Diabetic Nephropathy

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Introduction

Diabetic nephropathy (DN) occurs in 20–40% of patients with diabetes and is a major cause of morbidity and mortality. It occurs not only in persons with type 1 (T1) and type 2 (T2) diabetes mellitus (DM) but also in diabetes of exocrine pancreas, previously called secondary pancreatic DM or type 3c diabetes forms of DM, which results from a disruption of the global architecture or physiology of the pancreas caused by a process such as inflammation, neoplasia, or surgical resection [1, 2].

The number of individuals known to have end-stage renal disease (ESRD) worldwide is growing rapidly, as a result of improved diagnostic capabilities, the global epidemic of type 2 diabetes (T2DM), and other causes of chronic kidney disease (CKD) [3]. CKD is mainly related to diabetes and/or hypertension. About one out of three adults with diabetes and one out of five adults with hypertension have CKD [4]. Diabetes is the most frequent cause of severe CKD [1] and in Western countries is the leading cause of ESRD [5]. Nowadays, it's estimated that 40–50% of patients with T2DM and 30–33% with T1DM will develop kidney disease. The amount of people with CKD and ESRD is increasing in consonance with the rising incidence of diabetes [6, 7].

In the United States, 2011–2012, the estimated prevalence of CKD (stages 1–4) in adults with 20 years of age or more and diagnosis of diabetes was 36.5% (CI 95%, 32.2–40.8%). In 2014, a total of 52,159 people developed ESRD with diabetes as the main cause of renal disease, and the prevalence ratio adjusted for age, sex, and ethnicity was 154.4 per million inhabitants [7, 8].

The progression to ESRD is similar in type 1 and type 2 diabetes. However, as T2DM is more prevalent, the majority of patients with ESRD are type 2 diabetics. The tenth edition of the International Diabetes Federation (IDF) Diabetes Atlas reported an estimated increase of 46% on world prevalence of diabetes. This means an estimated raise from 537 million in 2021 to 783 million in 2045, on the number of diabetic patients [9, 10]. The prevalence of diabetic nephropathy has increased [3] because of the epidemic of diabetes, longer periods of disease without a good glycemic control, and improvements in the treatment of hypertension and coronary heart disease, which have prolonged the lifespan of patients with T2DM and increased the risk of developing complications such as nephropathy and ESRD. The end-stage renal disease (ESRD) is up to ten times more prevalent in people with diabetes [9–11].

However, a greater number of patients with diabetes are in developing countries [9], which do not have sufficient resources or a health infrastructure that would enable them to provide universal renal replacement therapy. Furthermore, even in developed countries, fewer than 1 in 20 patients with DM and CKD survives to ESRD, succumbing to cardiovascular disease (CVD), heart failure, or infection, and the severity of diabetic renal disease significantly contributes to this outcome [3]. The number of deaths related to CKD associated with diabetes increased 94% between 1990 and 2012, and the great majority was mainly related to cardiovascular disease [7]. Hence, it is of great importance to obtain an early diagnosis, appropriate management, and the development of new strategies of treatment, particularly those related to the control of glycemia, blood pressure, and other comorbidities associated with diabetes, that may lead to better outcomes.

Diagnosis

The term diabetic nephropathy is used to describe a specific renal condition caused by diabetes, characterized by hyperfiltration; persistent albuminuria, with a continuous decline in the glomerular filtration rate (GFR); raised arterial blood

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pressure (BP); and enhanced cardiovascular morbidity and mortality [11] (Table 37.1). Diabetic kidney disease (DKD), diabetic nephropathy, is clinically diagnosed based on the presence of persistent albuminuria (>30 mg/g creatinine) and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage [12].

Albuminuria, urinary albumin excretion rates (UAE), can be measured easily by albumin-to-creatinine ratio (ACR) in a random spot collection, but also in 24-h or timed collections, which are less predictive and accurate [13]. If albuminuria is abnormal, the test should be confirmed by two or three samples within 3 or 6 months, 4–6 weeks apart, due to the variability in albumin excretion. Albumin excretion may rise due to exercise within 24 h of sampling, infection, fever, congestive heart failure (CHF), marked hyperglycemia, hypercholesterolemia, and high blood pressure. Persistent albuminuria ≥30 mg/g creatinine indicates microalbuminuria and requires treatment with ACE inhibitor or ARB, even in the absence of hypertension [14].

The glomerular filtration rate is estimated using validated formulae (eGFR). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) Study equation are recommended in most guidelines, and eGFR is considered abnormal when below 60 mL/min/1.73 m^2. CKD-EPI is generally preferred [4, 13].

Persistent albuminuria in the range of 30–299 mg/g Cr (microalbuminuria) is considered the earliest stage of DN in type 1 diabetes (T1DM) and a marker for development of nephropathy in T2DM and for increased CVD risk [15].

The pathophysiological mechanisms in the development of DN are multifactorial. Hyperglycemia is related to structural and functional changes such as glomerular hyperfiltration, glomerular and tubular epithelial hypertrophy, and microalbuminuria, followed by the development of glomerular basement membrane (GBM) thickening, accumulation of mesangial matrix, evident proteinuria, and eventually glomerulosclerosis and ESRD. Nevertheless, intensive therapy to improve glycemic control is able to attenuate the development of nephropathy, as assessed by urinary albumin excretion (UAE), but not fully prevent it [16] (Fig. 37.1).

Hemodynamic and metabolic pathways are involved in the development of DN. Hyperfiltration and hyperperfusion injuries occur very early in DN and are glomerular hemodynamic changes related to the decrease of arteriolar resistance, more evident on the afferent side, which lead to a rise in glomerular capillary pressure. In addition to hyperglycemia, other factors, such as prostanoids, angiotensin II (ANGII), nitric oxide (NO), atrial natriuretic factor, growth hormone, glucagon, and insulin, may be related to the increase in filtration and perfusion. Vascular endothelial growth factor (VEGF) and cytokines such as transforming growth factor-beta (TGF-β) increase NO production and mediate hyperfiltration. Glomerulosclerosis occurs as a result of high intraglomerular pressure, an increase in mesangial cell matrix production, and GBM thickening [17, 18].

Hyperglycemia augments the oxidative stress and overproduction of reactive oxygen species (ROS) that stimulate protein kinase C (PKC) pathways, advanced glycosylation end product (AGE) formation, TGF-β, and ANG-II [17].

