CHRONIC KIDNEY DISEASE AND TYPE 2 DIABETES

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All authors researched and wrote their respective sections. Lead author M.R.W. reviewed all content and is the guarantor of this work.

About the Covers

Male kidneys. Credit: Science Photo Library / Sebastian Kaulitzki / Getty Images

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Introduction

Matthew R. Weir, MD

Diabetic kidney disease (DKD) remains an important clinical problem with substantial medical comorbidity despite many recent medical advances (1,2). More focus on the earlier identification of patients with type 2 diabetes who are at risk for developing chronic kidney disease (CKD) is needed, especially with regard to biomarkers, genetics, and high-risk phenotypes. Another key area of opportunity is the need for better clinical care models to eliminate socioeconomic and racial disparities.

Fortunately, in the past few years, new therapeutic opportunities have been discovered, and more are being considered, for possible use in improving clinical outcomes. Angiotensin receptor blockers were the last major advance for the treatment of DKD, in 2001 (3,4). The serendipitous observations of improved cardiovascular and renal outcomes with sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists in cardiovascular outcomes trials were a major surprise (5–7). These observations were followed by the improved cardiorenal outcomes in two large renal protection trials in patients with DKD: the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (8) using the SGLT2 inhibitor canagliflozin and the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) study (9) using the novel and not-yet-approved selective nonsteroidal mineralocorticoid receptor antagonist finerenone.

As more therapeutic opportunities become established, we need an improved understanding of the mechanisms underlying the progression of diabetic vascular disease and target organ damage so that newer and traditional therapeutic options can be used together most efficiently to improve clinical outcomes. We need to consider the therapeutic index of these treatments and appreciate the massive amount of pharmacopeia that patients with diabetes and CKD consume on a daily basis. Thus, to enhance the precision of therapy, we need more knowledge of the mechanisms of kidney and cardiovascular disease progression in type 2 diabetes.

The results of newer clinical trials are another important area for discussion, as well as trials that are planned or are currently underway. The newer clinical trials have been conducted in patients who are already on optimal medical therapy, including improved blood pressure control, highest tolerated doses of renin-angiotensin system blockers, and lipid-lowering therapy.

Ultimately, we need more precision in guiding pharmacotherapy given the many new therapeutic options available. This compendium will provide an updated opportunity to gauge our progress in the efforts underway to improve longer-term outcomes for patients who have diabetes and CKD.

See references starting on p. 34.

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Pathogenesis of Diabetic Nephropathy

Rajiv Agarwal, MD, MS

Our understanding of the natural history of diabetic nephropathy has emerged largely from patients with type 1 diabetes. However, histological manifestations among those with type 2 diabetes are similar (10). Both the clinical manifestations and the histological appearances of kidney disease associated with diabetes have been well characterized. The pathogenesis, however, is less well understood, and there are gaps in our understanding of how various causal factors relate to the histological manifestations of diabetes; in part, this is because of a paucity of kidney biopsies and longitudinal data. Here, we will focus on the pathogenesis, summarizing our current understanding of the histological and clinical correlates and pointing out remaining controversies in the context of pathogenesis.

The pathogenesis of diabetic nephropathy is initiated and maintained by four causal factors, which can be classified broadly into metabolic, hemodynamic, growth, and proinflammatory or profibrotic factors (**Figure 1**). Although there is both a substantial overlap among these factors and variability in their relative contribution among individuals and over time, for ease of discussion, we will describe the pathogenesis as if each factor played an isolated role. These pathogenetic factors produce lesions in various kidney compartments: glomeruli, tubuli, interstitium, and vasculature. A complex series of molecules, receptors, enzymes, and transcription factors participate in the process that drives the earliest stages of kidney disease to an enlarged kidney with hypertrophy, expanded extracellular matrix (ECM), glomerulosclerosis, vascular hyalinosis, interstitial fibrosis and tubular atrophy, and loss of function culminating in end-stage renal disease (ESRD).

Metabolic Factors

The earliest changes are triggered by metabolic factors, namely hyperglycemia. Damage resulting from hyperglycemia can occur by alteration of tissues or can be induced by products of glucose metabolism (11). An overview of the deranged metabolic pathways that mediate the pathogenesis of nephropathy in people with diabetes is shown in **Figure 2**.

Glycation of Tissues

Hyperglycemia through a nonenzymatic mechanism can lead to production of advanced glycation end products (AGEs), which by glycation of various tissue constituents such as proteins, collagen, lipids, and ECM can provoke organ dysfunction. This process is likened to that of accelerated aging through browning of tissues or the Maillard reaction (11).

