells (APC), activate naïve T cells and result in the maturation of autoreactive $CD8^+$ cytotoxic cells (CTLs) and $CD4^+$ helper T cells. The $CD8^+$ CTLs can kill β cells directly by releasing cytolytic granules containing granzymes and perforin, by FasL-Fas interaction and cytokines such as IL-1β, IFN-γ, and TNF-α. $CD4^+$ T cells induce β cell death through multiple mechanisms: they can release cytokines that directly harm β cells and promote the actions of CTLs, macrophages, and autoantibody-generating B cells. The regulatory T cells (Tregs) have inhibitory roles on $CD4^+$ T cells, $CD8^+$ T cells, and B cells, acting as a gatekeeper for preventing autoimmunity in normal individuals. In T1D-predisposed patients, Tregs are downregulated so the spontaneous β cell death eventually leads to vicious autoimmune attack on β cells, and T1D manifests

The advancement in the understanding of the etiology and mechanisms of autoimmune T1D has inspired many therapeutic developments aiming to slow or even reverse T1D development. Immunotherapies targeting on T cells, B cells, and proinflammatory cytokines have been explored extensively in mouse models, and dozens are being conducted in clinic trials for T1D [56, 57]. In the past few years, IL-2/

IL-2R signaling has emerged as a potential target to promote Treg function and restore self-tolerance in T1D. IL-2 stimulates Treg proliferation, enhances Foxp3 expression, and is essential in maintaining Treg homeostasis [58]. On the other hand, IL-2 also plays important roles in mounting optimal immune response by stimulating several key effector T cells including autoreactive T cells. Pre-clinical studies have shown a low level of IL-2 effectively stimulates Treg development, but does not activate effector T cells [59, 60]. Therefore, low-dose IL-2 therapy may be used to boost Treg function without unwanted effector T cell activation. Currently several clinical trials using low-dose IL-2 are ongoing, including Interleukin-2 Therapy of Autoimmunity in Diabetes (ITAD) clinical trial for T1D (NCT03782636), the "PROREG" study (NCT03243058) for established T1D, and the "DIABIL-2" study for recently diagnosed T1D (NCT02411253) [56, 58]. These trials are expected to complete in the next few years, which shall shed light on the effectiveness of IL2 and Treg-based immunotherapy strategies.

Immunotherapies targeting on other molecules also hold a potential as novel treatment for T1D. Notably, anti-CD3 monoclonal antibodies, which target the T cell receptor (TCR)-associated molecule CD3, have been shown to slow C-peptide decline and T1D progression in new-onset T1D patients [61–64]. The anti-CD3 antibody Teplizumab is now in a phase 3 trial for recent-onset T1D (NCT03875729, the PROTECT trial). Moreover, Teplizumab has been shown to delay T1D progression into symptomatic diabetes in high-risk participants in a phase 2 clinical trial (NCT01030861), suggesting it is beneficial for T1D prevention [65]. A recent 2-year trial has demonstrated that selective depletion of B lymphocytes with rituximab, an anti-CD20 monoclonal antibody, slows a decline of β cell function in recent-onset T1D, although it does not appear to fundamentally alter the underlying pathophysiology of the disease [66]. Another approach is to target co-stimulatory receptors in T cells. For example, abatacept, a CTLA-4-based recombinant protein, competitively inhibits the co-stimulation factor CD28 and thus reduces T cell activation. A clinical trial assessing abatacept for T1D prevention in high-risk population is ongoing (NCT01773707). In addition, a phase 2 trial (NCT03929601) was initiated recently to evaluate whether a combination of abatacept and rituximab, when administered sequentially, can prevent or reverse T1D development in high-risk subjects [56].

Currently, there are also ongoing studies exploring the immunomodulatory effect of dietary supplements such as omega 3 and vitamin D in the prevention and treatment of T1D [67–69]. Pre-clinical and clinical studies have demonstrated that vitamin D has anti-inflammatory and immunomodulatory effects. Vitamin D deficiency is associated with T1D pathogenesis. More importantly, many clinical studies have demonstrated that vitamin D supplementation decreases the risk of T1D development in at-risk subjects and alleviates disease symptoms in established patients [68, 69]. Therefore, vitamin D may be used as an adjuvant immunomodulatory therapy in T1D prevention or treatment schemes.

Although considerable progresses in T1D immunotherapy have been made over the past decade, there is plenty of room for improvement. In fact, thus far, none of the immunotherapies have achieved complete T1D prevention or reversal in clinical

studies. Given the complexity of adaptive and innate immunity involved in T1D development, an effective treatment scheme will require a combination of multiple immunological interventions with complementary effects [57]. Moreover, current immunotherapies are often unspecific because the target molecules are usually part of normal immune responses, thus leading to adverse effects. To overcome the problem, antigen-specific approaches need to be developed. One such approach under development is to generate islet antigen-specific Tregs, which can be accomplished by isolation, ex vivo expansion, and infusion of autologous islet-specific Tregs. Alternatively, antigen-specific Tregs can be generated by genetic engineering with T cell receptor (TCR) or with chimeric antigen receptors (CAR) so that the Tregs display islet specificity [56, 70, 71].

The Immune System and Type 2 Diabetes

Type 2 diabetes (T2D) is caused by insulin resistance, but chronic low-grade inflammation appears to play essential roles in its pathogenesis [72]. Glycemic control reflects the balance between dietary intake and gluconeogenesis (rate of appearance of glucose in circulation) and tissue uptake for oxidation or storage as glycogen or fat (rate of glucose disappearance from circulation). This is coordinated primarily by insulin secretion from the β cells in the pancreas along with interplay of other glucoregulatory hormones including glucagon, amylin, the incretins GLP-1 and glucose-dependent insulinotropic peptide (GIP), epinephrine, cortisol, growth hormone, etc. [73]. Insulin regulates serum glucose through its actions on the liver, skeletal muscle, and fat tissue. When there is insulin resistance, insulin cannot suppress hepatic gluconeogenesis, which leads to hyperglycemia. On the other hand, insulin resistance in the adipose tissue and skeletal muscle leads to increased lipolysis causing hyperlipidemia in addition to hyperglycemia and compensatory hyperglycemia. Evidence suggests that when there is insulin resistance, the pancreas is forced to increase its insulin output, which stresses the β cells, eventually resulting in β cell exhaustion. The high blood glucose levels and high levels of saturated fatty acids create an inflammatory environment resulting in activation of the innate immune cells in metabolic tissues, which result in activation of the nuclear factor-kappa B (NF-κB), and release of inflammatory mediators, including interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), promoting systemic insulin resistance and β cell damage as a result of insulitis [72]. The consequent insulin resistance further leads to high glucose levels, along with high serum levels of free fatty acids and IL-1; leads to glucotoxicity, lipotoxicity, and IL-1 toxicity; and results in apoptotic β cell death. These studies have revealed that, in obesity, adipose tissue is an immunologically active site for both MHC class I- and MHC class II-mediated antigen presentation by macrophages to $CD8^+$ and $CD4^+$ T cells, which contribute to adipose tissue inflammation and peripheral insulin resistance [72, 74]. Furthermore, a systemic review and meta-analysis of ~90 clinical studies has revealed that there is an increase in IL-6, TGF-β, and TNF-α serum levels but a

decrease in $CD4^+CD25^+Foxp3^+$ Tregs in T2D patients compared to control subjects [75]. The role of Tregs in the pathogenesis of T2D, however, remains to be examined in stringent experimental settings.

Also on the horizon are therapies aimed at countering the inflammation in T2D. Based on the discoveries that IL-1β is a key cytokine involved in T2D pathogenesis, therapy attempts utilizing IL-1β neutralizing antibody or IL-1 receptor antagonist (IL-1Ra) have shown promise in early-stage clinical studies. For instance, in a phase 2 clinical trial (NCT00303394) with T2D patients, after 13 weeks daily injection of anakinra (an IL-1Ra) or placebo, the anakinra group shows better glycemic control, improved beta cell function, and reduced systemic inflammation compared to the placebo group [76]. Another T2D trial involving anakinra (NCT04227769) is ongoing. Canakinumab, an IL-1β neutralizing antibody, has been shown to lower A1c and reduce inflammation markers in T2D patients when used as add-on therapy to metformin in a clinical trial (NCT00900146), although other glycemic control parameters are not affected [77–79]. It should be noted that contradicting or varying results may be obtained from different trials using different anti-inflammation drugs. Nonetheless, in general, it is clear that anti-inflammation strategies, if used appropriately, will benefit diabetes management and slow the development of diabetes-related complications.

Epithelial-to-Mesenchymal Transition and Kidney Fibrosis: Potential for Reversibility

Regardless of the etiology, kidney disease progresses predominantly through tubulointerstitial fibrosis, which is another major consequence of the heightened immune environment present in the diabetic kidney. The inflammatory milieu leads to the activation of both the innate and adaptive immune systems that results in the production of IL-1β, activation of NF-κB, and increased transcription and release of a cascade of cytokines. These cytokines include TNF-α, MCP-1, interleukins 6 and 8, etc., but most prominently TGF-β1, which has been recognized as a major mediator of kidney fibrosis in both diabetic and non-diabetic kidney diseases [80–83]. Studies show the expression levels of TGF- β1, p53, and microRNA-192 (miR-192) increase in the kidney cortex of diabetic mice, and these changes were associated with glomerular expansion and fibrosis [84]. Other studies have shown that the inflammatory setting responsible for these events includes recruitment of monocytes from the circulation and $CD14^+$ fibrocytes from the bone marrow. The monocytes differentiate into both M1 and M2 macrophages and contribute more cytokines in the medium perpetuating the cycle of inflammatory events [85]. The major cellular components contributing to kidney fibrosis have now been shown to include the resident macrophages, kidney tissue fibroblasts, epithelial cells (via epithelial-to-mesenchymal transition (EMT)), and endothelial cells (via endothelial-to-mesenchymal transition (EndoMT)) driven through the effects of TGF-β1/Smad pathway [81, 82, 86, 87].

The residential fibroblasts proliferate, the kidney epithelial and endothelial cells acquire myofibroblast phenotype, and with increased synthesis and decreased degradation of matrix proteins resulting in increased collagen and matrix deposition especially in the tubulointerstitial space, the kidney function is progressively destroyed [84, 85, 88, 89]. Studies also suggest that intrarenal renin-angiotensin system may have a key role in this process, which may be independent of circulating angiotensin [90–94]. Urinary angiotensinogen levels have a particular value in identifying patients at risk of diabetic kidney disease and have been proposed as a marker of abnormalities in intrarenal renin-angiotensin system [92–94]. In addition, a recent study showed that angiotensin-converting enzyme 2 (ACE2) expression was substantially reduced in kidney specimens of patients with diabetic nephropathy, although their circulating ACE2 levels increased; furthermore, the authors show ACE2 overexpression inhibits TGF-β/Smad activation and reduces EMT in cultured human kidney proximal tubular epithelial cells, suggesting kidney ACE2 is protective against kidney fibrosis [95]. Taken together, these studies suggest that kidney renin-angiotensin system plays a key role in the pathogenesis of diabetic kidney disease.

Our improved understanding of the process of fibrosis has identified some exciting therapeutic opportunities that can halt the process and, conceivably, even reverse established fibrosis. First, antagonizing pro-fibrotic cytokines, especially TGF-β, and other growth factors including PDGF, VEGF may slow progression of kidney disease [83, 85, 96]. Of interest is the relation between angiotensin II and TGF-β1 and the well-known role of renin-angiotensin-aldosterone system (RAAS) antagonists in slowing progression of kidney disease [85, 88, 97]. A novel approach may be the introduction of the newer non-steroidal aldosterone antagonists. Recent trials suggest that adding a non-steroidal mineralocorticoid receptor antagonist, such as finerenone or esaxerenone, to a regimen that includes a renin-angiotensin system inhibitor leads to further decrease in albuminuria, may slow progression of CKD, and improves cardiovascular outcomes [98–100].