Glucose transporter-1 (GLUT-1) regulates the entry of glucose into the kidney cell, and glucose activates the metabolic pathways. Nonenzymatic glycosylation of glucose produces AGE, activates PKC, and accelerates the polyol pathway; hemodynamic changes activate VEGF, TGF-β, interleukin-1 (IL-1), IL-6, IL-18, and tumor necrosis factor alpha (TNFα) and together increase albumin permeability in GBM and extracellular matrix accumulation, leading to elevated proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis [18].

Pathologic abnormalities in the kidneys occur before the onset of microalbuminuria. The hallmark of DN is a nodular glomerulosclerosis, the Kimmelstiel-Wilson lesion [19], but less than one-third of diabetic patients with microalbuminuria have the typical glomerulopathy [20]. The earliest changes are an increase in the extracellular matrix and mesangial cell hypertrophy. There is an increased deposition of type 4 collagen in GBM, and the thickening may start as early as 1 year after the onset of T1DM, and later in glomerulosclerosis, the deposition of collagen types 1 and 3 also occurs. Hyperglycemia impairs integrin expression and the structure and function of the podocytes, which are glomerular epithelial cells that cover the GBM. Hyperglycemia also reduces the number of podocytes, which is related to proteinuria, although this decrease is observed even in the absence of proteinuria and occurs before the development of glomerulosclerosis and tubulointerstitial damage [18] (Fig. 37.2).

Recent data suggest that epigenetic modifications may be involved on the pathogenesis of diabetic nephropathy. Hyperglycemia and other factors, such as inflammation, hypoxia, and cytokines, may induce aberrant DNA methylation leading to fibroblast proliferation and fibrosis and regulating other genes associated with DN. Some other epigenetic processes may also have a role on DN such as noncoding RNA and histone modifications. The importance of identifying epigenetic changes relies on the fact that they are reversible changes which may enable therapeutic devel-

Table 37.1 Laboratory tests for the screening and diagnosis of diabetic nephropathy

Albuminuria—albumin/creatinine ratio
Serum creatinine
[a]eGFR-MDRD or CKD-EPI

[a]*eGFR* estimated glomerular filtration rate, *MDRD* Modification of Diet in Renal Disease, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration—equation

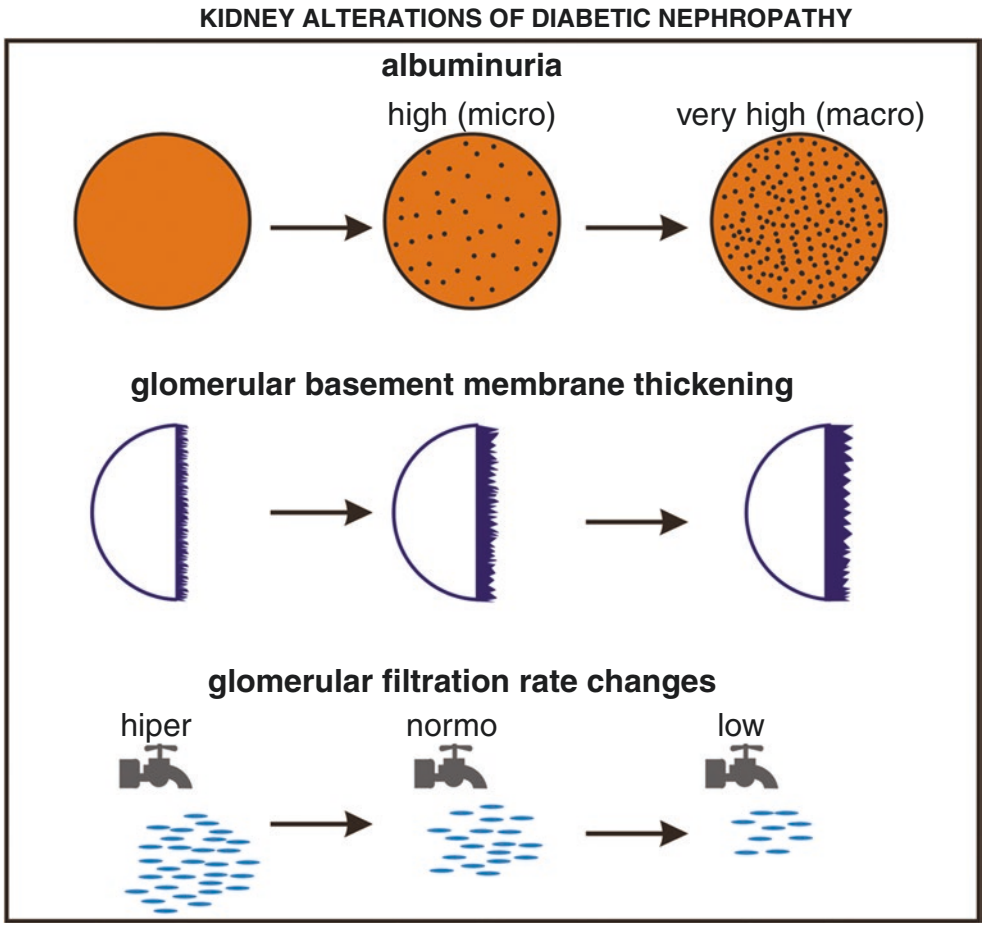

Fig. 37.1 Kidney alterations of diabetic nephropathy

opment. Nevertheless, these mechanisms are not fully understood and need further researches [6].

In view of the heterogeneity of kidney lesions and the complexity of the natural history of DN, Tervaert et al., in 2010, defined four classes of DN according to the glomerular lesions found on electron microscopy that can be applied in both type 1 and type 2 diabetes [21]. In this classification, class I is identified by an isolated GBM thickening (>430 nm in males over 9 years of age and >395 nm in females), with no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving more than 50% of the glomeruli, and glomeruli lesions then increase progressively to class IV, which is characterized by advanced diabetic sclerosis (>50% global glomerulosclerosis).

The "conventional" natural history of DN was defined in the 1980s, based on longitudinal studies of patients with type 1 and type 2 diabetes, and divided DN into five stages [22] as follows: stage 1 with a reversible glomerular hyperfiltration; stage 2 with normal GFR and normoalbuminuria; stage 3 GFR still normal but associated with microalbuminuria (5–10 years after diagnosis of DM); stage 4, in which proteinuria appears and may reach nephrotic range levels (after 10–20 years of diabetes progression); and stage 5, characterized by a GFR slope below 10 ml/min/year and CKD, leading to ESRD.