Glycation of molecules provokes downstream injury by several mechanisms that can be broadly classified into receptor-mediated and non–receptor-mediated categories (12).

Glycation leads to activation of receptors on cells—the best characterized of which is the receptor of advanced glycation end products (RAGE)—that trigger the synthesis and release of nuclear

FIGURE 1 Overview of pathogenic factors in diabetic nephropathy. The key drivers of diabetic nephropathy can be broadly classified as metabolic, hemodynamic, growth, and proinflammatory or profibrotic factors.

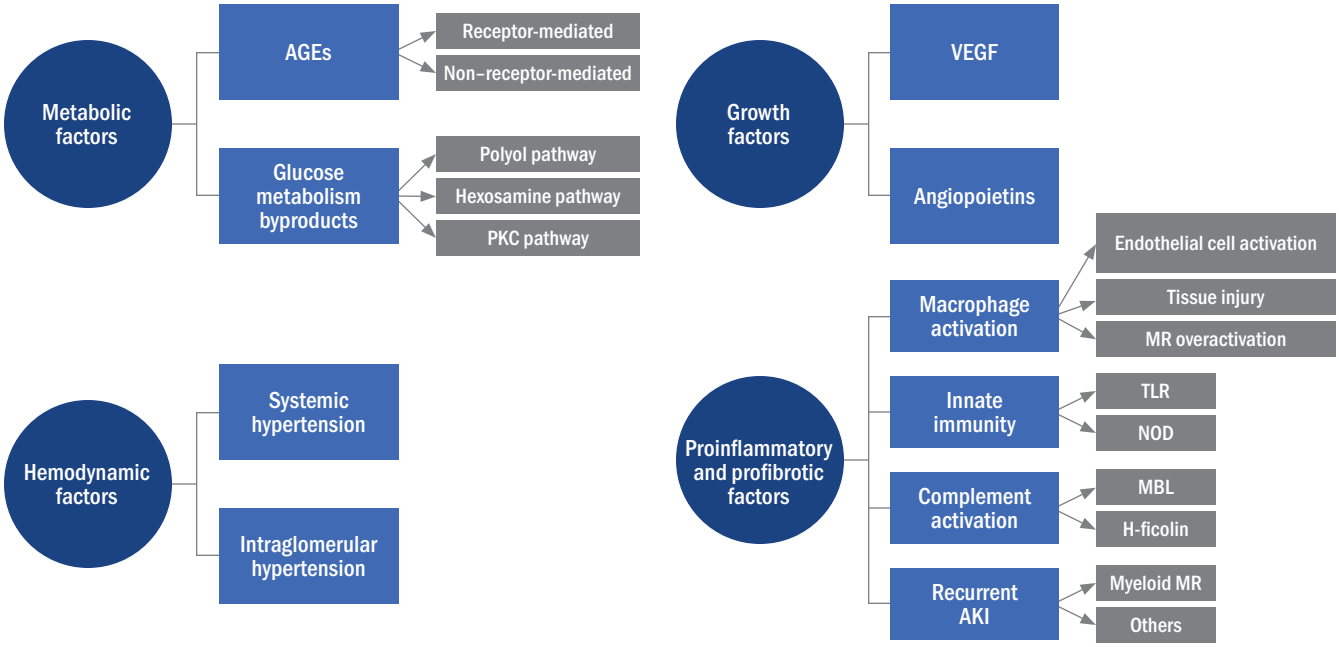
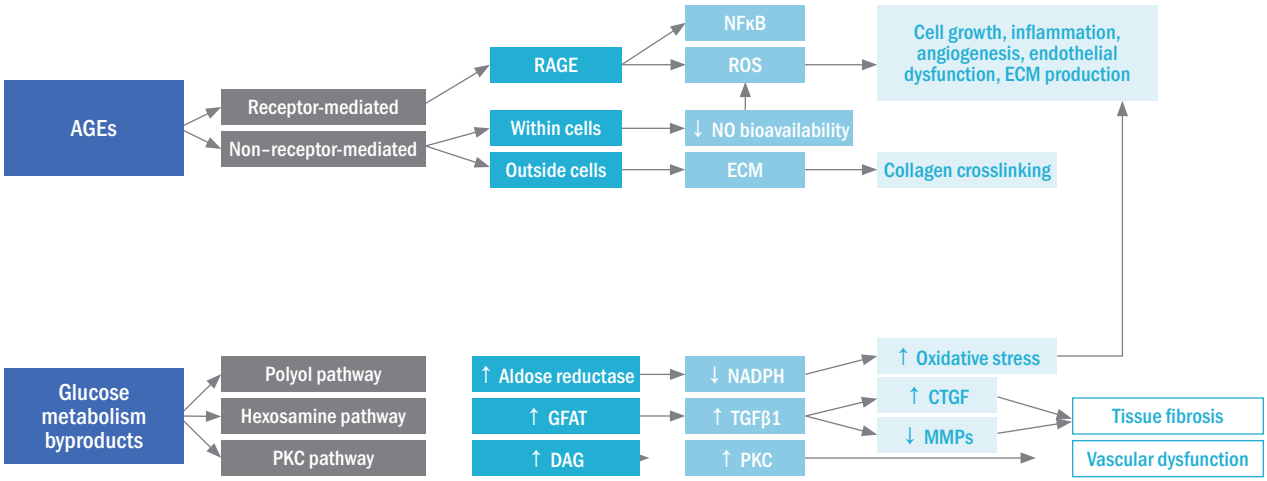