Another promising therapeutic target in diabetic kidney disease is the nuclear factor-erythroid 2-related factor 2 (Nrf2), a master regulator of oxidative stress, which has an anti-EMT effect through its interaction with hemeoxygenase-1 (HO-1) [101–103]. Interestingly, simvastatin, a cholesterol-lowering drug, also attenuates TGF-β1-induced fibrosis through HO-1 activation and subsequent suppression of reactive oxygen species (ROS) production in cultured kidney proximal tubule cells [104, 105]. In addition, TNF-related apoptosis-inducing ligand (TRAIL) has been shown to reduce kidney inflammation, inhibit fibrosis, and protect against kidney damage in mice with severe T2D [106]. Trimetazidine, an anti-ischemic drug used for coronary artery disease, has also been shown to have anti-fibrotic and protective effects in the kidney, which appears to act through FoxO1/ROS and TGF-β/Smad pathways as assessed in diabetic rats [107–109].

These interventions, although found helpful in slowing progression, have not reduced the incidence of diabetic kidney disease. Strategies that can reverse kidney and other tissue fibrosis are now imaginable through the use of agents that can reverse EMT and thus restore original phenotypes of the epithelia or endothelia. For

example, the BMP7 receptor Alk3 in kidney tubules is essential for anti-fibrogenesis and tissue repair and appears to be an attractive therapeutic target in diabetic nephropathy. Indeed, Alk3 agonists showed renoprotection in experimental kidney fibrosis models, including models of diabetic nephropathy; this kidney protection was associated with the inhibition of EMT, inflammation, and apoptosis [85]. In addition, Snail1, a zinc finger transcription factor, has been shown to play a central role in EMT induction [110]. A recent study has demonstrated that Snail1 activation in kidney epithelia is required for inducing EMT and kidney fibrosis and, more importantly, inhibition of Snail1 reversed fibrosis and ameliorated nephropathy in mice [111]. Strategies to prevent or reverse EMT need to be part of the future therapies in diabetic kidney disease as well as other complications associated with diabetes.

It has been recognized for some time that the kidneys may have an intrinsic ability for self-regeneration. An earlier 10-year follow-up study of eight T1D patients who received pancreas transplants and who had varying degrees of diabetic kidney disease before reaching end stage demonstrated reversal of all the kidney lesions after 10 years of normoglycemia [112]. In experimental models as well as in humans with diabetic and non-diabetic kidney disease, reversal of kidney lesions and functional restoration was observed. Research since then has confirmed the existence of a "renopoietic" kidney stem cell/progenitor system that can replace tubular cells as well as podocytes, which are neuron-like cells with a limited ability to regenerate and which are the principal drivers of the characteristic glomerular sclerosis in diabetic kidney disease [113]. There are indications that these podocyte- and tubule-committed progenitor cells can be pharmacologically manipulated to promote kidney regeneration, or also isolated, clonally expanded, directed to injury site by molecular manipulations and transplanted into the injured kidney to reverse kidney damage [113]. Further research into understanding the molecular mechanisms of activating progenitor cells is likely to contribute to regenerative nephrology and be part of future strategies for the treatment of diabetic and non-diabetic kidney disease.

Vascular changes seen in diabetes are largely responsible for not only kidney disease but also are the main cause of cardiovascular morbidity as well as retinopathy. Accelerated atherosclerosis is the main feature of diabetes, and multiple factors along with hyperglycemia, including advanced glycation end products (AGE), increased free fatty acids and LDL cholesterol, reactive oxygen species, angiotensin II, activation of NF-κB, and production of inflammatory cytokines, contribute to vascular injury [114]. The effects of insulin receptors beyond glucose regulation have been shown to promote the integrity of both the vascular endothelial cells and podocytes, thus identifying another mechanism through which vasculopathy, and podocytopathy, which aggravates both atherosclerosis and glomerulosclerosis, is mediated as a result of insulin resistance [85, 114]. Ongoing research suggests that enhancing the protective effects of insulin-regulated genes on vascular endothelial cells and delivery of non-diabetic endothelial progenitor cells can prevent or even reverse the vascular disease in diabetes [114–116]. Countering accelerated atherosclerosis through the use of statins and renin-angiotensin system antagonists is already an established therapy in diabetes. These newer insights are likely to

generate more effective treatments through gene manipulations that can lead to induction of antioxidant and anti-inflammatory factors that promote vascular survival and preserve vascular integrity, which in turn would be expected to help prevent both diabetic kidney disease and retinopathy [114].

The Promise of Metabolomics and Proteomics

A significant constraint in the approach against treatment of diabetic nephropathy is the limited availability of biomarkers. Microalbuminuria has its limitations and is not always predictable. Some investigators have suggested that increased urinary excretion of non-albumin low-molecular-weight proteins such as polyclonal immunoglobulin light chains, particularly kappa light chains, as a reflection of early tubular dysfunction, i.e., decreased endocytosis through the endocytic receptors megalin and cubilin, may be a more reliable marker [117–121]. Other studies indicate zinc-alpha-2-glycoprotein (ZAG) may be a useful early biomarker for diabetic nephropathy because urine and serum ZAG levels increase with nephropathy development and the changes are detectable earlier than microalbuminuria [122, 123]. A more comprehensive search for biomarkers through metabolomics studies using gas chromatography-mass spectrometry to screen for a large number of metabolites in the urine of patients with diabetic nephropathy are under way and have yielded promising clues. In a pilot study, Sharma et al. observed that urine from subjects with diabetic kidney disease showed reduced levels of metabolites, and many were soluble organic anions related to mitochondrial function and reflecting globally suppressed mitochondrial function in patients with diabetic kidney disease. The authors also found that exosomes from patients with diabetes and kidney disease had less mitochondrial DNA and kidney tissues from patients with diabetic kidney disease had lower gene expression of PGC1a (a master regulator of mitochondrial biogenesis). These observations suggest that urine metabolomics may be a promising strategy to identify early biomarkers of kidney disease in diabetic patients and that organic anion transporters and mitochondrial function may be dysregulated in diabetic kidney disease [124].

The field is likely to expand as studies on urinary exosomes are more closely investigated. Exosomes are 40–100 nm vesicles that contain proteins, mRNA, and microRNAs that have the potential to serve as biomarkers of kidney dysfunction [125]. Newer methodologies including various ultracentrifugation techniques are now allowing more efficient exosome isolation enabling proteomics analysis and RNA and microRNA analysis [126, 127]. Such techniques are likely to lead to identification of newer biomarkers of kidney involvement in diabetics, as well as newer insight into mechanisms of kidney disease.

Proteomic analyses from diabetic kidneys and other organs, such as the liver and skin, are relatively new and appear to identify differential expression of various proteins in affected organs compared to healthy organs. These studies have identified accumulation of protein aggregates due to impaired proteasomal activity, novel

oxidative and glycolytic mechanisms, and novel regulators of TGF-β signaling, tight junction maintenance, oxidative stress, etc. [128–131]. In a recent study, urine from T1D patients was processed to proteomics analysis, and the results show significant alterations in prostaglandin and ceramide metabolism that are specifically associated with nephropathy development [132]. In other studies, urine exosomes are isolated from diabetic patients and then subjected to proteomics analysis. These studies have identified several proteins as potential biomarkers for diabetic nephropathy, which include the water channel aquaporins (AQP2 and AQP5), the endocytic receptor C-megalin, the epithelium-specific transcription factor Elf3, and the calcium-binding protein regucalcin [125, 133–136]. These investigations not only identified new biomarkers for diabetic nephropathy but also revealed novel therapeutic targets awaiting pre-clinical and translational studies.

Genes, Epigenetics, and MicroRNAs

The genetic determinants of kidney disease in diabetes are still not fully defined. Although nearly half of the diabetics will develop kidney disease, the other half will not, suggesting a genetic basis of vulnerability independent of hyperglycemia, hypertension, or albuminuria. Earlier studies have focused on angiotensin-converting enzyme (ACE) insertion/deletion polymorphism as a determinant of susceptibility to kidney disease in both T1D and T2D and suggested that the D allele or DD homozygous might be associated with an increased risk of nephropathy [137–141]. It has also been suggested that the DD genotype may respond better to ACE inhibitors or angiotensin receptor blockers prompting investigators to suggest a pharmacogenomics approach to treatment in diabetic populations [142]. However, most of the studies were not definitive, suggested a much more complex gene-environment interaction, and pointed to the need for further investigations [141]. Nearly two decades of the use of ACE inhibitors and angiotensin receptor blockers may have helped slow the progression of diabetic nephropathy in many people, but the incidence of diabetic nephropathy continues to increase.

More recent genetic research has broadened our understanding of the role of genetics and epigenetics in the pathogenesis of diabetic kidney disease and suggested novel directions of therapeutic interventions. Genome-wide association scans (GWAS) for single-nucleotide polymorphisms (SNPs) have pointed to previously unidentified pathways that may be responsible for susceptibility to diabetic nephropathy [143–145]. Multiple chromosomal loci including 3q, 7q, 10p, 14q, and 18q have been identified as possible determinants of susceptibility to diabetic nephropathy in both type 1 and type 2 diabetes; however, the specific roles of these loci in the pathogenesis of diabetic nephropathy have not been fully established [146]. Recently, studies have shown that Hae III polymorphism of the solute carrier family 2 facilitated glucose transporter membrane 1 (SLC2A1) gene, which encodes glucose transporter 1 (GLUT1), is associated with nephropathy susceptibility in

patients with T2D [147, 148]. In addition, apolipoprotein E (Apo E) genetic polymorphism also appears to affect DN susceptibility in patients with T2D [149]. These genetic polymorphisms may serve as independent risk factors for nephropathy in diabetic patients.

Gene-environment interactions and the role of epigenetics appear to be closely involved in the pathobiology of diabetes, obesity, and diabetic nephropathy [150–152]. Some of these studies have focused on the intrauterine environment and alterations in DNA methylation and histone post-translational modification that results in disease in adult life, and some even persist across generations [150]. Dysregulation of post-transcriptional modifications of histones in chromatin and DNA methylation can result in aberrant gene behavior that favors development of diabetes and its complications. Experimental studies in vitro have shown long-lasting epigenetic alterations at inflammatory gene promoters after prior exposure to diabetic conditions implying a possible mechanism for metabolic memory [151]. Histone deacetylases, especially sirtuins, which deacetylate histones and various transcription factors, have also been explored as epigenetic therapeutic targets in many acute and chronic diseases. Sirtuin is downregulated in the kidneys of diabetic mice before the onset of albuminuria, and its overexpression in the proximal tubules of mice prevents diabetic nephropathy [153].

In order to have a complete understanding of epigenetic mechanisms in diabetic kidney disease, researchers performed novel genome-wide studies, namely, epigenome-wide association studies (EWAS), by analyzing DNA methylation profiles using whole blood samples from patients with or without kidney disease [152]. In a recent study, Chu et al. performed DNA methylation EWAS on thousands of blood samples from participants and identified 19 CpG sites that are significantly associated with chronic kidney disease, of which 5 also show similar DNA methylation changes in kidney cortex and are associated with kidney fibrosis [154]. Qiu et al. identified 77 CpG sites with methylation alterations that are associated with eGFR decline in Pima Indian diabetic patients and that the top CpG sites associated with eGFR decline are localized to the regulatory regions of metabolic genes [155]. The epigenetic signatures not only serve as another line of biomarkers in the prognosis of diabetic kidney disease but may also provide novel therapeutic targets for the disease.