Information on the likelihood of passing from one stage to another in newly diagnosed patients was provided by the findings of the UK Prospective Diabetes Study (UKPDS) [23]. However, the study also emphasized that the risk of mortality increased in parallel with the worsening of renal disease. After 10 years of diagnosis, 25% of the patients with T2DM developed microalbuminuria and 5% macroalbuminuria, and in the latter, the death rate exceeded the rate of progression to an advanced stage of nephropathy [24].

The Diabetes Control and Complications Trial (DCCT) showed that less than 2% of patients on intensive treatment developed renal failure after 30 years of diagnosis. The development of microalbuminuria in patients with T1DM usually begins 5–15 years after the onset of diabetes and increases progressively. Patients without proteinuria after 20–25 years have an approximately 1% per year risk of developing clinical renal disease [16].

Nevertheless, another natural history of DN has been identified, particularly in type 1 and type 2 diabetic patients, although it is not clear why some patients develop the "clas-

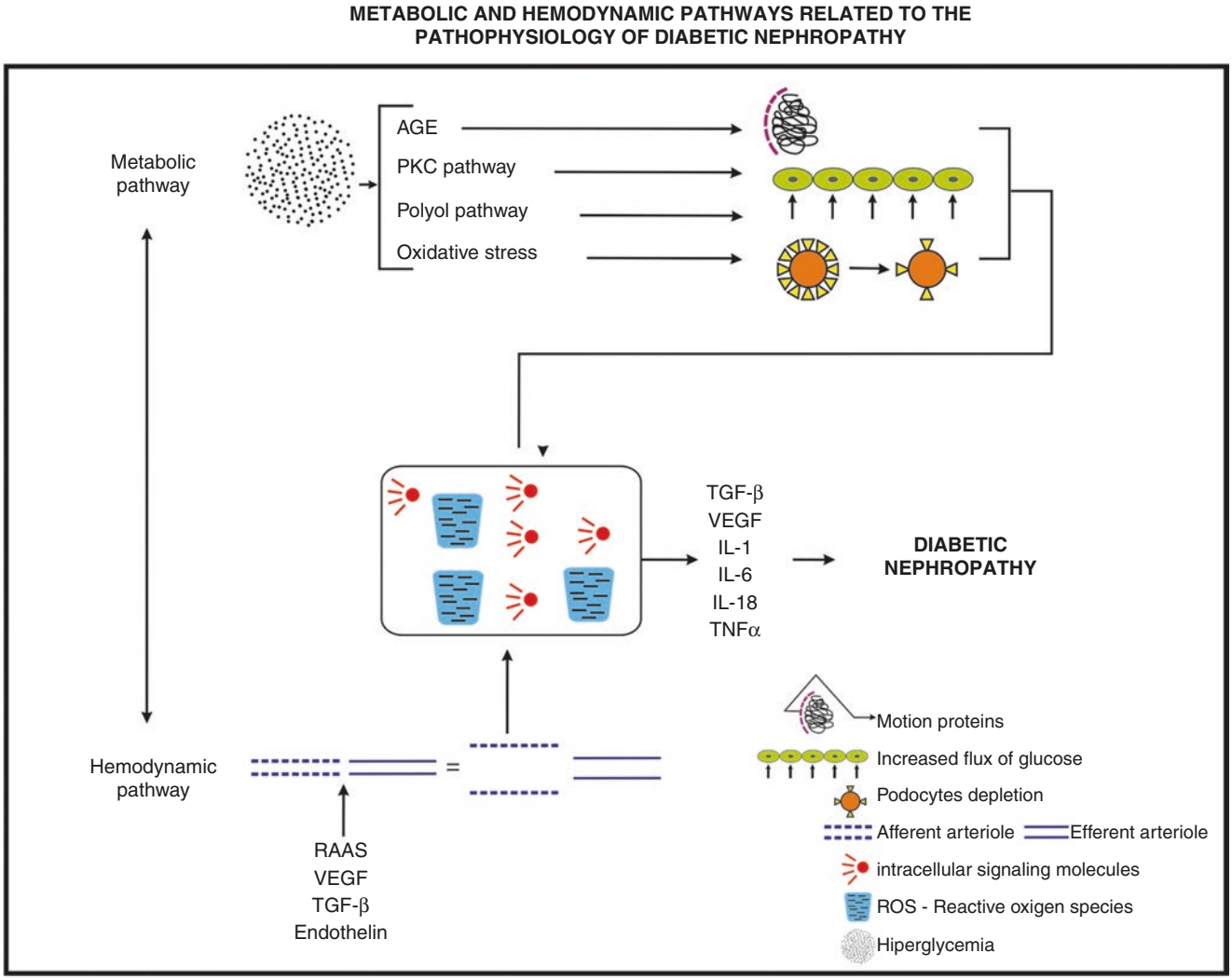

Fig. 37.2 Metabolic and hemodynamic pathways related to the pathophysiology of diabetic nephropathy. (AGE advanced glycosylation products, PKC protein kinase C, TGF-β transforming growth factor, VEGF vascular endothelial growth factor, IL-1,6,18 interleukin-1,6,18, TNFα tumor necrosis factor α, RAAS renin-angiotensin-aldosterone system)

sical" DN with significant proteinuria, while others have impaired renal function associated with very low levels of proteinuria that may persist until the ESRD [16, 22].

It would be useful to identify individuals, still normoalbuminuric, whose likelihood of progression to microalbuminuria is increased, but this is not yet possible. In addition to environmental influences, there is evidence in support of genetic susceptibility to microvascular complications of nephropathy in diabetic patients. Earlier investigations that focused on genetic mapping have generally yielded conflicting results, probably because, like other human diseases or syndromes, DN can develop from the interactions of several genes that in isolation would have no effect but which, when subtly altered, could predispose to DN [25].

Hence, it is important to enquire about the family history of DN and to screen periodically all diabetic patients. Microalbumin and serum creatinine (SCr) tests are valuable laboratory markers used to detect early signs of kidney damage [9, 11]. A recent study that evaluated the risk stratification of kidney disease emphasized that both the urine microalbumin level and urine albumin/creatinine ratio tests are needed to fully assess kidney disease and its associated risks of death and progression to ESRD [26] (Table 37.2).