FIGURE 2 Metabolic pathways of diabetic nephropathy. Hyperglycemia provokes the accumulation of AGEs and other products of glucose metabolism. Activation of each of these pathways can injure the kidney. AGEs can produce cell injury by receptor and non-receptor pathways. Outside the cells, they can cause tissue damage by glycating molecules such as collagen that can reduce tissue compliance through crosslinking. Increased glucose flux can result in activation of pathways such as polyol, hexosamine, and PKC that can result in cellular injury and organ dysfunction.



factor κB (NFκB) and the generation of reactive oxygen species (ROS). These molecules, although transcription factors, initiate and maintain kidney damage by several processes (12), including cell growth and hypertrophy, inflammation, angiogenesis, endothelial dysfunction, and ECM production.

Within the cells, AGEs can produce cellular dysfunction without binding to a receptor. For example, glycation of cytosolic proteins can reduce nitric oxide (NO) bioavailability and provoke oxidative stress (12). Similarly, outside the cells, AGEs can provoke tissue dysfunction without binding to a receptor. For example, glycation of connective tissue constituents such as collagen can crosslink molecules in the ECM and cause dysfunction (12).

Histological manifestations of AGE accumulation include basement membrane thickening, reduced protein degradation that results in an increase in mesangial matrix, and an increase in interstitial extracellular volume.

Damage Induced by Products of Glucose Metabolism

Glucose can induce damage in cells independent of glycation such as by the activation of the polyol pathway, hexosamine pathway, or protein kinase C (PKC) pathway or through the generation of ROS.

Polyol Pathway

The polyol pathway involves the activation of the enzyme aldose reductase within cells when intracellular concentrations of glucose rise to hyperglycemic levels (11). This depletes the cellular nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) concentration and alters the redox ratio, which can reduce NO bioavailability and alter enzyme function. Although aldose reductase inhibitors were found to be effective in rodent models of diabetes, human trials have failed to reveal protection from an important microvascular complication of diabetes—eye disease—in a randomized trial (13).

Hexosamine Pathway

The hexosamine pathway is important for the synthesis of proteoglycans, glycolipids, and glycoproteins (14). The synthesis of these molecules requires an amino sugar substrate called UDP-N-acetylglucosamine, which is the final product of the hexosamine pathway. The rate-limiting enzyme of the hexosamine pathway is glutamine:fructose-6-phosphate-amidotransferase (GFAT), which catalyzes the reaction between fructose-6-phosphate and the amine-donor glutamine to produce glucosamine-6-phosphate (14). In cultured mesangial cells, high glucose levels provoke production of transforming growth factor β1 (TGF-β1); this effect is eliminated by inhibition of GFAT. In contrast, stable overexpression of GFAT increases TGF-β1 production. Furthermore, the effects appear to be transduced by PKC. In humans, GFAT is absent in glomerular cells. However, in patients with diabetic nephropathy, GFAT is expressed in the glomerulus, suggesting that it may play a pathophysiological role (14).

PKC Pathway

PKC is a family of enzymes that are critical intracellular signaling molecules and are important for vascular function. In the physiological state, receptor-mediated activation of PKC releases intracellular calcium ions and diacylglycerol (DAG) and activates these enzymes. In pathological states such as in diabetes, DAG production can be abnormally increased and can lead to activation of PKC. In diabetes, DAG production is increased by increased glycolysis and an elevated level of intracellular glyceraldehyde-3-phosphate and glycerol-3-phosphate. PKC

can also be activated by ROS and AGEs. An inhibitor of PKC-β—ruboxistaurin—has been tested in a phase 2 randomized clinical trial in patients with type 2 diabetes and persistent albuminuria (albumin-to-creatinine ratio [ACR] 200–2,000 mg/g creatinine) despite therapy with renin-angiotensin system inhibitors (15). Compared to placebo, the reduction in ACR at 1 year—the primary endpoint of the study—was not significant.