In addition to DNA methylation and histone modifications, microRNAs have also been implicated in diabetic kidney disease [156, 157]. MicroRNAs (miRNA) are small (19–23 nucleotide long) non-coding RNA molecules that play important roles in the transcriptional and post-transcriptional gene expression through either mRNA degradation or translational repression [158]. Studies have demonstrated that a long non-coding RNA, the plasmacytoma variant translocation 1 (PVT1), increases plasminogen activator inhibitor 1 (PAI-1) and TGF-β1 in mesangial cells, the two main contributors to ECM accumulation in the glomeruli under hyperglycemic conditions, as well as fibronectin 1 (FN1), a major ECM component, and miR-1207-5p, a PVT-derived microRNA, plays a key role in this process [159, 160]. Recent studies in diabetic mice have suggested that cross talk between mRNAs, TGF-β1, and p53 may play an important role in the pathogenesis of diabetic

nephropathy. Among many miRNAs, this study has suggested that microRNA-192 (miR-192) is increased in the kidneys of diabetic mice along with p53, TGF-β1, and blocking miR-192 reversed increased expression of p53 and TGF-β1. This intervention resulted in reduced and reversed kidney fibrosis, suggesting an important role for miRNAs in the pathogenesis of diabetic nephropathy and identified miRNA targeting as a novel therapeutic strategy [84].

In a streptozotocin model of diabetes, high concentrations of miR-375 appeared as a marker of beta cell death and a potential predictor of diabetes in mice [161]. Other investigators showed similar associations with miR-21, i.e., increased expression in the kidney as a potential marker for diabetic nephropathy, and as a therapeutic target as MiR-21 knockdown plasmid delivery, similar to opposing miR-192, also reduced TGF-β1 expression, suppressed NF-κB activation, and helped reverse proteinuria and kidney inflammation in db/db diabetic mice, a model for T2D [162]. To date, numerous miRNAs have been shown to contribute to diabetic kidney disease, such as miR-192, miR-216a, miR-217, miR-377, miR-21, miR-29c, and miR-1207-5p, and miRNA-targeted therapies are being explored as a possible strategy to treat diabetes and diabetic kidney disease [159, 160, 163].

Thus, genetics and search for loci and SNPs in GWAS, along with exciting new epigenetic insights revealed through EWAS, and the role of miRNAs have opened up new areas of research in the pathobiology of diabetes and its complications. This research is identifying new mechanisms and new therapy approaches that are on the verge of translational studies, which may enable us to not only treat diabetes and its serious complications including diabetic nephropathy but, more importantly, identify susceptible populations and possibly prevent diabetes through pre-emptive strategies.

Nanotechnology in Diabetes Research and Treatment

Imagining the future of diabetes and diabetic nephropathy must include the exciting developments in nanotechnology. Indeed, nanotechnology is being actively investigated in diabetes research, especially with regard to drug delivery [164, 165]. Nanoparticles, i.e., particles with diameter in the range of nanometers, can be generated from various biodegradable, biocompatible, and non-antigenic materials such as alginate, chitosan, dextran, polylactic-co-glycolic acid (PLGA), and many other natural or synthetic polymers [164, 166]. The nanoparticles can be designed to serve many purposes for drug delivery, such as protecting the enclosed drug, releasing the drug in a controlled manner, enhancing drug absorption, and targeting to specific tissues.

One of the major efforts in diabetes nanotechnology is to employ nanoparticles as carriers for oral insulin delivery [166, 167]. The traditional route of insulin administration is subcutaneous injection, which is a challenge for many patients, and especially hard for those who are fearful of needles (trypanophobia). Therefore, the availability of oral insulin delivery can improve patient compliance and reduce

discomfort/complications at the injection sites. The effective oral insulin delivery needs to resolve several major issues, which include maintaining stability in the acidic pH environment, resisting degradation by digestive enzymes, and permeating through the mucus and epithelial barrier in GI tract. A wide variety of biomaterials and formulations have been developed and tested in vitro and in animal models, and much progress was made in the past few years. For instance, PEGylation of insulin-chitosan nanoparticles has been shown to permeate through fresh mucus, and 65% insulin be released within 4 hours [168]; PLGA-based nanoparticles containing insulin are developed using various formulations and show insulin release and glucose-lowering effects when administered orally in animal models [169, 170]. Alginate−/chitosan-complexed insulin nanoparticles have also been developed and tested in animal models, in which they have been shown to result in effective drug bioavailability and reduced blood glucose levels [171]. Currently researchers are trying to optimize insulin nanoparticle formulations. Glucose-responsive and pH-responsive nanoparticles are under development; layer-by-layer technique is being adopted to make nanoparticles with the desired properties [166]. With the rapid development in nanotechnology, it is highly likely that nanoparticle-based oral insulin will be advanced to clinical use in the near future.

In addition to oral insulin, considerable efforts have been dedicated to developing other nanoparticle-based medicines in the treatment of diabetes and its complications. The drugs are either attached to the surface of or entrapped within the nanoparticles, and the nature of the nanoparticles is designed based on the needs of drug delivery. One particularly interesting field is the development of nanomedicine for diabetic retinopathy (DR) [172, 173]. Neuroprotective agents can ameliorate DR, but drug administrations via either systemic or intraocular injection severely limit their bioavailability to the targets—retinal neurons. Researchers are attracted to nanocarriers because of their potential to improve drugs' pharmacodynamics and pharmacokinetics. As examples, Pandit et al. have developed chitosan-coated PLGA nanoparticles for bevacizumab, an anti-VEGF drug, for effective and sustained delivery to ocular tissue [174]. Amato et al. have developed magnetic nanoparticles functionalized with octreotide (a drug that inhibits oxidative stress), and the nanomedicine reduced retinal cell apoptosis after intraocular injection in mice [172]. Another interesting development is nanomedicine for wound healing. Masood et al. recently reported the development of silver nanoparticle impregnated chitosan-poly ethylene glycol (PEG) hydrogel [175]. Silver nanoparticles have strong antibacterial activities and thus are helpful for wound healing. The researchers have shown that the silver nanoparticles are released from the hydrogel in a slow and sustained manner and observed improved antibacterial, antioxidant, and wound healing activities in diabetic rabbit [175]. In addition, nanoparticles are widely explored as non-cytotoxic carriers for miRNA-based drug delivery in vivo [176].

As described above, innate and adaptive immune systems play essential roles in the pathogenesis of diabetes and its complications. Therefore, many efforts are attracted to develop immunomodulatory nanomedicine for diabetes treatment [165, 177]. Various nanoparticles have been employed to deliver immunosuppressive or tolerogenic agents via intravenous injection, which have been shown to be effective

in targeting immune cells in the circulation and in spleen [165]. In a comprehensive study, Clemente-Casares et al. developed nanoparticles carrying major histocompatibility complex class II (MHCII)-conjugated autoantigens (viz., pMHCII-NPs). They showed that systemic administration of the pMHCII-NPs into diabetic non-obese diabetic (NOD) mice stimulated the generation and expansion of antigen-specific Tregs, reduced autoimmunity, and resulted in normoglycemia [178]. In another study, Yeste et al. engineered gold nanoparticles to deliver the aryl hydrocarbon receptor ligand (a tolerogenic molecule) and proinsulin. When administered into NOD mice, the nanoparticles induced a tolerogenic phenotype, which is characterized by a decrease in inflammatory effector T cells and a concomitant increase in Tregs, and prevented T1D development [179]. In addition, nanoparticles coated with specific targeting agents are engineered to deliver immunomodulatory cargos to specific immune cells. For example, PLGA nanoparticles loaded with cytokines TGF-β and IL-2 and coated with anti-CD4 antibody have been shown to target $CD4^+$ T cells, which result in Tregs induction and maintenance [180].

Moreover, researchers are developing nanotechnology-based implantable devices that can sense blood glucose concentration and deliver appropriate doses of insulin continuously. Recent advances in nanotechnology and biosensors raise the expectation that biochips can be designed that can continuously monitor blood glucose as well as other disease biomarkers. Such devices would need to be fully integrated into closed loop systems and be implantable via minimally invasive methods, possibly subcutaneously. Issues such as long-term biocompatibility, reliability, and high degree of integration need to be overcome before such technology can be introduced clinically [181, 182].

In Pursuit of Futuristic Therapies

As discussed above, with the development of new technologies and better understanding of the disease, many novel therapies are being explored to treat diabetes and diabetic nephropathy (Fig. 28.2), which include incretin therapy, SGLT2 inhibition, RAS inhibition, immunotherapy, and so on. In addition, studies have now demonstrated some degree of residual β cell function or existence (at autopsy) in long-standing T1D. This has inspired studies aimed at the preservation and even regeneration of the β cells, with the expectation that restoring endogenous insulin secretion will yield better glycemic control and prevent the development of the dreaded complications of diabetes, such as retinopathy and kidney disease [183]. Currently, researchers are exploring innovative gene and cell therapy strategies to restore β cell function.

Gene Therapy During the past few years, significant progress has been made with gene-based therapies in animal models, and we can expect that some translational studies will be initiated in humans in the near future. Gene therapy aimed at protection and regeneration of β cells is one area that has attracted attention. A broad array

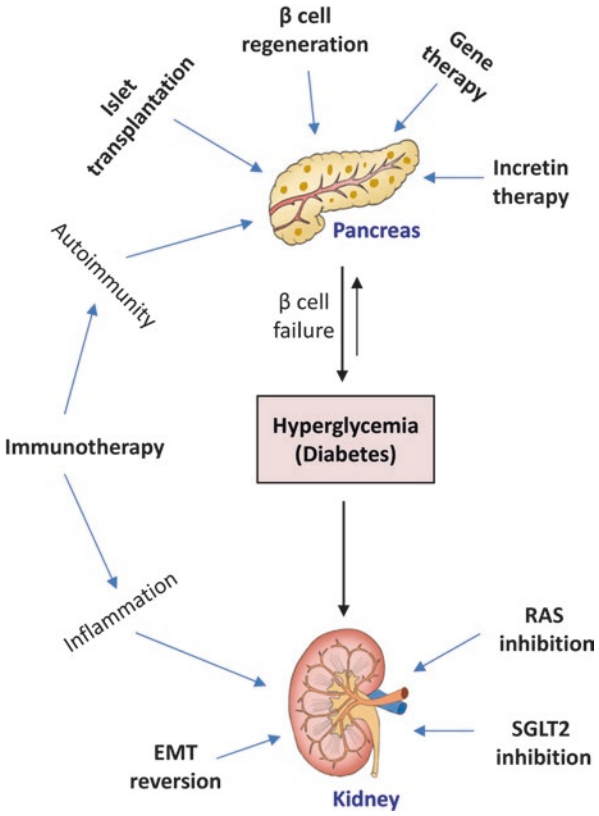

Fig. 28.2 Diagram depicting novel therapies for diabetes and diabetic nephropathy. Hyperglycemia (diabetes) results from insulin deficiency due to autoimmune-mediated β cell destruction in the pancreas (T1D) or insulin resistance that eventually leads to β cell dysfunction (T2D). Most of the novel therapies aiming to ameliorate diabetes and diabetic kidney disease act on either the pancreas or kidney. Immunotherapies primarily act on the immune system, but their ultimate purposes are to protect β cells in the pancreas by countering autoimmunity or to prevent kidney fibrosis and kidney injury by reducing inflammation

of targets is being explored with gene therapy approaches, including anti-apoptotic genes, various growth factors, transcription factors promoting β cell regeneration, and modulators of the inflammatory pathways involved in the pathogenesis of β cell death [184, 185]. Gene transfer of anti-apoptotic and proliferative genes such as Bcl-2 and Akt1 into pancreatic islets showed protective effects on β cells and against experimental T1D [186–188], but concerns of potential tumorigenesis effects have hindered their advancement beyond pre-clinical studies. Recent gene therapy endeavors are focused on better therapeutic genes (with regard to safety, potency, and specificity) and more efficient gene delivery vectors. For instance, gene delivery of Pax4, a β cell-specific transcription factor, alleviates streptozotocin-induced diabetes because Pax4 promotes α-to-β cell transdifferentiation and β cell survival [189, 190]. Gene delivery of insulin-like growth factor 1 (IGF1) into the pancreas via an adeno-associated viral (AAV) vector has been shown to slow T1D development in NOD mice [191]; the anti-aging gene Klotho, when delivered by AAV vectors in vivo, has been shown to reduce β cell apoptosis, improve β cell function, and attenuate diabetes development in both T1D and T2D mouse models [192, 193]. Moreover, gene therapy strategies can be used in combination with other therapies including immunotherapy and cell therapy. Genetic modification of immune cells

(CAR-Ts) or islet cells has been under investigations and, if succeeded, would represent a major breakthrough in finding a cure to diabetes and its complications.