"Kidney Disease: Improving Global Outcomes" (KDIGO) conducted a meta-analysis of nine cohorts from the general population and another eight cohorts with a high risk for CKD, which confirmed that lower eGFR and higher albuminuria are risk factors for ESRD, acute kidney injury, and progressive CKD in both the general and high-risk popula-

Table 37.2 Treatment targets of glycemia, blood pressure, and dyslipidemia

Glycemic control	HbA1C < 7.0% < 6.5%	Caution with patients with advanced kidney disease and high-risk CVD[a]
BP[b] control	≤130 × 80 mmHg	Caution with patients with high-risk CVD
LDL[c]	CVD risk <100/dl, <70 mg/dl	Stage 5 of kidney disease: start statin only if specific CVD risk

[a]*CVD* cardiovascular disease
[b]*BP* blood pressure
[c]*LDL* cholesterol low-density lipoprotein

tions, independent of each other and irrespective of cardiovascular risk factors [27].

The gold standard for GFR measurement is urinary clearance of an exogenous filtration marker, which is expensive and troublesome, and in addition to which it varies during the day. In clinical practice, SCr is used to estimate GFR, applying the modification of diet in real disease (MDRD) and/or CKD Epidemiology Collaboration (CKD-EPI) equations [28], which use clinical variables as substitutes for unmeasured non-GFR determinants and provide more accurate estimates than SCr alone. Estimates of the CKD burden depend in part on the equation used to define the eGFR: when the more recent CKD-EPI equation is used, the prevalence of eGFR below 60 ml/min/1.73 m^2 is lowered by a factor of 0.88 (6.9 versus 7.8%), compared with the estimate from the older MDRD study equation [9].

In patients with T1DM, the first screening is recommended at 5 years after the diagnosis [29], but it is suggested that patients with poor metabolic control be evaluated at the onset of puberty, which is an independent risk factor for microalbuminuria [30]. On the other hand, as about 7% of the patients with type 2 diabetes will already have microalbuminuria at the time of diagnosis of diabetes, the screening must be started by then. If microalbuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients [24].

In general, the medical societies recommend that an assessment of UAE be performed annually [14, 31], starting at the diagnosis of T2DM and 5 years after that for T1DM, in combination with a measurement of SCr in order to estimate GFR and determine the stage of CKD.

Kidney disease is classified in five stages [31] according to the GFR (ml/min per 1.73 m^2 body surface area), considering kidney damage as abnormalities on pathologic, urine, blood, or imaging tests. Stage 1 is characterized by kidney damage with normal or increased GFR (≥90), stage 2 also by kidney damage associated with mildly decreased GFR (60–89), stage 3 by a moderately decreased GFR (30–59), stage 4 by a severely decreased GFR [15–28], and stage 5 as kidney failure defined as GFR below 15 or dialysis.

In February 2007, a consensus conference in the United Kingdom [32] approved the division of stage 3 CKD into stage 3A (eGFR 45–59) and stage 3B (eGFR 30–44) and added the suffix "p" to the GFR-based stage for patients with proteinuria (random urine protein/creatinine ratio >100 mg/mmol). These changes have been endorsed by the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI). Patients at stages 1–3 are considered to have early CKD.

Differential Diagnosis

Very often clinicians tend to attribute proteinuria and renal impairment to DM, but that is not the only renal abnormality found in diabetics [33]. Other causes of CKD should be considered in patients that present with an absence of diabetic retinopathy, low or rapidly decreasing GFR, rapidly progressive proteinuria or nephrotic syndrome, refractory hypertension, presence of active urinary sediment, signs or symptoms of other systemic disease, or a reduction in GFR of more than 30% within 2–3 months after starting angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) [31]. Moreover, in some patients, the DN may be associated with other kidney diseases.

Nondiabetic renal disease (NDRD) includes a heterogeneous mixture of the following glomerular and nonglomerular conditions [33]:

1. Glomerular disease other than diabetic nephropathy: immunoglobulin A nephropathy, focal and segmental glomerular sclerosis, microvascular complications of diabetes, membraneous glomerulonephritis, membranoproliferative glomerulonephritis, pauci-immune, systemic lupus erythematosus, and others
2. Nonglomerular renal disease: macrovascular (renovascular), acute kidney injury (acute interstitial nephritis, e.g., contrast nephropathy, sepsis, and ACEI/ARBs/direct renin inhibitor (DRI) induced, and acute tubular necrosis, e.g., sepsis and diuretic toxicity), electrolyte abnormality, urinary tract infection, etc.

Nevertheless, no consensus classification is available at the moment for kidney biopsy in a diabetic patient with any pathological condition.

Treatment (Table 37.2)

Interventions that have been reported to be useful in preventing or retarding the progression of DN include the following: good glycemic and blood pressure control, treatment of hyperlipidemia, cessation of smoking, and restriction of protein intake. Patients who develop ESRD will require renal replacement therapy. Thus, when the patient has an eGFR <30 mL/min/1.73 m^2, he/she should be referred to evaluation of specialist for renal replacement treatment [15, 34].

Blood pressure and glycemic control represent the major cornerstones for preventing and treating diabetic nephropathy [16]. The DCCT reported that any decrease in hemoglobin A1C (HbA1C) was strongly associated with a reduction in the risk of developing microalbuminuria and progression to overt nephropathy [16], and UKPDS clearly demonstrated a role for intensified glycemic control in subjects newly diagnosed with T2DM, in whom treatment led to a fall in HbA1C from 7.9% to 7.0% [35].

To reduce the risk or slow the progression of nephropathy, the American Diabetes Association (ADA) recommends the optimization of glucose and control of blood pressure. The ADVANCE study demonstrated that the decrease in HbA1C to a mean of 6.5% was associated with a further reduction in renal events, as assessed by the development and progression of microalbuminuria [36]. However, the findings of the ACCORD study [37] led to controversy regarding the appropriate HbA1C target for reducing macrovascular disease.

The major risk of reaching HbA1C levels below 7.0% is the increased likelihood of developing hypoglycemia. For people with decreased kidney function (CKD stages 3–5), hypoglycemia is a major concern because it impairs the clearance of insulin and a number of oral agents used to treat diabetes, as well as reduces kidney gluconeogenesis [31]. Drug adjustments must be made to prevent or, at least, reduce the risk of hypoglycemia.