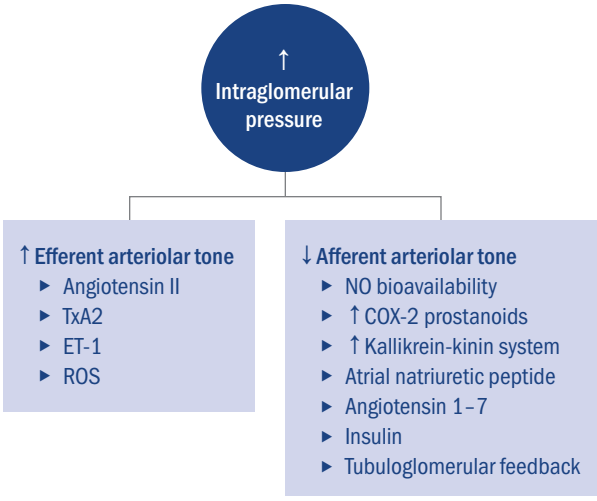
Hemodynamic Factors

The increases in glomerular capillary pressure increase the single nephron glomerular filtration rate—hyperfiltration—and this occurs early in the course of diabetes. An increase in intraglomerular pressure is the result of an increase in efferent arteriolar tone and a reduction in afferent arteriolar tone (**Figure 3**) (16). How this process occurs is not settled, but two theories have emerged.

One group believes that hyperfiltration is mediated by circulating molecules that primarily operate within the glomerulus (17). Several mediators have been proposed to increase intraglomerular pressure via increasing efferent arteriolar tone and reducing afferent arteriolar tone. Increase in efferent arteriolar resistance can result from an increase in the concentration of angiotensin II, thromboxane A2 (TxA2), endothelin 1 (ET-1), and ROS (16). Reduction in afferent arteriolar resistance can be provoked by reduction in NO oxide bioavailability; increased cyclooxygenase-2 (COX-2) prostanoids; activation of the kallikrein-kinin system, atrial natriuretic peptide, and angiotensin 1-7; and an increase in insulin (16).

However, another group proposes that tubular mechanisms remain the primary driver of the intraglomerular hypertension (12). The activation of glucose transporting pathways in the proximal tubule early in the course of diabetes stimulates the reabsorption of both glucose and sodium in the proximal nephron (12). Sodium delivery to the distal nephron is reduced. This triggers tubuloglomerular feedback; the afferent arteriole dilates, and the efferent arteriole constricts (12). An increase in insulin by itself can increase sodium and glucose transport in the proximal tubule and provoke tubuloglomerular feedback. Insulin, as noted above, can also reduce afferent arteriolar tone directly. Thus, insulin can both directly and indirectly cause hyperfiltration.

FIGURE 3 Mechanisms of intraglomerular hypertension. Intraglomerular pressure can increase as a result of either an increase in efferent arteriolar tone or a reduction in afferent arteriolar tone. The mediators of these alterations are shown.



Growth Factors

It has long been recognized that microangiopathy such as that occurs in the eye also associates with kidney disease. Therefore, investigators have explored the relation between vascular proliferation and endothelial permeability—factors known to be important in the pathogenesis of diabetic eye disease—with the occurrence of diabetic nephropathy. Vascular endothelial growth factor (VEGF) is activated early and leads to vascular expansion, which can provoke hyaline arteriosclerosis and hypertensive changes in the kidney (18). Similarly, angiopoietins can cause vascular proliferation and have been implicated in the pathogenesis of diabetic nephropathy (19).

Proinflammatory and Profibrotic Factors

Inflammation and fibrosis are important causes of diabetic nephropathy (20). Whether this is causal or in response to injury remains a matter of debate. However, there is a strong relation between the degree of infiltration of macrophages and subsequent occurrence of tubular interstitial fibrosis and progression of diabetic kidney disease (21,22).

Macrophages are attracted to the kidney by a variety of mechanisms (23). Endothelial cell dysfunction, activation, and injury all stimulate the production of adhesion molecules on the endothelial surface that facilitate transendothelial migration of macrophages. Injury and activation of resident kidney cells such as podocytes, mesangial cells, and tubular cells result in secretion of chemokines that facilitate intrarenal macrophage infiltration. Macrophages are activated to the proinflammatory (M1) phenotype by ROS, angiotensin II, and the activation of mineralocorticoid receptors (MRs). That by itself can damage podocytes, endothelial cells, mesangial cells, and tubular cells. Activated macrophages, by releasing profibrotic cytokines, can increase cell proliferation and matrix volume expansion and provoke fibrosis. Fibrosis at a molecular level is mediated in part because of activation of TGFβ1, which has two synergistic effects: activation of connective tissue growth factor (CTGF) and a reduction in matrix metalloproteinases (MMPs). In contrast, MR antagonists can coax macrophages to the antiinflammatory (M2) phenotype and be protective (24). Thus, macrophages play an important role in the pathogenesis of diabetic nephropathy (23).