While viral vectors, especially AAV vectors, appear to be the most efficient in vivo gene delivery vector for diabetes treatment, it is noteworthy to mention an innovative non-viral gene delivery strategy, namely, ultrasound-targeted microbubble destruction (UTMD). In this technique, intravenous microbubbles carrying therapeutic DNA or RNA are destroyed within the pancreatic microcirculation by ultrasound, achieving local gene expression, which can be further targeted to β cells by a rat insulin promoter (RIP3.1). In one study, a series of genes that are involved in the development of endocrine pancreas were delivered to streptozotocin-induced diabetic rats. RIP3.1-NeuroD1 promoted islet cell regeneration, with normalization of glucose, insulin, and C-peptide levels, although the improvement was transient [194]. UTMD has also been used to successfully deliver therapeutic genes into other organs including the kidney, heart, and muscle [195–197]. These proof-of-concept studies demonstrated the feasibility of selective gene delivery to the target organs/tissues in vivo without using viral vectors, opening up further possibilities for successful gene therapy [194].

Stem Cell Therapy (in Vitro β Cell Regeneration) A curative therapy for T1D needs replenishment of functional β cells in addition to induction of immune tolerance. One of the most attractive strategies is to regenerate functional β cells from stem cells in culture and then transplant them into diabetic patients. Over the past two decades, stem cell therapy has attracted tremendous interest, and considerable progresses have been made as regenerative medicine for T1D [198–201]. The stem cells that are used to induce β cell differentiation in vitro include pancreatic stem cells, human embryonic stem cells (hESCs), and induced pluripotent stem cells (iPSCs). Many early studies focused on pancreatic stem cells and achieved some success in inducing the formation of islet-like cells from pancreatic tissue, especially adult human pancreatic ductal tissue [202, 203]. However, isolation and in vitro expansion of pancreatic stem cells are challenging. The hESCs, on the other hand, are highly proliferative and highly capable of differentiation into various cell types including β cells in vitro and have become the most popular choice for β cell regeneration. Indeed, hESC-derived β cells are leading the way to clinical studies [198, 201]. The iPSCs are generated by reprogramming adult somatic cells with transcription factors such as Oct4, Sox2, Klf4, and c-Myc [204, 205]. The unique advantage with iPSCs is that they can be generated from the patients' own somatic cells, thus minimizing immune rejection of these iPSCs-derived β cells upon transplantation.

Several key milestones have been achieved thus far for stem cell-based β cell regeneration. The first one is the development of a differentiation process that successfully induces the formation of islet-like cells from hESCs, as demonstrated by the expression of all pancreatic hormones (insulin, glucagon, ghrelin, somatostatin, and polypancreatic peptide) [206–208]. Another milestone is the development of a protocol that allows scalable and reproducible in vitro production of functional β

cells, namely, stem cell-derived β (SC-β) cells [209]. The protocol employs a unique combination of various factors including wnt, activin, hedgehog, EGF, TGFβ, thyroid hormone, retinoic acid, and γ-secretase inhibition, at different stages of differentiation. These SC-β cells have been shown to display similar property and functionality to the bona fide β cells and are able to ameliorate hyperglycemia immediately after transplantation into T1D mouse models, as effectively as human islets do [209]. A third milestone is to generate SC-β cells from iPSCs that are derived from somatic cells of T1D patients [210]. In the study, the researchers first generated iPSCs from the skin fibroblast of T1D patients and differentiated into functional SC-β cells using the same differentiation protocol as described above for hESCs. The results demonstrate the feasibility to generate SC-β cells from the patients' own somatic cells in vitro, thus minimizing immune rejection upon transplantation, and this is a key to the development of personalized regenerative medicine for T1D treatment.

With the establishment of the technology in producing SC-β cells in vitro at a large scale, the next step is to move it into clinical studies. The major obstacle is safety concerns—the potential of tumorigenesis. Stem cells are very proliferative, so any undifferentiated (or not fully differentiated) cells in the SC-β cell preparations may lead to tumor formation in vivo. For example, teratomas have been observed in recipient mice when transplanted with hESC-derived endocrine cells [208]. In addition to optimizing the SC-β cell preparation procedures, another strategy is to place the SC-β cells in an encapsulation device and then implant the device into the patients [211, 212]. Ideally, the device will be constructed with materials that allow nutrients and gaseous exchange but block cell migration between the host and the implant. This way, the implanted cells can be removed if tumorigenesis or β cell dysfunction is observed. In addition, the device can protect the implanted cells from host immune attack, thus leading to better therapeutic outcome. This technology has been under intense investigation during the past decade, and many progresses have been made. For example, it has been shown that SC-β cells encapsulated with alginate derivative-based polymers are successfully implanted into immune-competent T1D mice and achieved long-term normoglycemia without the use of immunosuppression [212]. These advances have led to the first clinical trial using hESC-derived β cells to treat T1D patients. The ongoing study is a phase 1/2 trial aiming to evaluate the safety, efficacy, and tolerability of the encapsulated SC-β cells in T1D patients when implanted subcutaneously (NCT02239354). Thus it is reasonable to expect that stem cell-based therapies for T1D will come to fruition in the foreseeable future [201].

In Vivo β Cell Regeneration Another attractive strategy to overcome β cell deficiency is to regenerate β cells directly in vivo. This strategy, if successful, would bypass cell transplantation and avoid immune rejection. Spontaneous β cell regeneration occurs in vivo under normal physiological conditions, which accounts for normal β cell turnover and compensates for increased insulin needs in conditions such as obesity or during pregnancy. Studies have demonstrated that spontaneous and adaptive β cell regeneration occurs by three mechanisms: duplication of exist-

ing β cells, differentiation from progenitor cells, and transdifferentiation from other islet cell types such as glucagon-producing α cells and somatostatin-producing δ cells [198, 213–215]. In addition, it has been known that embryonic development of β cells is controlled by sequential activation of distinct transcription factors [198]. Among them, the most critical ones include Pdx1, Ngn3, MafA, and Pax4 (Fig. 28.3a). With the understanding of the molecular and cellular mechanisms governing β cell differentiation, researchers have been exploring various strategies to induce β cell regeneration in vivo (Fig. 28.3b).

One of the most interesting and highly innovative strategies is to reprogram other cell types into insulin-producing β cells [198]. The process is also termed transdifferentiation because it converts one terminally differentiated cell type into another. The cells that have been explored for transdifferentiation include the liver cells, the gastrointestinal (GI) tract cells, pancreatic exocrine cells, and islet α cells (Fig. 28.3b). Ferber and her colleagues have shown the transcription factor Pdx1, when delivered into the liver by adenoviral vector, is able to induce insulin

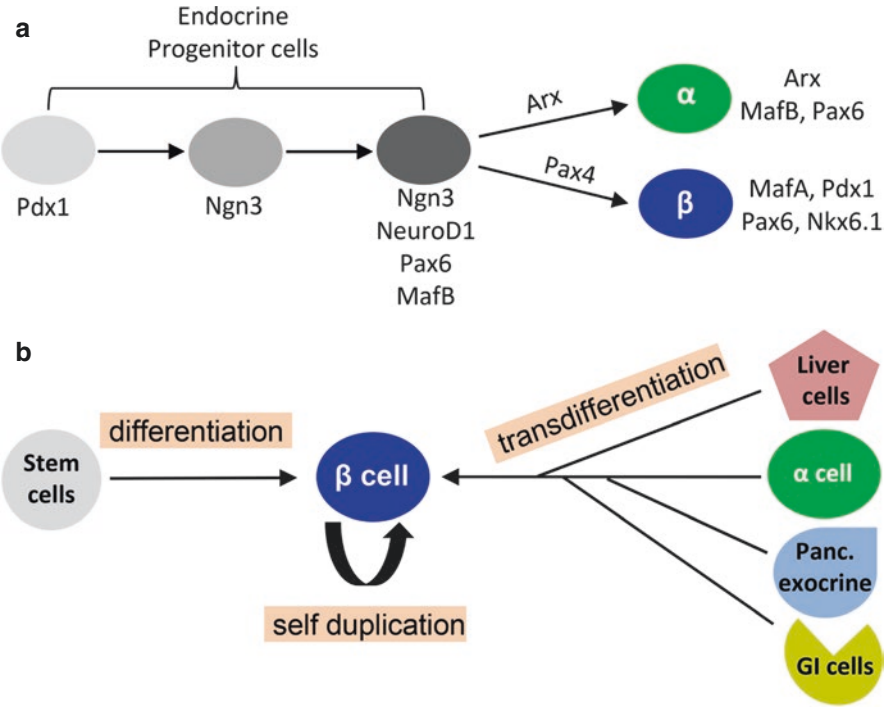

Fig. 28.3 Diagram of β cell development and its regeneration strategies. (**a**) Sequential expression of transcription factors controls islet cell differentiation during embryonic development. Shown are major transcription factors involved in islet α and β cell development. (**b**) Strategies to regenerate islet β cells: stem cell-based differentiation mimicking embryonic β cell differentiation, transdifferentiation into β cells by reprogramming other cell types, and β cell self-duplication induced by growth factors and other proliferative genes

expression in the liver and reduces hyperglycemia in T1D mouse models [216]. The efficiency of liver cell-to-β cell reprogramming is significantly improved when co-treated with MafA, NKx6.1, and/or Pax4, all of which are essential transcription factors for β cell development [217, 218]. The GI tract is another target tissue that has been used for reprogramming into β cells [219–221]. The transcription factors Ngn3, Pdx1, and MafA have been introduced into the intestines or antral stomach and resulted in the reprogramming of the epithelial cells into insulin$^+$ cells and amelioration of hyperglycemia in diabetic mice or rats [219, 220]. As the natural home for β cells, pancreatic tissue is another attractive site to induce β cell regeneration. Researchers have attempted to reprogram pancreatic exocrine cells into β cells and achieved some success in inducing acinar cells or ductal cells to become insulin-expressing cells [222, 223]. Furthermore, the glucagon-producing α cells have also been targeted for transdifferentiating into β cells [189, 190]. Pancreatic α and β cells share the same route of differentiation during embryonic development until very late stage (Fig. 28.3), and they both reside in the islets. During embryonic development, Arx expression leads to α cell formation, whereas Pax4 expression leads to β cell lineage [224, 225]. Therefore, reprogramming α cells into β cells may be achieved with simple manipulation of the key transcription factors that determine α vs β cell lineage. Indeed, ectopic expression of a single transcription factor, Pax4, in α cells converts them into β cells in transgenic mice [226]. Building on this knowledge, researchers recently explored the therapeutic potential of Pax4 gene delivery in improving β cell function. The studies show that gene delivery of Pax4 into pancreatic islets not only induces α-to-β cell transdifferentiation but also promotes the survival of existing β cells, thus substantially improving β cell function and ameliorating hyperglycemia in T1D mouse models [189, 190].

Despite the impressive progresses and potential benefits of β cell regeneration in vivo, these strategies remain in pre-clinical stage. The major obstacle is the lack of an efficient gene/drug delivery system in vivo. Gene/drug delivery into the pancreas and islet cells in vivo is especially challenging, and extensive investigation is needed to move this field forward.

Islet Transplantation Since the first implementation of Edmonton protocol about 20 years ago, islet transplantation has achieved tremendous success and has become a treatment option for selective T1D patients and for preventing surgical diabetes in pancreatitis patients who undergo total or near-total pancreatectomy [227, 228]. Islet transplantation in clinic occurs via portal vein infusion, so the islets mostly engraft in the liver. Studies have demonstrated that islet transplantation results in smoother glycemic control in the islet recipients than insulin therapy, with very few hypoglycemia events, even though the patients might not have achieved insulin independence [228–230]. Nonetheless, there are two major obstacles that have limited its broader use: the limited supply of donor human islets and inefficient islet engraftment.