Sulfonylureas in general have predominantly renal elimination and are not recommended for patients with creatinine clearance (CrCl) below 50 ml/min, except for glipizide, which has hepatic elimination of inactive metabolites and should be interrupted when CrCl falls below 30 ml/min. Malnutrition, acute illness, liver disease, and alcoholism are risk factors for hypoglycemia. Meglitinides are oxidized by the liver but still entail a risk of hypoglycemia because active metabolites may accumulate in renal dysfunction, repaglinide being the one that accumulates the smallest amount of metabolites. Metformin is eliminated unchanged by the kidneys; NKF-KDOQI contraindicated its use with a serum creatinine over 1.5 mg/dl in males and 1.4 mg/dl in women due to the risk of lactic acidosis, although NICE recommends that it should be used with care for patients with an eGFR below 45 ml/min/1.73 m^2 and discontinued if the eGFR falls below 30 ml/min/1.73 m^2. Acarbose is not recommended if CrCl is below 25 ml/min, and miglitol produces renal elimination, but as there are no studies in patients with kidney disease, FDA does not recommend either of them if serum creatinine is ≥2 mg/dl. The risk of side effects when using thiazolidinediones increases with renal disease [31, 38].

Exenatide and its formulation with extended release are eliminated by renal filtration and need no adjustment with CrCl above 50 ml/min. Increases in the dosage from 5 to 10 μg should be applied with care if CrCl is 30–50 ml/min, and, according to FDA, when CrCl is below 30 ml/min, it should be stopped. Liraglutide should be used with care when CrCl is below 60 ml/min, and when below 30 ml/min, its side effects increase, but experience of its use is still limited in CKD. It's not necessary to adjust dulaglutide dosage in patients with mildly to moderately decreased eGFR, but it shouldn't be used when the eGFR is below 30 ml/min/1.73 m^2. The usage of SGLT-2 inhibitor does not require dose adjustment with mild kidney dysfunction (eGFR ≥ 60 mL/min/1.73 m^2), but as it depends on the kidney's ability to filtrate glucose, it's not recommended when the eGFR is below 45 ml/min/1.73 m^2 [39].

The dipeptidyl peptidase-4 (DPP4) inhibitor agents need no adjustment if CrCl ≥ 50 ml/min; sitagliptin should be reduced to 50 mg/d if it is 30–50 ml/min and to 25 mg if <30 and saxagliptin to 2.5 mg if <50 ml/min. Linagliptin is fecally eliminated unchanged, so it may be safely used in patients with CKD. Colesevelam and bromocriptine need no adjustments. As up to 50% of insulin is eliminated by the kidney, it is recommended that it be reduced by 25% when CrCl is 10–50 ml/min and by 50% if it falls below 10 ml/min [31, 38].

In addition to the importance of glycemic control, it has been shown that a more aggressive BP reduction reduces the progression of DN. The mechanism of hypertension in DN is complex and not fully understood, being related to excessive sodium retention, activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), augmented oxidative stress, and endothelial cell dysfunction (ECD) [40].

The UKPDS provided strong evidence that control of BP can slow the development of nephropathy [41]. Treatment using angiotensin-converting enzyme inhibitors (ACEi) retards the progression from micro- to macroalbuminuria and can slow the reduction of the GFR in patients with macroalbuminuria [42, 43]. In T2DM with hypertension and normoalbuminuria, renin-angiotensin system (RAS) inhibition has been shown to delay the onset of microalbuminuria [44, 45]. The evidences suggest that ACE inhibitors [46] have renoprotective actions in addition to their antihypertensive effects for primary prevention [47].

Angiotensin receptor blockers have also been shown to reduce the rate of progression from micro- to

macroalbuminuria, as well as ESRD, in patients with T2DM. The Irbesartan in Diabetic Nephropathy Trial (IDNT) [48] and Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus (NIDDM) study, as well as the Angiotensin Antagonist Losartan (RENAAL) studies, have reported the efficacy of ARBs in nephropathy [37].

The ROADMAP trial investigators evaluated type 2 diabetics with normoalbuminuria and reported that olmesartan was associated with a delayed onset of microalbuminuria, with BP control according to the current standards (<130 × 80 mmHg), but there was a higher rate of fatal cardiovascular events with olmesartan among patients with preexisting CVD [45].

It is not known whether the RAS blockade reduced progression to microalbuminuria in normotensive T2DM. Mauer et al. reported that the early blockade of the RAS in patients with T1DM did not slow progression of nephropathy [49].

Furthermore, as it is not yet possible to predict the patients at risk of developing nephropathy, present evidence does not support the use of RAS blockade for the primary prevention of DN [25].

Some reports show that the risk of progressive DN continues to decrease with falls in BP even below the normal range, and such reductions are associated with better clinical outcomes. A recent subanalysis from the BP arm of the ADVANCE study suggested that optimal BP control is less than 125/75 mmHg, particularly in those patients with overt nephropathy [50].

The ideal BP goal in diabetic patients with nephropathy remains questionable, and currently the recommended target is considered to be the same as that for the general diabetic population [51]. An ACE inhibitor or an ARB, usually in combination with a diuretic, should be used to treat hypertensive diabetics if CKD is at stages 1–4 with the target of <130/80 mmHg [31].

As the ACEi and ARB are individually renoprotective, questions have arisen regarding the usefulness of combined therapy. The suggestion that a more complete inhibition of angiotensin II, through non-ACE pathways, would improve the results stimulated some trials, the older ones, that studied combinations of ACEi and ARB reported effects that were promising, with significant reductions in albuminuria and/or BP and a good tolerability. Nevertheless, the Candesartan and Lisinopril Microalbuminuria (CALM II) [52] study reported that after 12 months of treatment, the effect of the combined therapy was no different from the maximization of each therapy alone in relation to BP or albuminuria. Concerns about this strategy came up with the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [53]. This study tested patients at high risk for a CV event with an ACEi and/or ARB and observed no differences between groups at the primary endpoint, comprising stroke, myocardial infarction, and sudden cardiac death. However, those patients randomized to combination therapy had higher rates of renal impairment and hyperkalemia, a more rapid decline in eGFR, and a greater need for dialysis for acute renal failure episodes during the trial.

The Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) Study: Nephropathy iN Diabetes Study (VA NEPHRON) study is a multicenter, prospective, randomized parallel group trial which tested the efficacy and safety of ACEi (lisinopril)/ARB (losartan) versus ARB on the composite endpoint of reduction in GFR to 30 ml/min (if GFR >60 ml/min), reduction in GFR by 50% (if GFR <60 ml/min), ESRD, or death in patients with DM2 and nephropathy. The results of this trial confirmed that the dual blockade with ACEi and ARB had no significant benefit in the primary endpoints of renal disease progression or death [54].

Other drugs, such as diuretics, calcium channel blockers, and β-blockers, should be used as additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs or as alternative therapy for individuals unable to tolerate those classes of drug. What is generally recommended is the combination of an ACEi or ARB with another class of drug, preferably a diuretic, and calcium channel blockers [31, 42].