Acute Kidney Injury, Inflammation, Chronic Kidney Disease, and the Role of MRs

Inflammation and fibrosis may also be important promoters of progression of chronic kidney disease (CKD) in patients with

diabetes, and this may be the result of acute kidney injury (AKI). It is increasingly being recognized that single or repeated bouts of AKI on a background of CKD in diabetes may play a vital role in the progression of CKD to ESRD (25). Macrophage infiltration is commonly seen in AKI, and depletion of macrophages in preclinical models can protect from AKI (26). In two different rodent models of AKI, bilateral ischemia reperfusion (IR) pretreatment with the nonsteroidal MR antagonist finerenone prevented the development of AKI (27). In a separate set of experiments, unilateral IR injury was also associated with reduced fibrosis when animals were pretreated with finerenone (27). Furthermore, in a pig model of IR AKI, the administration of the MR antagonist potassium canrenoate prevented the progression of AKI to CKD at 90 days (27).

The relative contributions of the knockout of MRs in smooth muscle cells versus their knockout in myeloid cells have been investigated in mouse models (**Figure 4**) (27). With MR knockout in smooth muscle cells, IR models demonstrated that the short-term elevation of serum creatinine and blood urea nitrogen was prevented. However, at 30 days, there was no difference between wild-type and smooth muscle cell MR knockouts. In contrast to MR knockout in smooth muscle cells, among myeloid MR knockout mice, there was no immediate protection from AKI. However, at 30 days, there was a marked improvement in renal function and markers of inflammation. Furthermore, there was a shift in the polarization of macrophages infiltrating the kidney. Although the total number of macrophages in wild-type and myeloid MR knockouts were similar, there was a shift in the nature of macrophages such that the M2 macrophages associated with an antiinflammatory response were increased in relation to the M1 macrophages, which are proinflammatory (27).

Although these studies were done in animals without diabetes, the experiments demonstrate the importance of inflammation and MRs in mediating CKD after AKI; similar mechanisms likely operate in patients with CKD resulting from diabetes (**Table 1**) (28,29).

FIGURE 4 Short- and long-term effects of MRs are location dependent. In smooth muscle cells, MRs protect from short-term AKI. In contrast, MRs in myeloid cells have no short-term effects but prevent long-term inflammation and fibrosis. These experiments are helpful in understanding the long-term consequences of repeated AKI in the progression of kidney disease in diabetes.

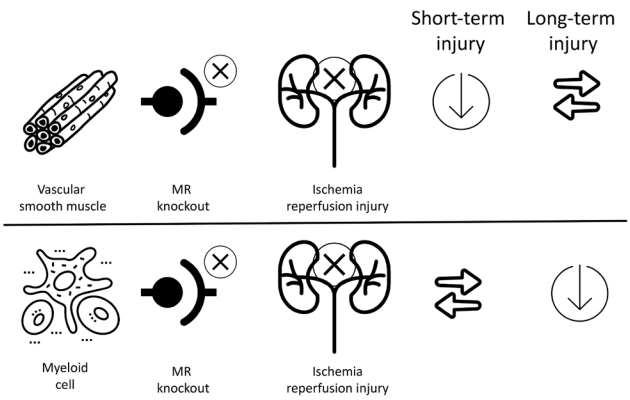


TABLE 1 MR Blockade and Kidney Protection in Diabetes

- Reduced maladaptive response
- Reduced ROS
- Improved endothelial function
- Shift in macrophage phenotype from proinflammatory (M1) to antiinflammatory (M2)
- Better blood pressure control

Innate Immunity, Complement Activation, and Diabetic Nephropathy

Activation of the innate immune system through pattern recognition receptors such as membrane-bound toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors may play an important role in the pathogenesis of diabetic nephropathy (30). The complement system, in addition to fighting infections, facilitates the removal of damaged cells by antibodies and phagocytic cells. The activation of the complement component C3 generates the membrane attack complex (MAC) that lyses, damages, or activates target cells. Mannose-binding lectin (MBL) activates the lectin pathway; pattern recognition molecules called ficolins can also activate the lectin pathway. The lectin pathway is activated after binding of ficolins to glycated proteins. Glycation of complement regulatory proteins such as CD59 might by itself activate complement; this is so because CD59 normally inhibits MAC (30).