Currently, novel strategies are emerging to improve the chances of islet cell survival and to prevent islet rejection. One line of research is to explore strategies to protect β cells of donor islets. For example, Pax4 gene delivery into donor islets has

been shown to improve therapeutic outcome of islet transplantation in mouse T1D models, owing to its dual functionality in β cell survival and reprogramming from α cells [189]. In addition, studies have shown co-transplantation of mesenchymal stem cells (MSCs) and human islets significantly enhances the efficacy of islet transplantation in the clinic [231]. In another line of research, various methodologies are being pursued to encapsulate human islets before implantation to improve the chances of engraftment and reduce the risk of rejection. In one study, alginate-encapsulated islet cells yielded superior outcomes in a mouse model of diabetes as well as a T1D patient [232], while another study used coating by biosilicification to improve survival and function of islet cells in culture [233]. Other strategies include directing engraftment to other sites, such as the small intestine rather than the portal vein, which seems to yield better control of diabetes in an animal model [234]. Furthermore, novel immunosuppression protocols are being explored to improve the success rate in single donor islet cell transplants, and in one study the use of anti-thymocyte globulin plus anti-inflammatory agents, anakinra and etanercept, for induction and tacrolimus plus mycophenolate mofetil for maintenance was shown to result in successful single-donor islet cell transplantation in eight patients [235]. With the implementation of the novel strategies, it is likely that the success rate in single-donor islet transplantation will greatly improve in the coming years.

Islet Xenotransplantation Cross-species transplantation of organs from animals into humans was attempted since as early as the seventeenth century. An early example in the twentieth century was when Dr. Keith Reethma transplanted chimpanzee kidneys to 13 patients at Tulane during 1963–1964. Although the patients lived only 9 to 60 days, one patient survived for 9 months and even returned to work, indicating potential feasibility [236, 237]. Attempts to cross-species transplantation of organs including the kidney, liver, neuronal cells, pancreas, and islet cells continued despite many hurdles [238, 239]. Over the past decade, xenotransplantation using engineered pigs as organ donors made considerable progresses, especially with regard to islet xenotransplantation [240–242]. Porcine islets are fully functional in humans. Porcine insulin differs from human insulin only by one amino acid residue; insulin secretion pattern from porcine islets is similar to human islets; and insulin extracted from pigs have been used in the clinic for diabetes treatment for decades [243]. Plus, pigs are easy to breed and grow, can produce large amount of islets, have low maintenance cost, and are more ethically acceptable than other large animals [240]. Therefore, porcine islets are considered the most promising alternative islet sources.

However, in order to translate pig islet xenotransplantation into the clinic, two major issues, acute immune rejection and potential zoonosis, need to be resolved. Recently, genetic engineering provided several breakthroughs in the field. First, CRISPR/Cas9 technology allowed genome-wide elimination of porcine endogenous retroviruses (PERV), thus significantly reducing the concern of zoonosis [244]. In addition, researchers have identified multiple genes that are involved in rejection and coagulation upon islet transplantation, and attempts are being made to modify or edit them in donor pigs. Moreover, transgenic pigs are generated to express multiple human proteins to facilitate immune tolerance of pig islets in humans [240, 242,

245]. These progresses have boosted the enthusiasm on pig islet xenotransplantation in the past few years, and clinical trials are likely coming in the near future worldwide [239, 242, 245, 246].

Concluding Remarks

The recent insights into the immunopathogenesis and immunogenetics of diabetes have yielded a large number of promising biomarkers, which can identify diabetics in the earliest phases of the disease and may even help identify patients at risk. This in turn would allow preventive interventions, taking advantage of our increased understanding of pathophysiology. Studies evaluating the effect of various immunotherapies aimed at preventing β cell destruction in type 1 diabetics with residual c-peptide or patients developing diabetes are under way. Clinical trial networks such as TrialNet and the Immune Tolerance Network in the USA and similar networks in Europe have started exploring such pre-emptive strategies. It is now in the realm of possibility that with early biomarkers, pre-emptive interventions to avert clinical diabetes will become available. These pre-emptive therapies include new therapies that will halt β cell destruction and even help regenerate residual β cells to sufficient mass. Advanced technologies will likely help with the replenishment of islet cells or interventions to regenerate islet cells, and new drugs help correct the metabolic disorders associated with diabetes beyond glucose control, which in turn would help prevent diabetic nephropathy and other crippling organ damages associated with diabetes, such as retinopathy, neuropathy, etc. Emerging technologies and interdisciplinary efforts are likely to produce increasingly sophisticated solutions for not only diabetic patients with kidney disease but also for other organ failures. We are thus hopeful that one day we will be able to prevent or reverse diabetes before it presents as full-blown clinical disease.

However, we should not lose sight of the fact that the increase in the diabetes epidemics and the associated organ damage that wreaks havoc on lives and the societies across the globe is a consequence of the modern lifestyle that involves unhealthy diet as well as decreased physical activity and the rising epidemic in the closely associated metabolic disorder, obesity. Without doubt, there is a need for more effective medical and technological treatments for diabetes, as our ability to intervene pre-emptively before full-blown disease develops. Yet, there is little question that millions of patients can be helped much more cost effectively through an internationally coordinated program that can help reduce obesity, increase physical activity, and educate populations on healthy diet. The future strategies must therefore include coordinated efforts globally to implement lifestyle changes that will likely have the greatest impact on lowering the burden of diabetes and diabetic kidney disease.

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Chapter 29
Putting it All Together: Practical Approach to the Patient with Diabetic Kidney Disease

Eudora Eng and Susan Quaggin

Scope of the Problem

Diabetes is a worsening worldwide epidemic. The World Health Organization noted that the global number of diabetics quadrupled in the 34 years from 1990 to 2014 (https://www.who.int/news-room/fact-sheets/detail/diabetes), and the International Diabetes Federation (IDF) reported a prevalence of 9.3%, affecting almost a half billion people worldwide. It further projected a 25% increase by 2030 and 51% by 2045 [1]. The loss of life is substantial, with an estimated 1.6 million deaths in 2016 directly attributable to diabetes, making it the seventh leading cause of death that year. It is a major cause of morbidity in affected patients who can suffer blindness, cardiovascular disease (CVD), lower limb amputations, and kidney failure. Diabetes is the most common etiology of chronic kidney disease (CKD) in the majority of developed, and in many developing, countries [2, 3]. In the United States, it is the leading cause of end-stage kidney disease (ESKD) (USRDS, 2015, https://www.usrds.org/media/2293/vol2_usrds_esrd_15.pdf), and globally, 80% of all ESKD cases are caused by diabetes, hypertension, or both [3]. The financial consequences are also dire, with the IDF estimating the annual global health expenditure on diabetes at USD 760 billion (https://diabetesatlas.org/en/sections/individual-social-and-economic-impact.html). In the United States, the 2020 US National Diabetes Statistics Report which analyzed data through 2018 found that the disease which affects one in ten Americans cost the economy $327 billion annually or 1.7% of the gross domestic product (GDP) (https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html).

More alarming than these figures are data which show that many diabetics are not even aware of their condition. In the United States, a US Centers for Disease

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Control and Prevention (CDC) report examined this issue by analyzing data from the 1999–2016 National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). "Diagnosed" diabetes was based on self-report, whereas "undiagnosed" diabetes was based on fasting plasma glucose and hemoglobin A1c levels among people self-reporting no diabetes. 7.3 million Americans (age 18 and older), or 21.4% of all diabetic adults, were unaware of their diagnosis. Asian Americans were the most uninformed among all ethnic groups, with one in two unaware they were diabetic, likely due to lower truncal, but increased visceral, fat, and thus the perception that they were not at risk. Worldwide, the same percentage of diabetics are unaware of their condition [1].

Patients with pre-diabetes are even more oblivious of their risk for serious disease. Using definitions of fasting plasma glucose 100–125 mg/dl or hemoglobin A1c values of 5.7–6.4%, in 2018 an estimated 88 million US adults had pre-diabetes, but of these, only 15% reported being informed of this by a healthcare professional.

Strikingly, even developing serious end-organ damage by diabetes does not improve patient awareness of their disease. Thirty-seven percent of diabetic patients have stage 1–4 CKD, with over half at stages 3–4. Yet among patients with CKD stages 3–4, more than 75% were unaware of their condition.

It is imperative that *physicians ensure all diabetic patients are aware of their diagnosis and pre-diabetics of their risk for developing diabetes. Patients must be fully educated about the sequelae of diabetes, including cardiovascular and renal disease, particularly if they have already experienced decreased renal function.*

Risk Factors for Development of Type 2 Diabetes

Population Considerations

The percentage of adults with diabetes increases with age, reaching 26.8% among those 65 years or older. However, the numbers of newly diagnosed cases of type 1 and type 2 diabetes have increased significantly among US youth.

Compared to Asians and whites, new cases are higher among non-Hispanic blacks and in people of Hispanic origin, whereas the highest percentage of existing cases is among native American Indians and Alaskan natives. In young people aged 10–19 years, the incidence is increasing for all ethnic groups except non-Hispanic whites and is especially increasing in non-Hispanic blacks. Among adults of Hispanic origin, Mexicans and Puerto Ricans have the highest prevalences, followed by Central/South Americans and Cubans. In Asian populations, Filipinos and Asian Indians have the highest prevalence.

Lastly, among adults, the prevalence varied significantly by the level of education, a surrogate of socioeconomic status. 13.3% of those with less than a high

school education had diagnosed diabetes compared to 9.7% of those with a high school education, and 7.5% of those with more than a high school education.

Additional Risk Factors

Recognized risk factors for development of diabetes include modifiable and non-modifiable factors. Patients should be encouraged to address modifiable factors (poor glycemic control, overweight/obesity, hypertension, hyperlipidemia, low level of physical activity, smoking) through a multi-disciplinary approach of lifestyle management, nutritional counseling, and medications where needed.

Patients should also be educated about their risk based on non-modifiable factors such as family history, ethnicity (above), and history of cardiovascular disease (CVD) (heart disease or stroke) and for women, those having polycystic ovary syndrome or a history of gestational diabetes.

Screening for Diabetes

The American Diabetes Association recommends that all adults ≥45 years be screened for diabetes. Those with major risk factors can be considered for earlier screening (Table 29.1).

Table 29.1 Screening for diabetes or pre-diabetes in asymptomatic adults

BMI ≥ 25 kg/m^2 (≥ 23 kg/m^2 in Asians) with any of the following (test every 3 years if normal):
High-risk ethnicity (African-American, Latino, native American, Asian American, Pacific islander)
Hypertension (on medications or blood pressure ≥ 140/90)
Cardiovascular disease
Hyperlipidemia (HDL ≤ 35 mg/dl [0.9 mmol/L] and/or triglyceride ≥250 mg/dl [2.82 mmol/L)
Sedentary lifestyle
Diabetes in first-degree relative
History of gestational diabetes or baby weighing ≥9 pounds
Women with polycystic ovary syndrome
Previously identified elevated fasting glucose or glucose tolerance test (test annually)
Women with gestational diabetes (test at least every 3 years)

	Pre-diabetes	Diabetes
Hemoglobin A1c	5.7–6.4%	≥ 6.5%
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L	≥126 mg/dL (7.0 mmol/L)
Random plasma glucose		≥200 mg/dL (11.1 mmol/L)
Oral glucose tolerance test	140–199 mg/dL (7.8–11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)

Screening for and Diagnosis of Diabetic Kidney Disease

Thirty percent of type 1 and 40% of type 2 diabetics develop diabetic kidney disease (DKD) (USRDS 2015, reviewed in [4]). Clinicians should be aware of characteristics of diabetic patients placing them at higher risk for the development of DKD: older individuals, male gender, family history of DKD, and races/ethnicities (black, Hispanic, Native American, Asian/Pacific Islander). Modifiable risk factors include suboptimally or poorly controlled diabetes and hypertension.