ACEi/ARBs are recommended for people with diabetes, proteinuria, CKD, and ACR over 2.5 mg/mmol (men) or 3.5 mg/mmol (women), irrespective of the presence of hypertension or stage of CKD, and should be titrated to the maximum tolerated therapeutic dose before the addition of a second-line agent, with monitoring of the eGFR and serum potassium [42]. An established clinical strategy is the association of mineralocorticoid receptor (MR) antagonists to control blood pressure. A recent randomized clinical trial supports the beneficial use of Finerenone on CKD and CVD outcomes in people with type 2 diabetes, already in treatment with an ACE inhibitor or ARB. Treatment with Finerenone in a median follow-up of 2.6 years reduced in 18% the death from renal causes and the decline above 40% in eGFR. https://doi.org/10.1056/NEJMoa2025845 [55].

The treatment of other comorbidities such as obesity and dyslipidemia should also be considered in patients with DN. Obesity is associated with glomerular hyperfiltration and an increase in transcapillary hydraulic pressure, hemodynamic changes that may accelerate the development and progression of CKD [36]. Weight loss ameliorates obesity-induced glomerular hyperfiltration and decreases proteinuria, in addition to its beneficial effects on BP and diabetes control [56].

Dyslipidemia is a risk marker for progressive kidney injury and a risk factor for CVD. However, the evidence that the treatment of dyslipidemia reduces CKD progression is mostly restricted to post hoc subgroup analyses from large

cardiovascular clinical trials, such as the Heart Protection Study and the Cholesterol and Recurrent Events (CARE) study. Results from the Study of Heart and Renal Protection (SHARP) trial showed no significant differences in the number of patients with CKD suffering from kidney failure. People with DM and nondialysis CKD should be treated according to current guidelines for high-risk groups [56]. All guidelines agree that statins are the best choice to start the treatment of dyslipidemia in patients with T2DM, and most continue to recommend a low-density lipoprotein cholesterol (LDL-C) target <70 mg/dL (1.8 mmol/L) in people with T2DM and established CVD or at a high risk based on the estimated 10-year risk calculated with the UK Prospective Diabetes Study (UKPDS) risk engine or the Atherosclerotic Cardiovascular Disease (ASCVD) pooled equation. And the LDL-C target for those without established CVD and without a high 10-year CVD risk should be <100 mg/dL (2.6 mmol/L) [13].

For patients on dialysis, it is more complex, and the guidelines recommend not to initiate lipid-lowering therapy in dialysis patients and to keep incident dialysis patients on their preexisting lipid-lowering treatment. However, some data suggest that high-risk patients with high baseline LDL-C may benefit from treatment, particularly, with statin/ezetimibe combination [57, 58].

Further studies are needed to evaluate the extent of CVD benefits associated with the use of new lipid-modifying agents, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and cholesteryl ester transfer protein (CETP) inhibitors in patients with DKD. And the trials should be designed to compare effects on the profile of lipid abnormalities observed in CKD or dialysis populations [59].

The target for low-density lipoprotein cholesterol (LDL-C) in people with DM and CKD stages 1–4 should be below 100 mg/dl, but may be considered to be below 70 mg/dl, while patients whose level is above the target should be treated with a statin, which is the preferred therapy [14, 31]. However, a statin should only be started in patients on hemodialysis therapy if there is a specific cardiovascular indication.

No adjustment of dosage is necessary for bile acid sequestrants, niacin, ezetimibe, atorvastatin, or pravastatin. The dosage of rosuvastatin should not exceed 10 mg if CrCl is below 30 ml/min/1.73 m^2 and the patient is not on hemodialysis; it is recommended that simvastatin therapy be started at 5 mg daily in patients with severe kidney disease; daily doses of lovastatin above 20 mg should be used with care if CrCl is below 30 ml/min, while fluvastatin may be used with care in patients with severe kidney disease, but there are no studies using doses greater than 40 mg. The dose of gemfibrozil should be decreased or alternative therapy considered in patients with SCr over 2 mg/dl. Therapy with fenofibrate should be started at 54 mg daily; its effects on kidney function and lipid concentrations should be assessed and the dose reduced in patients with CrCl below 50 ml/min [31].

Smoking has also been shown to increase the risk of progression of CKD to end-stage renal disease (ESRD) irrespective of the primary renal disease; hence, the indication is a total cessation of smoking.

A diet therapy with protein restriction is recommended for patients with CKD as it has a great impact on this population. Although dietary protein is limited, adequate caloric intake should be maintained by increasing calories from carbohydrates and/or fats, and the qualitative and quantitative aspects of proteins, carbohydrates, and fats should also be taken into consideration.

A reduction in protein intake to 0.8–1.0 g/kg body wt/day in individuals at the earlier stages of CKD and below 0.8 g/kg body wt/day at the later stages of CKD may improve the results of renal function as assessed by UAE rate and GFR [31]. For adults with eGFR < 45 mL/min/1.73 m^2 and for the management of substantial proteinuria (urinary protein excretion, >0.3 g/day), 0.6–0.8 g/kg body wt/day is the most frequently recommended [60]. Nevertheless, reducing the amount of dietary protein below 0.8 g/kg/day does not alter glycemic control, cardiovascular risk measures, or the course of GFR decline. On the other hand, it's recommended to avoid high-protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression [61]. However, in patients on dialysis, it's commonly observed protein energy wasting, and increased dietary protein intake may be necessary to help preserve muscle mass [62].

An intake of 800–1000 mg of elemental calcium per day (20–25 mmol per day) is suggested for people with stage 3 or 4 chronic kidney disease, as studies report that this procedure can result in a stable calcium balance. It is also recommended to supplement vitamin D when serum level is documented as low [60]. The KDIGO suggests avoiding hypercalcemia in adult patients with CKD stages 3a–5D and supports that patients on treatment with calcimimetic who develop hypocalcemia should require intense calcium treatment. However, the Work Group recommend an individualized approach on hypocalcemia treatment due to unproven benefits and potential risk for harm [63].

The optimal time for the initiation of chronic dialysis remains unknown. There is a trend in the nephrology literature toward an earlier initiation of dialysis. However, prospective data that could guide physicians are not yet available [64].

Patients with CKD stage 4 should be referred to a nephrologist. Late nephrology referral before dialysis initiation is associated with increased morbidity and mortality [65].