A causal relation between MBL activation and diabetic nephropathy is firmly established in animals. For example, compared to wild-type mice with streptozotocin-induced diabetes, MBL knockout mice have less kidney damage, less kidney hypertrophy, lower urine albumin excretion, and less type IV collagen expression (31).

Several lines of evidence in humans suggest the important role of complement activation in CKD progression. As examples, *1*) in patients with type 1 diabetes, concentrations of MBL associate with progression of kidney disease from macroalbuminuria to ESRD (32); *2*) in a prospective cohort study of 270 patients with newly diagnosed type 1 diabetes, H-ficolin was associated with an increased risk of worsening of albuminuria (33); and *3*) MAC detected by antibodies directed against the C9 component of MAC localize it to the glomerular basement membrane (GBM), tubules, and Bowman capsule in patients with type 1 diabetes (34–36).

Taken together, these data point out the important role of the complement system and its components in the pathogenesis of diabetic nephropathy.

Interrelations Among Pathogenic Factors in Diabetic Nephropathy

The interplay of metabolic, hemodynamic, growth, and profibrotic factors is illustrated by consideration of the following preclinical experiments (37). Cultured mesangial cells exposed to CTGF

increase production of profibrotic molecules such as fibronectin and collagen type I (37). Although the baseline production of CTGF by mesangial cells is low, exposure of mesangial cells to increased glucose concentration (a metabolic factor) or cyclic metabolic strain (a hemodynamic factor) increases the production of CTGF (a growth factor). The induction of CTGF protein by a high glucose concentration is blocked by TGFβ1-neutralizing antibody. This suggests that another growth factor—TGFβ1—mediates the effect of high glucose concentration to provoke CTGF production. In vivo studies in obese db/db diabetic mice demonstrate that CTGF transcription was increased 28-fold after ~3.5 months of diabetes (37). At 3.5 months of diabetes, mesangial expansion was mild, and interstitial disease and proteinuria were absent. Furthermore, rather than being diffusely increased throughout the kidney, the CTGF production was limited to the glomerular compartment. These experiments demonstrate the interplay of all the pathogenic factors discussed above and underscore the complex interrelations of these factors, over time and at different locations in the kidney, in producing the histological manifestations of diabetic nephropathy.

Pathological Classification of Diabetic Nephropathy

According to an international consensus conference, the histological manifestations of diabetic nephropathy follow four progressive classes (**Table 2**) (38). The classification acknowledges lesions in the glomeruli, tubuli, and vessels, but the root of the classification system is based on the appearance of the glomerulus. According to this classification system, diabetic nephropathy progresses from thickening of the GBM, to mesangial expansion, Kimmelstiel–Wilson lesions, and global glomerulosclerosis, which is reflected in the four classes, as discussed further below. Although this system has not been validated with clinical outcomes, it serves as an important clinical and research tool to classify the severity of diabetic nephropathy lesions.

Class I Diabetic Nephropathy

On ultrastructural evaluation of the kidney histology, among the earliest change that occurs in the kidney is thickening of the GBM; light microscopy shows minimal, non-specific, or no changes. Thickening of the GBM does not directly correlate with clinical injury. Patients may have such thickening but have no increase in urine albumin excretion rate or impairment of glomerular filtration rate (39,40). Although an increase in diastolic blood pressure (40) or nocturnal blood pressure (39) is correlated with GBM thickening, the causal relation is not established because of a lack of longitudinal data and interventional studies. GBM thickening occurs as a result of either an increased rate of deposition or a reduced rate of removal of connective tissue. Target molecules include collagen IV and VI, fibronectin, and laminin (35,41).

TABLE 2 Pathological Classification of Diabetic Nephropathy

Class I	▸ GMB thickening on electron microscopy; minimal, non-specific, or no changes on light microscopy
Class II	▸ Increase in mesangial matrix
Class IIa	▸ Mesangial expansion ≤25%
Class IIb	▸ Mesangial expansion >25%
Class III	▸ Nodular glomerulosclerosis: Kimmelstiel-Wilson lesion
Class IV	▸ Advanced glomerulosclerosis; >50% glomeruli sclerotic

Class II Diabetic Nephropathy

Among the earliest manifestations on kidney histology that correlate with kidney damage is an increase in mesangial matrix, as seen in class II diabetic nephropathy. Class II is further subclassified based on the degree of mesangial expansion; class IIa is characterized by ≤25% mesangial expansion, and class IIb involves >25% of the mesangial expansion. An increase in mesangial matrix, glomeruli, and kidney volume is clinically manifested as kidney enlargement; kidneys are often 11 cm or larger on kidney ultrasound. Urine albumin excretion is often increased in these patients.