Guidelines from the American Diabetic Association (ADA) and the National Kidney Foundation (NKF) KDOQI (Kidney Disease Outcomes Quality Initiative) recommend that type 1 diabetics be screened annually starting 5 years after onset of disease. In type 2 diabetics, since duration of disease frequently is not known, the recommendation is that they be annually screened at diagnosis [5]. Screening consists of measurement of creatinine-based estimated glomerular filtration rate (eGFR) and assessment of albuminuria. Abnormal values should be confirmed in repeat testing at least 3 months apart.

Several equations are available for the estimation of GFR based on creatinine. The Chronic Kidney Disease-Epidemiologic Prognosis Initiative (CKD-EPI) equation is more accurate, especially in patients with normal or with only slight decrements in function. However, most clinical laboratories employ eGFR based on the Modification of Diet in Renal Disease (MDRD) equation.

Screening for albuminuria can be performed by three methods, but the preferred is an albumin-to-creatinine ratio (ACR) from a random urine sample, due to simple outpatient collection, its relative inexpense, and ease of performance. The sample is preferably a first void or other morning collection [6] which avoids diurnal variation in albumin excretion. If patients cannot give a morning urine, subsequent samples should be collected at the same time of day for uniformity. Alternatively, urine can be screened for albumin by a timed (overnight, or shorter, known duration) or 24-h collection with simultaneous creatinine. Moderately increased albuminuria (formerly termed "microalbuminuria") is present if the urinary albumin excretion is 30–300 mg/g creatinine on a random urine specimen, 20–200 mcg/min on a timed specimen, or 30–300 mg/24 h. Severely increased albuminuria ("macroalbuminuria") is defined as anything greater than the upper limits listed above. It is important to be aware of co-existing conditions which may increase urinary albumin, including uncontrolled hyperglycemia, exercise, urinary tract infection or acute febrile illness, moderate or marked hypertension, and heart failure. In addition to diurnal variation in albumin excretion, there is also a substantial day-to-day variability, which provides the rationale for requiring that at least two of three collections over a 3- to 6-month period confirm the albuminuria.

CKD in diabetic patients may not necessarily be due to DKD, but in the absence of another diagnosis, the CKD should be considered caused by diabetes if the eGFR is persistently less than 60 cc/min/1.73 m^2 and/or the ACR is ≥30 mg/gram creatinine [7]. Patients fulfilling these criteria, and who have (1) at least background diabetic retinopathy, especially in type 1 diabetics in whom retinopathy has high

concordance [8] and (2) any of the above risk factors, are generally considered to have DKD. Urine is often bland, although hematuria may be present. However, dysmorphic red blood cell, red blood cell, and white blood cell casts are not typical of DKD and should prompt investigation for other diagnoses. Diabetics with typical features, therefore, are not usually biopsied, but biopsy may be considered in patients with atypical presentations, including sudden onset of low eGFR or rapidly declining eGFR, particularly if >5 cc/min/1.73 m^2 per year, abrupt increase in albuminuria, especially a five- to tenfold increase over 1–2 years, development of nephrotic or nephritic syndrome, refractory hypertension, evidence of another systemic disease, or > 30% loss of GFR within 2–3 months of angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) initiation [5]. The criteria for the diagnosis of DKD are summarized in Table 29.2.

It is important to recognize that the presentation and course of DKD have changed. The term "diabetic nephropathy" historically was used to denote the presence of diabetic glomerulopathy caused by glomerular basement membrane thickening, endothelial damage, mesangial expansion, podocyte loss, and formation of nodules (Kimmelstiel-Wilson lesions). The development and progression of disease were first described in type 1 diabetics and involved sequential stages of glomerular hyperfiltration, "microalbuminuria," overt proteinuria, progressive loss of renal function and ultimate ESKD [9] with similar stages of progression in type 2 diabetes [10]. However, the current presentation is more heterogeneous, and practitioners should be aware that a large number of patients with type 2 diabetes and decreased

Table 29.2 Diagnosis of diabetic kidney disease

Patients with diabetes of sufficient duration can be considered to have diabetic kidney disease, in the absence of other diseases, if:
eGFR is persistently ≤60 cc/min/1.73 *and/or*
Albuminuria is present (confirmed in at least two of three samples obtained over 3–6 months):
ACR ≥ 30 mg/g (random sample) *or*
Urinary albumin excretion ≥20 mcg/min (timed specimen) *or*
Urinary albumin ≥300 mg/24 hours
AND
Background retinopathy is present (especially in type 1 diabetics) *with/without*
Presence of risk factors:
Susceptibility factors (older age, male gender, race/ethnicity, family history)
Initiation factors (poorly controlled diabetes, hypertension)
Biopsy may be considered to investigate other diagnoses in atypical presentations:
Sudden onset of low eGFR
Rapidly declining eGFR (especially if >5 cc/min/1.73 m^2/year)
Abrupt increase in albuminuria (especially a five- to tenfold increase over 1–2 years)
Development of the nephrotic or nephritic syndrome
Refractory hypertension
Evidence of another systemic disease
> 30% loss of eGFR within 2–3 months of ACE-I or ARB initiation or dosage change

kidney function have normal levels of albuminuria and may not have retinopathy [11–14]. Furthermore, even in patients with established albuminuria, regression of moderately increased albuminuria to normoalbuminuria is common in both type 1 [15] and type 2 diabetics [16]. Regression of severely increased albuminuria to moderately increased albuminuria or even to normoalbuminuria can occur in both types of diabetics [17–19]. Better blood pressure and glycemic control, improved cardiovascular care, and widespread use of inhibitors of ACE-I or ARBs explain some, but not all, of these presentations.

Clinicians should have heightened awareness of patients' risk factors for developing diabetes and DKD, and recognize that the spectrum of DKD includes non-albuminuric CKD.

Management

Lifestyle Management

In the 2020 CDC report, among adult diabetics, 15% were smokers, 89% were overweight, and nearly 40% were self-reported as inactive. These comprise, or contribute to, a number of the modifiable risk factors for the development and progression of diabetic kidney disease. We lack high-quality studies of sufficient duration supporting the benefit of lifestyle interventions in DKD, thus recommendations for lifestyle management are largely derived from guidelines set by the American College of Cardiology (ACC)/American Heart Association (AHA) [20].

Accordingly, all patients using tobacco should be counseled on tobacco cessation, strongly encouraged to quit, supported with nicotine replacement therapy (gum, patch, spray, inhaler) and pharmacotherapy, and referred to smoking cessation programs as needed.

Patients should be encouraged to avoid sedentary behavior and to engage in at least moderate-intensity physical activity. The recommendation for weekly time spent in moderately strenuous exercise (at least 150 min) as suggested by the ACC/AHA is derived from guidelines set by the US Department of Health and Human Services (https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf). Patients may be unable to reach this target due to coexisting diseases (e.g., heart or lung disease), and in the elderly, issues of balance may also be limiting. These patients should be encouraged to engage in the highest level of activity that is consistent with safety and tolerability.

In addition to exercise, overweight/obese patients should be counseled on caloric restriction. Diets should eliminate trans-fats and reduce to a minimum the intake of processed meats, refined carbohydrates, and sweetened beverages. Saturated fats should be replaced by mono−/polyunsaturated fats, and dietary cholesterol should

be reduced. Diets should include an abundance of fruits, vegetables, nuts, whole grains, and fish. Daily sodium intake should be reduced to <2 grams/day (90 mmol) or < 5 gram sodium chloride [21].

Cardiovascular and Renal Protection

Atherosclerotic vascular disease is a major cause of morbidity and mortality in diabetics [22], and half of type 2 diabetic patients die prematurely from a cardiovascular cause [23]. DKD develops in 30–40% of diabetics, with 10% dying with ESKD [23]. Thus, reducing risk for development and progression of cardiovascular and renal disease in diabetics is critical to alleviating the tremendous healthcare burden of these patients.

RAAS (Renin-Angiotensin-Aldosterone System) Inhibition

Angiotensin 2 Inhibition

Three decades ago, RAAS inhibition with ACE-I or ARBs was shown to protect against development of diabetic kidney disease, decrease albuminuria, slow GFR decline, and decrease rates of ESKD and death in both type 1 and 2 diabetics with albuminuria [24–29]. These important medications are disappointingly underutilized, with a minority of diagnosed DKD patients receiving either an ACE-I or ARB (NHANES III, https://health.gov/healthypeople/objectives-and-data/browse-objectives/chronic-kidney-disease/increase-proportion-adults-diabetes-and-chronic-kidney-disease-who-get-ace-inhibitors-or-arbs-ckd-05). Thus, standard of care for hypertensive DKD patients with albuminuria should include either an ACE-I or ARB, with titration to the highest dose tolerated. Normotensive diabetic patients with albuminuria may also benefit, although hard data are yet pending [21]. These agents are not recommended in normotensive, normoalbuminuric diabetic patients [7].

Because adverse and salutary effects on albuminuria are dose related, medications should be begun at low dose and upwardly titrated every 2–4 weeks until the maximum or maximum tolerated dose is achieved.

There are few head-to-head trials comparing the relative efficacy of ACE-I and ARB, and they are considered to be equivalent in their hemodynamic and kidney benefits. Well-known adverse effects of ACE-I include cough and angioedema, the latter occurring in 0.1–0.7% of patients. The mechanism is from ACE-I inhibition of degradation of vasodilatory peptides including bradykinin and substance P. These effects are not seen in ARB.

Angiotensin 2 inhibition causes vasodilation of glomerular afferent and efferent arterioles, but a greater effect on efferent arterioles, which may result in a drop in glomerular pressure and rise in creatinine. This effect usually is manifested in the first 2 weeks of drug initiation or dose increase and stabilizes in the following 2 weeks. The rise in creatinine is more likely to occur in the context of decreased effective arterial flow, so clinicians should be aware of potential exacerbating conditions such as co-administration of diuretics, use of non-steroidal anti-inflammatory drugs (NSAIDs), low cardiac output, etc. Creatinine should be monitored, but because of the compelling beneficial effects of ACE-I/ARB, these agents should be continued if the rise in creatinine doesn't exceed 30% [30].

Hyperkalemia arises from inhibition of angiotensin 2 stimulation of aldosterone and also usually occurs within the first 2 weeks of initiation or dosage increase. Persistent hyperkalemia should be managed by ensuring patients are adhering to a low-potassium diet and decreasing doses of, or discontinuing where possible, concurrent medications that cause hyperkalemia. Increased oral fluids with diuretics can increase kaliuresis, and avoidance of constipation can ensure gastrointestinal elimination of potassium. Metabolic acidosis frequently present in CKD patients can contribute to hyperkalemia, so oral alkali can be prescribed as needed. Finally, the advent of gastrointestinal cation exchangers such as patiromer or sodium zirconium cyclosilicate offers another option to allow treatment of hyperkalemia and continuation of ACE-I/ARB.

Angiotensin 2 is critical during fetal development and needed for embryonic kidney development. Teratogenic effects of ACE-I or ARB additionally include oligohydramnios, pulmonary hypoplasia, persistent patent ductus arteriosus, hypocalvaria, limb defects, cerebral complications, fetal growth retardation, miscarriages, and perinatal death, and these agents should be avoided in all trimesters of pregnancy [31–33]. Women of child-bearing age taking these agents must be using reliable contraception, and if pregnancy is contemplated, ACE-I/ARB should be discontinued. For women planning on breast feeding, captopril and enalapril are found in breast milk in very low quantities and judged by the American Academy of Pediatrics to be safe for breast feeding. Because detectable levels of active drug can be obtained in breast milk after a half maximal dose, fosinopril should not be used in lactating women. Insufficient data exist on other ACE-I and ARBs to make recommendations [34].

While RAAS inhibition has beneficial cardiovascular and kidney effects, dual therapy with both ACE-I and ARB should be avoided due to increased risk for hyperkalemia and worsening kidney function [35, 36]. A trial examining the effects of dual therapy with an ACE-I or ARB and a direct renin inhibitor was terminated early due to increased occurrence of hypotension, hyperkalemia, and acute kidney injury, with a trend toward higher rates of stroke and death [37], prompting a warning from the US Food and Drug Administration to issue a safety communication in April 2012 warning of possible risks of dual therapy of direct renin inhibitors and ACE-I or ARB in diabetic patients or those with GFR < 60 cc/min/1.73 m^2.