Kidney transplantation provides high-quality life years for patients with ESRD. The largest numbers of transplants are performed in the United States, China, Brazil, and India,

and the countries whose populations have the greatest access to transplantation are Austria, the United States, Croatia, Norway, Portugal, and Spain. However, access to transplantation is still considerably limited across the globe [5].

Guidelines [14, 31] recommend that all patients be evaluated annually with the measurement of creatinine, UAE, and potassium and that those whose GRF is 45–60 be referred to a nephrologist if a nondiabetic kidney disease is suspected. The eGFR should be monitored every 6 months and bicarbonate, hemoglobin, calcium, phosphorus, and parathyroid hormone at least once a year; ensure vitamin D sufficiency and consider bone density testing due to the relation between nephropathy and bone disease. The need for dose adjustment of medications should be evaluated and the patient referred for diet counseling. If the GFR is 30–44, the eGFR should be monitored every 3 months and electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, and weight every 3–6 months; dose adjustment of medications should be considered, and if GFR is below 30, the patient should be referred to a nephrologist.

Hemoglobin A1C (A1C) remains a widely used and trusted tool for assessing glycemic control in patients without advanced nephropathy or anemia, but there are conflicting data as to what A1C level should be targeted to prevent complications, especially cardiovascular ones, in patients with nephropathy. A lower value of A1C for similar glucose levels is seen in patients with DN than for those without nephropathy. This observation may reflect a shortened erythrocyte survival. The accuracy of the A1C assay is diminished by uremia, and unadjusted A1C results are not the optimal assay for patients on hemodialysis or peritoneal dialysis treatment as it may underestimate glycemic control in those patients [31, 66].

It is reported that glycated albumin (GA) more accurately reflects recent glucose control, but it is still necessary to prospectively assess the impact of GA on patient survival and hospitalizations. GA has also been considered a useful glycemic index, especially, in patients with diabetes and CKD, because it is not influenced by erythrocyte lifespan, uremia, or blood transfusions, all of which can interfere in HbA1C measurements. Freedman et al. reported that for each 5% increase in GA, the risk of death increased by 14% in patients under dialysis treatment, and A1C and casual serum glucose did not predict survival. Glycated albumin may be influenced by albuminuria, cirrhosis, thyroid dysfunction, and smoking and A1C not only by advanced nephropathy but also by a rapid change in diabetes control; severe anemia; hemolytic anemia; iron deficiency; recent blood transfusion; HIV positivity treated with antiretroviral therapy, erythropoietin, and other drugs interacting with erythropoiesis; and chronic alcohol abuse. However, until the GA assay is available, frequent measurements of serum glucose appear more valuable than A1C in patients on dialysis to evaluate glycemic control [66, 67]. GA was considered a better predictor and could be a useful marker to predict early DN in T2DM patients, as it was reported that higher GA levels were significantly associated with increased risk of early DN development, independent of A1C [68].

Novel Therapies

Some trials have reported that new groups of medication, recently developed for glycemic control in patients with T2DM, namely, dipeptidyl peptidase-4 (DPP4) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, possess renoprotective effects [69].

The SAVOR-TIMI trial showed that saxagliptin, a DPP-4 inhibitor, caused an improvement or less deterioration in albumin-to-creatinine ratio, but with no changes in eGFR [70]. Liraglutide, a GLP-1 receptor agonist, was tested on LEADER Trial with reported lower incidence of nephropathy, evaluated as new-onset albuminuria, doubling of SCr and CrCl below 45 ml/min/1.73m^2, need for renal replacement therapy, and death related to renal causes (1.5 number of events per 100 patients per year versus 1.9 number of events per 100 patients per year; p 0.003) [71].

The EMPA-REG OUTCOME trial evaluated empagliflozin, a SGLT-2 inhibitor, and reported relative risk (RR) reduction of doubling of SCr (RR: 44%, 1.5% versus 2.6%), progression to macroalbuminuria (RR: 38%, 11.2% versus 16.2%), and initiation of renal replacement therapy (RR: 55%, 0.3% versus 0.6%) and also slowed GFR decline (annual decrease 0.1960.11 versus 1.6760.13 ml/min per 1.73 m^2; p 0.001) [72].

The CANVAS Program Report which combines the data from two trials, CANVAS and CANVAS Renal, evaluated the safety and effect of canagliflozin (SGLT-2 inhibitor), on the occurrence of cardiovascular and renal events in patients with T2DM, and indicated a class effect in the reduction of cardiovascular and renal events when the SGLT-2 inhibitor was used in higher-risk diabetic patients with T2DM [72, 73]. The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial was a randomized, double-blind, placebo-controlled trial with canagliflozin in patients with type 2 diabetes, which primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR. It was early terminated because it showed a 30% lower relative risk of reaching the primary endpoint. 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 lower by 34% (hazard ratio, 0.66; 95% CI, 0.53

to 0.81; P < 0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P = 0.002)> <0.001). Moreover, the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P = 0.002). It also showed a lower risk of cardiovascular death, myocardial infarction, or stroke, hospitalization for heart failure, and no significant difference in the risk of fracture and amputation between canagliflozin and placebo groups. https://doi.org/10.1056/NEJMoa1811744 [74] DAPA-CKD (Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease) another multicentre, double-blind, placebo-controlled, randomized trial in which primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or kidney-related or cardiovascular death. Secondary efficacy outcomes were a kidney-specific composite (the same as the primary outcome but excluding cardiovascular death), a composite of cardiovascular death or hospitalization for heart failure (HHF), and all-cause mortality, it included about two-thirds of participants with type 2 diabetes and about one-third did not, with background ACE inhibition/ ARB treatment. Dapagliflozin significantly reduced the risk of a sustained decline in eGFR, progression to ESRD, death from renal or cardiovascular causes, and a 29% reduction in risk of death from cardiovascular causes or HHF irrespective of diabetes status. Additionally, dapagliflozin demonstrated a reduction in all-cause mortality (31% relative risk reduction with a 2.9% absolute risk reduction, hazard ratio [HR] 0.69, 95% CI 0.53–0.88, P = 0.0035). https://doi.org/10.1016/S2213-8587(20)30369-7 [75, 76]

Table 37.3 SGLT2 Inhibitors and Dose for Glycaemic control according to glomerular filtration rate

SGLT2 Inhibitor// eGFR, 3mL/ min/1.73 m²	≥ 60	45–60	30 to <45
Empaglifozin [77]	10mg–25 mg once daily	10mg – 25 mg once daily	Do not initiate; Discontinue
Dapaglifozin [78]	5 mg–10 mg once daily	5 mg – 10 mg once daily	No dose adjustment
Canaglifozin	100 mg–300 mg once daily	100 mg once daily 100 mg once daily	Do not initiate, but patient may continue if albuminuria > 300 mg/day