Class III Diabetic Nephropathy

An increase in mesangial matrix is followed by mesangial sclerosis. The hallmark lesion on a kidney biopsy is nodular glomerulosclerosis, or Kimmelstiel-Wilson nodules. The presence of Kimmelstiel-Wilson nodules on kidney biopsy correlates with the occurrence of diabetic retinopathy, suggesting activation of common pathogenetic pathways such as VEGF.

Class IV Diabetic Nephropathy

Advanced, or class IV, diabetic nephropathy is characterized by sclerosis in >50% of the glomeruli. These patients often have a loss of kidney function at the time of biopsy.

An enlargement of glomeruli is often seen along with thickening of the walls of the glomerular capillaries. Arteriolar hyalinosis of both the afferent and efferent arteriole should alert health care professionals to the possibility of diabetic nephropathy. The proximal tubules can contain protein resorption droplets. In the setting of severe persistent hyperglycemia, glycogen deposits may be seen rarely in the proximal tubules (i.e., Armanni Ebstein lesion). Interstitial fibrosis and tubular atrophy (IFTA) and interstitial inflammation are often seen. Despite tubular atrophy, the basement membranes are often thickened in patients with diabetes.

The Heterogeneity of Kidney Injury in Type 2 Diabetes: A Pathogenetic Explanation

Although kidney disease is histologically similar in type 1 and type 2 diabetes, the relative contributions of causes of kidney damage differ in these two conditions. Compared to patients

with type 1 diabetes, those with type 2 diabetes are older, have a greater BMI, and are more likely to have dyslipidemia, hypertension, and other cardiovascular risk factors and, consequently, atherosclerosis and arteriosclerosis. Thus, the nature of kidney injury in patients with type 2 diabetes may be modified by environmental factors and genetic background. This heterogeneity in environmental and genetic factors in patients with type 2 diabetes may explain the distinct kidney injury phenotypes.

As an example, consideration of an animal experiment provides evidence for interplay between genetics and environment with regard to kidney injury phenotype (42). Progeny of rats with one parent with heart failure and another with obesity were fed a diet either high in carbohydrate or high in fat; all progeny had diabetes (42). Compared to animals fed a high-carbohydrate diet, animals fed a high-fat diet demonstrated a greater preponderance of tubulointerstitial injury and non-nodular glomerulosclerosis. There was evidence of lipid peroxidation and increased kidney TGFβ1 that correlated with kidney injury. Furthermore, injury in animals fed a high-fat diet was seen in the arterial wall and renal microcirculation. In contrast, animals fed a high-carbohydrate diet had increased glycoxidation stress biomarkers, but these did not correlate with kidney injury (42).

Conclusion

The pathogenesis of diabetic nephropathy is similar in type 1 and type 2 diabetes. Diabetic nephropathy is classified histologically by the appearance of the glomerulus on kidney biopsy. It progresses from GBM thickening, to mesangial expansion, nodular glomerulosclerosis, and global glomerulosclerosis. Glomerulomegaly, vascular lesions, IFTA, and tubular resorption droplets are all commonly seen. The pathogenesis of diabetic nephropathy involves metabolic, hemodynamic, growth, and inflammatory and fibrotic factors. The relative contributions of these factors vary among patients, over time, and even in different compartments of the kidney, and genetic and environmental factors can modify the appearance of the kidney lesions. AKI plays an important role in the progression of kidney disease in patients with diabetes. MR activation, particularly in the myeloid cells, may be important in mediating inflammation and fibrosis in CKD and after AKI in individuals with type 2 diabetes, and MR antagonist therapy may be protective.

See references starting on p. 34.

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Risk Factors, Symptoms, Biomarkers, and Stages of Chronic Kidney Disease

Peter Rossing, MD, DMSc

Whereas the symptoms of chronic kidney disease (CKD) in diabetes are few, there are many risk factors and biomarkers that can be used to identify individuals at high risk for development of this complication, and many of these are targets for intervention to prevent or delay the disease. This article describes the risk factors and other markers of CKD and the various stages of the disease.

Risk Factors for CKD in Diabetes

Many factors are associated with CKD in diabetes (**Figure 1**). Associations may be with both albuminuria and glomerular filtration rate (GFR) or with one variable only. Some factors influence initial development of kidney disease and others progression of the disease. Duration of diabetes is one of the strongest risk factors for diabetic nephropathy, but because type 2 diabetes is often silent, CKD may be present at diagnosis of diabetes.