Mineralocorticoid Inhibition

By virtue of its pro-inflammatory and fibrotic effects, aldosterone is a significant factor in cardiovascular and kidney disease. Additionally, it is important to remember that aldosterone escape can occur in patients treated with an angiotensin 2 inhibitor. This phenomenon has been shown to cause worsening hypertension, left ventricular hypertrophy, and a GFR decrease in type 1 [38] and type 2 [39] diabetics.

Non-selective mineralocorticoid receptor antagonists (MRAs) (spironolactone and eplerenone) have been demonstrated to reduce morbidity and mortality in patients with mild to severe heart failure [40, 41] and are included in international guidelines for heart failure management [42]. Specifically, in diabetic or CKD patients treated with eplerenone, the risk for heart failure hospitalization and/or cardiovascular death was decreased by 40–50% [43].

In renal outcomes, MRA can reduce proteinuria in combination with an ACE-I or ARB, and a meta-analysis of 18 trials of DKD patients co-administered MRA and ACE-I/ARB showed a decrease in albuminuria. However, the use of non-selective MRA did not show benefit in slowing renal decline [44].

Because non-selective MRAs improve cardiovascular outcomes and are anti-proteinuric, they can be considered while awaiting availability of the newer selective MRA and wider confirmation of their salutary effects (below). Clinicians should monitor for development of gynecomastia and hyperkalemia or acute reversible decline in kidney function, particularly in patients with GFR < 45 cc/min/1.73 m^2.

- *An ACE-I **or** ARB should be prescribed for all hypertensive, albuminuric, non-pregnant patients and may be considered in normotensive, albuminuric diabetics, as tolerated.*
- *ACE-I or ARB may be continued if any rise in GFR is less than 30%.*
- *If hyperkalemia persistently occurs with RAAS inhibition, employ strategies to ensure kaliuresis and gastrointestinal excretion of potassium. For refractory hyperkalemia, consider starting a gastrointestinal cation exchanger.*

SGLT2 Inhibitors

In 2018 the American College of Cardiology, America Diabetes Association, and European Association for the Study of Diabetes, followed in 2019 by the European Society of Cardiology, published position papers all recommending addition of a sodium-glucose co-transporter-2 inhibitor (SGLT2i) to the care of type 2 diabetics with CVD [45–47]. The 2020 KDIGO guidelines strongly recommend the use of

SGLT2i in recognition of the beneficial cardiovascular and kidney effects, as well as lower risk for development of hypoglycemia.

In three major trials in type 2 diabetics, SGLT2i reduced major cardiovascular events (nonfatal myocardial infarction and stroke), cardiovascular deaths, and heart failure hospitalization, with hazard ratios of 0.83–0.86 [48–50]. Because CKD patients comprised a minority of enrolled subjects, a meta-analysis of these trials was performed [51] and, in conjunction with a trial of CKD patients [52], confirmed similar cardiovascular benefits in patients with reduced kidney function. The favorable cardiovascular effects are independent of the glucose-lowering effect, as demonstrated by the 25% reduction in rates of cardiovascular death or hospitalization in heart failure patients treated with a SGLT2i, regardless of diabetes status [53].

Importantly, in addition to cardiovascular benefits, SGLT2i have improved kidney outcomes, including reduction in albuminuria, decrease in progression to severely increased albuminuria (i.e., > 300 mg/g), slower rates of kidney decline, and need for renal replacement therapy, with kidney events seen in 30% fewer patients treated with SGLT2i [49–52, 54–56]. Similar to the cardiovascular benefits of SGLT2i, kidney events (sustained decline in GFR, ESKD, death from kidney, or cardiovascular causes) were reduced by 40% in CKD patients both with and without diabetes [57].

Further highlighting the importance of prescribing these medications is that the number of CKD patients to treat is only around 20 [52, 57].

Because SGLT2i exert their glycemic effects by inhibiting kidney proximal tubular reabsorption of glucose, patients experience a glucosuric-induced osmotic diuresis, with attendant salutary effects on blood pressure. Although most patients tolerate simultaneous administration of thiazide or loop diuretics, clinicians should be aware of situations of potential hypovolemia and reduce diuretic dose accordingly. Because of its mechanism of action, there is less of a risk for hypoglycemia when SGLT2i are used as monotherapy, since glucosuria tapers off as serum glucose levels approach normal, although the risk may increase if patients are on other agents with the potential to cause hypoglycemia, viz., insulin and sulfonylureas.

Analysis of adverse effects of SGLT21 in a single randomized controlled trial (RCT) of canagliflozin raised concern for an increased risk of fractures and amputations [58]. Fractures were observed only in older individuals with pre-existing cardiovascular and kidney disease and greater use of diuretics, but were not seen in the other major RCT of SGLT2i [49, 56]. Additionally, a meta-analysis of 30 studies showed no increased risk of fracture [59], although in single studies a trend toward increased fracture risk was seen in patients with established cardiovascular or kidney disease [60, 61]. It is not clear whether increased fractures occurred from falls resulting from orthostatic hypotension or because of an effect on bone and mineral metabolism. Clarity on this issue awaits further clinical trials. Other adverse effects include genital mycotic infections, possibly related to glucosuria, and are managed with topical anti-fungals. Diabetic ketoacidosis is also a concern, so practitioners should be cognizant of situations where there is an increased risk for ketosis, such as critical illness or prolonged fasting.

Because of the compelling cardiovascular and kidney benefits of SGLT2i, if addition of SGLT2i results in hypoglycemia, KDIGO recommends other non-metformin agents be discontinued in order to allow patients to stay on both metformin and the SGLT2i. SGLT2i result in a small decrement in GFR but long-term superior preservation of kidney function, so the agent should not be discontinued if the drop in GFR is <30% or eGFR falls below 30 cc/min/1.73 m^2, unless uremic symptoms ensue.

- *Most type 2 diabetic patients with GFR ≥ 30 cc/min/1.73 m^2, regardless of levels of albuminuria or glycemic control, should be treated with SGLT2i.*
- *SGLT2i may cause a modest rise in GFR but should be continued as long as the increase is not more than 30%.*
- *If hypoglycemia develops, doses of other non-metformin glycemic medications should be reduced or medications discontinued, to allow for continuation of SGLT2i.*

Newer Therapies

GLP-1RA

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have also shown beneficial cardiovascular and kidney effects and thus are now recommended as add-on therapy in patients already on metformin and a SGLT2i (or are not able to use them) who are not meeting glycemic targets.

Of the available GLP-1RA agents, the choice of the specific agonist should be based on demonstration of its cardiovascular benefit (reduction in nonfatal myocardial infarction, stroke, and cardiovascular death), viz., liraglutide [62], subcutaneous (but not oral) semaglutide [63], and dulaglutide [64]. Albiglutide [65] showed similar cardiovascular benefit, but is not yet on the market as of this writing. These agents were also shown to reduce albuminuria and worsening of kidney function (creatinine doubling, ≥ 40% decline in eGFR, ESKD), but a meta-analysis showed that the beneficial effect on kidney function was mostly attributable to the decline in albuminuria [66].

Adverse reactions to GLP-1RA are dose-dependent gastrointestinal effects including nausea, vomiting, and diarrhea, which can be managed by selecting low initial doses and gradually uptitrating. There are also injection site reactions and increase in pulse. GLP-1RA should be avoided in patients at risk for thyroid C cell cancers and those with a history of pancreatitis. Because dipeptidyl peptidase-4 (DPP-4) inhibitors reduce the clearance of GLP-1RA, these agents should not be prescribed together.

As with SGLT2i, the risk of hypoglycemia with GLP-1RA is low but may be increased in patients being prescribed insulin or sulfonylureas, so doses of those may need to be adjusted.

Selective Mineralocorticoid Receptor Antagonists

In addition to the inflammatory and fibrotic effects of aldosterone, since it may contribute to insulin resistance, there has been interest in whether MRAs are of benefit in DKD. Substantial side effects of the currently available non-selective MRAs, such as hyperkalemia and gynecomastia, prompted interest in exploring whether newer-generation MRAs have similar beneficial effects on albuminuria while decreasing undesirable side effects. Thus, an international study of type 2 diabetic patients with CKD (eGFR as low as 25 cc/min/1.73 m^2) and ACR 30 to 5000 mg/g was conducted to examine the effects of finerenone, a non-steroidal selective mineralocorticoid antagonist, on cardiovascular and kidney outcomes. Ninety-eight percent of patients were already taking an ACE-I or ARB, but addition of finerenone resulted in a 31% greater ACR reduction and a 20% lower risk for developing kidney failure (GFR $\leq$ 15 cc/min/1.73 m^2, initiation of long-term dialysis, or transplantation), sustained $\geq$50% GFR decrease, or death from renal causes [67]. Finerenone also lowered the risk of developing adverse cardiovascular events (cardiovascular cause of death, heart failure hospitalization, and nonfatal myocardial infarction or stroke) by 14%. As of this writing, the use of finerenone does not yet have FDA approval in the United States. When available, selective MRA can be considered in diabetics with albuminuria, even when the CKD is advanced to stage 4.

Glycemic Control

Landmark studies in type 1 and 2 diabetes have established the centrality of adequate control of blood glucose both in preventing onset of diabetic kidney disease and decreasing the risk for progression of established DKD [68–71]. Benefits of strict glycemic control were found to be long lasting ("legacy effect") with lower rates of incident moderately and severely increased albuminuria, development of impaired GFR, and hypertension [19, 72].

Monitoring

Glycemic control should be monitored on a regular basis in all diabetics. Hemoglobin A1c (HgbA1c) is most commonly used in clinical practice. It is an advanced glycation end-product (AGE) that reflects the level of glycemia over the lifespan of the red blood cell (12 weeks). In CKD patients, therefore, it is important to be aware of common conditions which affect RBC longevity, which are more common in advanced CKD, and thus HgbA1c may not be as accurate if the eGFR is <30 cc/min/1.73 m^2 [73]. HgbA1c may be decreased by shorter RBC survival,

transfusion, use of erythropoiesis-stimulating agents (ESA), or iron replacement therapies. Conversely, clinicians should be aware of situations promoting formation of AGEs, such as metabolic acidosis, inflammation, oxidative stress, etc. Alternative methods of assessing glycemic control include measurements of glycated albumin and fructosamine. These have a more limited survival in blood (2–4 weeks), thus reflecting glycemic control over a shorter span of time compared to HgbA1c. As with HgbA1c, physicians must bear in mind co-existing conditions in CKD patients when interpreting glycated albumin results, since hypoalbuminemia may be present in patients with proteinuria, malnutrition, and liver disease or are losing protein through peritoneal dialysis effluent. Measurements of fructosamine may be similarly biased by hypoalbuminemia. Thus, it is not clear that measurements of glycated albumin or fructosamine offer any substantial advantages over HgbA1c.

Continuous glucose monitoring is a new technology that directly measures blood glucose and is likely to see increasing use. It will be particularly useful in patients with low GFR, since it circumvents the inaccuracies of Hgb1C in patients with advanced CKD (above).

The current recommendations are to measure hemoglobin A1c at least twice annually or up to quarterly as needed for patients not at goal [21]. Selecting the appropriate target for any individual patient should balance risks and benefits. In this regard, it is important to note a U-shaped curve of HbgA1c and mortality was reported in type 2 diabetics [74], suggesting caution for overly aggressive glycemic control. Since these patients were treated with agents with hypoglycemic risk (sulfonylureas or insulin), it is not yet known whether the same relationship exists with current medications that do not cause hypoglycemia. In setting HgbA1c targets, physicians should also bear in mind that cumulative years of strict glycemic control are needed to realize benefits. Thus, a strict HgbA1c target of <6.5% may be appropriate for a younger patient with no or only mild CKD, whereas a more liberal target of <8% may be more suitable for older patients, those with advanced renal disease and/or inability to sense hypoglycemia.