Rosenwasser RF, Sultan S, Sutton D, Choksi R, Epstein BJ. SGLT-2 inhibitors and their potential in the treatment of diabetes. Diabetes Metab Syndr Obes. 2013;6:453–467 [77]

AstraZeneca. Farxiga (dapagliflozin) prescribing information, 2020. Available from https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/0be9cb1b-3b33-41c7-bfc2-04c9f718e442/0be9cb1b-3b33-41c7-bfc2-04c9f718e442_viewable_rendition__v.pdf. Accessed 11 December 2021 [78]

Boehringer Ingelheim. Invokana (canagliflozin) prescribing information, 2020. Available from https://docs.boehringer-ingelheim.com/Prescribing%20 Information/PIs/Jardiance/jardiance.pdf. Accessed 11 December 2021 [79]

The AWARD-7 study in patients with type 2 diabetes and moderate to severe CKD showed a steeper decline in eGFR (−3.3mL/ min/1.73 m^2) with insulin compared to dulaglutide, with an eGFR decline of −0.7mL/min/1.73 m^2 for both low-dose (0.75 mg weekly and high-dose (1.5 mg weekly) groups over one year. The gradients of eGFR decline between the groups were maintained even among patients with a urine albumin-to-creatinine ratio >300 mg/g creatinine, with eGFR declines of −0.7 and −0.5 mL/min/1.73 m^2 for dulaglutide 1.5 mg and 0.75 mg, respectively, compared to −5.5 mL/min/1.73 m^2 for insulin. More patients on insulin reached the composite renal endpoint of ESRD or >40% decline in eGFR than the patients on high dose dulaglutide (10.8 vs. 5.2%, P <0.038). https://doi.org/10.1016/S2213-8587(18)30104-9 [80]. And recently, it released data from clinical trials of semaglutide, another GLP-1 receptor agonist, that show reduced risk of albuminuria onset and progression. The SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) [81], and also the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) [82], and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) [80] placebo-controlled trials reported significant risk reductions of 36, 22, and 15%, respectively, in secondary composite renal end-points (new onset of macroalbuminuria, doubling of serum creatinine, sustained 45% reduction in eGFR, RRT, or renal death), with macroalbuminuria reduction. https://doi.org/10.1016/S0140-6736(19)31150-X The consistency of these recent data across glucagon-like peptide-1 receptor agonists suggests a class effect of protection from DKD [83].

These studies suggest that GLP-1 receptor agonists may have similar efficacy as SGLT2 inhibitors for reducing cardiorenal risk, particularly for patients with a lower renal reserve who have a higher risk for DKD progression. The ongoing EMPA-SEMA (Renal Effects of Treatment with Empagliflozin Alone or in Combination with Semaglutide in Patients with Type 2 Diabetes and Albuminuria) trial was designed to determine whether GLP-1 receptor agonists and SGLT2 inhibitors act synergistically to optimize renal outcomes. ClinicalTrials.gov. Renal effects of treatment with empagliflozin alone or in combination with semaglutide in patients with type 2 diabetes and albuminuria (EmpaSema). Available from https://clinicaltrials.gov/ct2/show/NCT04061200. Accessed 11 December 2021 [84].

The mechanisms involved in injury to the kidney glomerular, interstitial, and vascular functions consist of inflammation, oxidative stress, endothelial dysfunction, and accelerated fibrosis, as described above. Endothelium dysfunction consists of the impairment of many aspects of endothelial functions, including the anti-inflammatory, antiproliferative ones and vasodilatation. Vascular inflammation is a result of a combination of an impaired vasomotor

response, an increase in cell proliferation and platelet aggregation, and vascular permeability.

Extensive research is currently underway in this field, and several new pathogenic mediators for DN have been discovered, including renin, AGE, PKC, transforming growth factor-beta1 (TGF-β1), NO, VEGF, and oxidative stress.

Studies have focused on the role of these mediators and possible novel treatments using these approaches, and the following new classes of treatment are under investigation: protein kinase C-inhibitor (ruboxistaurin); AGE formation inhibitors (aminoguanidine, ALT-946, pyridoxamine, thiamine); direct renin inhibitor (aliskiren); AGE breakers (alagebrium, TRC4186); AGE receptor antagonists (endogenous secretory RAGE, RAGE antibody); TGF inhibitors (pirfenidone, SMP-534); connective tissue growth factor (CTGF) inhibitors (anti-CTGF ab); VEGF inhibitors (SU5416); anti-oxidant (curcumin); and hemorheologic properties and phosphodiesterase inhibitor (pentoxifylline).

Some of these have yielded promising results in trials, but more clinical studies are still needed to establish their effects on DN, as with aliskiren, pentoxifylline, ruboxistaurin, pirfenidone, and anti-CTGF antibody (Table 37.3) [85]. The Ruboxistaurin Study reported an outcome of decreased albuminuria and stabilized kidney function; and the PREDIAN trial reported on the pentoxifylline group an eGFR decline 4.3 ml/min per 1.73 m^2 less than the control group and a mean difference in albuminuria of 21% [7, 86].

Adverse events requiring cessation of randomized therapy (usually hyperkalemia) were significantly more frequent with aliskiren (13.2 vs. 10.2%). Due to the lack of apparent benefit and higher risk of side effects, the trial was prematurely stopped. There is little evidence for the clinical use of direct renin inhibitor (DRI) in DKD, and its use warrants careful monitoring for hyperkalemia, hypotension, or acute kidney injury [87]. Pirfenidone is a promising agent for the treatment of diabetic nephropathy and should be further investigated [88].

Other agents are under investigation targeting mechanisms, such as glomerular hyperfiltration, inflammation, and fibrosis, and have been a major focus for the development of new treatment. Baricitinib, a JAK1/2 inhibitor, was related to albuminuria reduction by 40%, but showed no effect on eGFR. Atrasentan (ETA) was evaluated on the RADAR and RADAR/JAPAN trial that showed 35% reduction of albuminuria, and this drug is also being tested on the Study of Diabetic Nephropathy with Atrasentan (SONAR) which is a randomized, multicountry, multicenter, double-blind, parallel, placebo-controlled study of the effects of atrasentan on renal outcomes in subjects with type 2 diabetes and nephropathy. However, there are no available phase 3 clinical trial data for these new agents, and none are approved for use in DKD [7].

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