Choice of Agents

A wide variety of classes of oral and injectable agents are now available to control hyperglycemia in type 2 diabetics, with the newer agents posing a lower risk for the development of hypoglycemia. Guidelines for choice of agents have evolved following a number of well-conducted RCTs showing benefits on kidney outcomes, both in reducing albuminuria and slowing progression of kidney decline, in addition to reduction of cardiovascular events (reviewed above). Choice of specific agents may be guided by the presence of co-morbid conditions and/or preference of the patient and physician (Fig. 29.1). Clinicians should be aware of medications with kidney excretion and GFR cutoffs for their usage (Table 29.3).

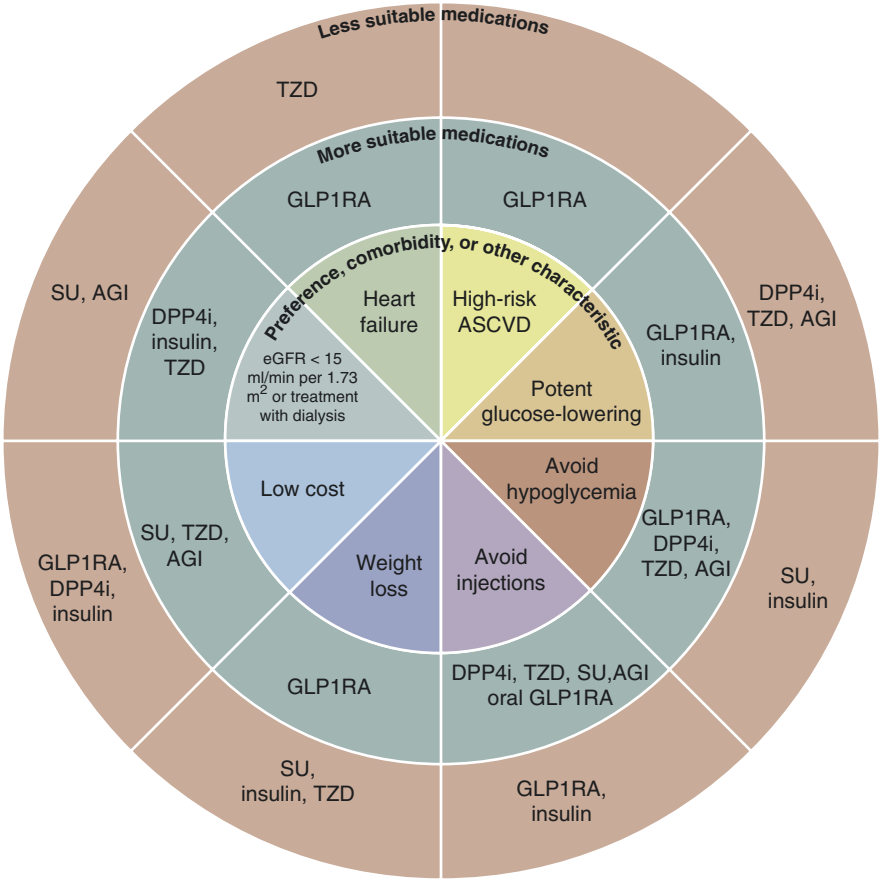

Fig. 29.1 Patient factors influencing the selection of glucose-lowering drugs other than sodium-glucose cotransporter-2 inhibitors and metformin in type 2 diabetes and chronic kidney disease. *AGI* alpha-glucosidase inhibitor, *ASCVD* atherosclerotic cardiovascular disease, *DPP4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *SU* sulfonylurea, *TZD* thiazolidinedione. From the KDIGO 2020 guideline on diabetes in CKD [1]. (Reprinted by permission)

Metformin

The 2020 KDIGO guidelines recommend metformin in type 2 diabetic patients with GFR ≥ 30 cc/min/1.73 m^2 as first-line therapy since metformin has advantages of low hypoglycemic risk compared to insulin and sulfonylureas, prevents weight gain, and may in some patients even lead to weight loss. As it is excreted unchanged in the urine, it is prudent to increase frequency of monitoring for GFR < 60 cc/min/1.73 m^2, but dosage adjustments often are not needed for GFR above 45 cc/min/1.73 m^2. Due to concern for development of lactic acidosis, metformin frequently was not prescribed in CKD, but a 2010 Cochrane review of 347 trials

Table 29.3 Anti-glycemic medications for type 2 diabetes

Class	Medication	Dosage adjustment in CKD	Major adverse effects	Comments
Biguanides	Metformin	GFR 45–50, follow renal function q 3–6 months GFR 30–44, reduce maximum dose to 1000 mg, follow renal function q 3 months GFR < 30, do not use	GI effects: Bloating, diarrhea, cramping B12 deficiency with prolonged use	First-line therapy (with SGLT2i as tolerated)
SGLT2i	Canagliflozin Dapagliflozin Empagliflozin	After initiation, may continue if GFR drops <30%, or if GFR <30 but no uremic symptoms Do not initiate if GFR <30	Genital mycotic infections Diabetic ketoacidosis Unclear if increased fracture risk	First-line therapy (with metformin as tolerated)
GLP-1RA	Dulaglutide Liraglutide Semaglutide (subcutaneous)	None needed	GI effects: Nausea, vomiting, diarrhea Injection site reactions	Add-on therapy after metformin and SGLT2i, if needed or intolerant Avoid in patients at risk for thyroid C cancer or history of pancreatitis Do not use with DPP-4 inhibitor
	Exenatide Lixisenatide Oral semaglutide	Exenatide: Cautious use if GFR 30–50, do not use if GFR <30		Not preferred as no cardiovascular or renal benefit
DPP-4i	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	Alogliptin: GFR 30–60: maximum dose 12.5 mg, GFR < 30, maximum dose 6.25 mg Linagliptin: No dosage adjustment needed in CKD Saxagliptin: GFR <50, maximum dose 2.5 mg Sitagliptin: GFR 30–50: maximum dose 50 mg, GFR <30, maximum dose 25 mg	Infections (upper respiratory or urinary tract), nasopharyngitis, headaches Hypersensitivity reactions in sitagliptin w/in 3 months of initiation	Do not use with GLP-1RA

(continued)

Table 29.3 (continued)

Class	Medication	Dosage adjustment in CKD	Major adverse effects	Comments
Sulfonylureas	Glimepiride Glipizide Glyburide	Glimepiride: Use with caution for GFR <60, do not use for GFR <30 Glipizide: Use with caution for GFR ≤ 30 Glyburide: Dosage adjustment needed for GFR < 60	Hypoglycemia Weight gain	Glipizide or glimepiride preferred in CKD due to shorter half-life and hepatic metabolism
Meglitinides	Nateglinide Repaglinide	Nateglinide: GFR < 30, reduce dose to 60 mg tid, don't use for GFR < 15 Repaglinide: For GFR <20–40, start with 0.5 mg before largest meal, then titrate to 0.5 mg before other meals	Weight gain	
Thiazolidinedione	Pioglitazone Rosiglitazone	None needed	Weight gain, fluid retention, fracture	Contraindicated if heart failure, fluid overload, liver disease, bladder cancer, risk for/fracture

covering over 70,000 patient-years metformin use showed no evidence that metformin was associated with increased lactic acidosis [75]. Subsequently, the US Food and Drug Administration (FDA) revised its warning, allowing use for GFR ≥30 cc/min/1.73 m^2. Nonetheless, it seems reasonable to consider reducing the dose in cases with the risk for lactic acidosis such as hypoxemic or underperfused states. Renal function should be monitored at least annually for GFR ≥ 60 cc/min/1.73 m^2, with more frequent monitoring (semi-annually or quarterly) when GFR falls below 60 cc/min/1.73 m^2. Metformin should be reduced by half for GFR 30–45 cc/min/1.73 m^2 and discontinued for GFR <30 cc/min/1.73 m^2. KDIGO recommends that B12 levels should be monitored in patients on metformin for more than 4 years since it decreases GI absorption [76].

Hypertension Control

Patients with diabetes and CKD stages 1–4 should aim for a target blood pressure of ≤130/80 [5]. Lifestyle changes mentioned above (tobacco cessation, weight reduction, increased physical exercise, low sodium diet) all positively impact blood pressure control and should be enacted wherever appropriate.

Whenever possible, as above, hypertensive patients should already have been prescribed an ACE-I or ARB and MRA, with the latter of particular utility in resistant hypertension ([77], and reviewed in [78]). However, in some patients, additional agents may be needed to reach blood pressure targets. Non-dihydropyridine calcium channel blockers (CCB) have substantially greater anti-proteinuric effect and are more efficacious in slowing kidney decline than dihydropyridine CCB [79], although alone or when added to an ACE-I, they were no better than placebo in preventing onset of albuminuria [80]. Dihydropyridine CCB may be reasonable as add-on medications in patients already on ACE-I or ARB [5]. Addition of thiazide or loop diuretics may mitigate hyperkalemia and thus allow higher doses.

- *In diabetic CKD stages 1–4, it is recommended to control blood pressure to a target of ≤ 130/80.*
- *All hypertensive, non-pregnant DKD patients should be on an ACE-I or ARB, at the maximum tolerated dose.*
- *Mineralocorticoid antagonism should be included as standard therapy, as tolerated. Monitor for hyperkalemia and decrease in GFR, especially in patients on ACE-I/ARB and with GFR < 45 cc/min/1.73 m^2.*

Cholesterol Management

Dyslipidemia is common in DKD, and CVD is a major cause of morbidity and mortality. Patients with CKD are considered to be in the highest-risk category for CVD [81, 82], diabetic patients with microalbuminuria have twice the CVD risk

compared to normoalbuminuric patients [83], and CVD risk increases progressively as albuminuria and kidney function worsen [10]. Patients reaching stage 3 CKD are more likely to die of CVD than progress to ESKD [10, 84]. Based on five clinical trials, the 2007 and 2012 KDOQI/NKF guidelines recommend lowering LDL cholesterol to reduce the risk of major atherosclerotic events [5, 7]. LDL should be targeted to <100 mg/dL and, if achievable, to <70 mg/dL. For patients above this target, it is recommended they be treated with a statin or statin/ezetimibe. While these mediations improve CV outcomes, data is lacking to support a favorable effect on kidney outcomes. The 2012 KDOQI/NKF guidelines recommend that statins not be initiated in diabetic patients on dialysis due to studies showing lack of benefit.

Resources

Diabetes management is currently in a fast-evolving state. New and exciting therapeutics initially developed for glycemic control have subsequently been shown to target two major causes of morbidity and mortality, cardiovascular and kidney disease. Online resources are an important means to stay updated with the changing landscape of medical management. The American Diabetes Association website (https://professional.diabetes.org/content-page/practice-guidelines-resources) contains updated information on standard of care for providers. The most recent KDIGO diabetes guidelines and other resources are available at https://kdigo.org/guidelines/diabetes-ckd.

Because many diabetics are unaware of their disease, additional helpful resources at the ADA website include an extensive patient education library with topics in multiple languages to inform patients about and manage various aspects of diabetes. Additional helpful patient educational material is available at the CDC diabetes website (https://www.cdc.gov/diabetes/basics/index.html), including clear and concise infographics.

Because the newer therapeutics are not yet available in a generic form, the cost of these important medications can be prohibitive for widespread use. Physicians and nephrology societies should work closely and doggedly with governmental organizations and third-party payors to reduce the financial barriers for these life-saving drugs.

Summary

Diabetes is a worsening epidemic of global proportions, with substantial morbidity and mortality, and increasing financial burden. Important measures to curb the impact of the disease include awareness of persons at risk, vigilant screening for pre-diabetes and development of overt diabetes, and modification of risk factors

through lifestyle management and medications. The advent of medications for glycemic control that have substantial favorable effects on kidney function and cardiovascular disease gives hope that we can lessen the impact of the disease that is the leading cause of kidney failure in many parts of the world.

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