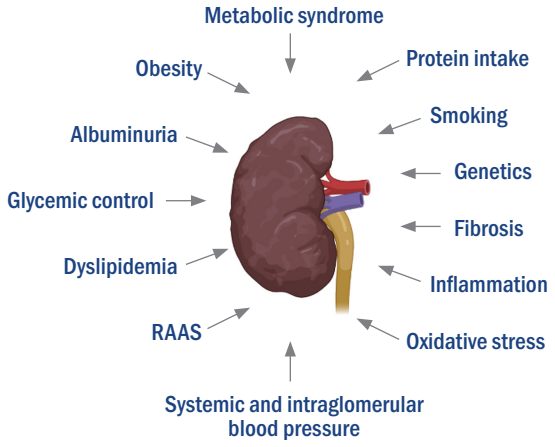
Hyperglycemia

Several studies demonstrate the importance of hyperglycemia in the development and progression of CKD in diabetes (or diabetic kidney disease [DKD]) (43,44). The UK Prospective Diabetes Study documented a progressive beneficial effect of intensive metabolic control on the development of microalbuminuria and overt proteinuria (45), and a 10-year post-study follow-up demonstrated long-lasting benefit, which was termed a "legacy effect" (46).

Greater variability in A1C is associated independently with albuminuria and diabetic nephropathy (47,48). The beneficial effect of improved glycemic control was confirmed in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, in which 11,140 patients with type 2 diabetes were followed and a 21% reduction (95% CI 7–34%) in development of nephropathy was seen in patients randomly assigned to strict glycemic control (49). Even end-stage renal disease (ESRD) was reduced in the ADVANCE trial, although it was a very rare event (50).

Overall, it has been difficult to demonstrate the benefit of improving glycemic control on established CKD in type 2 diabetes, in contrast to the benefit on development of CKD. Recent studies with glucose-lowering agents such as glucagon-like peptide 1 receptor agonists found reduced progression of albuminuria and loss of kidney function (51,52). Sodium–glucose cotransporter 2 (SGLT2) inhibitors in particular have demonstrated benefit on progression of albuminuria, decline in kidney function, and development of kidney failure; but, although the mechanisms are not clear, the reduction in glucose is probably of minor importance (8,53). Thus, SGLT2 inhibitors are even beneficial in people with CKD who do not have diabetes (53).

FIGURE 1 Putative promoters of CKD progression in diabetes.



Blood Pressure

Blood pressure is crucial to the development and progression of CKD in diabetes (44,54,55). The excess prevalence of hypertension in type 1 diabetes is confined to patients with nephropathy (56). Once severely increased albuminuria is present, frank hypertension is present in 80% of individuals and is almost universal in those with ESRD. In type 2 diabetes, the link between hypertension and kidney disease is less striking because hypertension is so common. Almost all patients with moderately elevated or worse albuminuria have hypertension. In people with diabetic nephropathy, variability in systolic blood pressure is independently associated with the development of ESRD (57).

Treatment of blood pressure, particularly with inhibitors of the renin angiotensin system (RAS), has been a standard of care for both prevention and treatment of CKD in diabetes based on studies with angiotensin II receptor blockers in moderately elevated albuminuria (microalbuminuria) and type 2 diabetes (58), as well as in established proteinuria in type 2 diabetes (3,4). Even prevention of CKD has been suggested, at least in hypertensive type 2 diabetes, when treated with RAS-blocking agents (59).

Renin-Angiotensin-Aldosterone System

Several components of the renin-angiotensin-aldosterone system (RAAS) are elevated and considered to contribute to the progression of diabetic nephropathy. Accordingly, blocking the RAAS has been demonstrated to be kidney protective.

Experimental studies have suggested that succinate, formed by the tricarboxylic acid cycle, provides a direct link between high glucose and renin release in the kidney (60). Focus was initially on the damaging effect of angiotensin II.

As discussed for blood pressure, RAS-blocking agents have been a standard of care in CKD in 20 years. Aldosterone represents another component of the RAAS that should be considered important in the pathophysiology of diabetic nephropathy. Aldosterone is a hormone that, in addition to regulating electrolyte and fluid homeostasis, has widespread actions through genomic and nongenomic effects in both the kidney and tissues not originally considered targets for aldosterone such as the vasculature, central nervous system, and heart (61).

Obesity

Obesity is an increasing problem in the general population and among people with diabetes. Several studies have indicated that severe obesity (BMI >40 kg/m^2) enhances ESRD risk sevenfold (62). Even a BMI >25 kg/m^2 was found to increase ESRD risk (62). This effect is independent of the effects of hypertension and diabetes, the prevalence of which are increased in individuals with obesity. An effect of obesity on renal hemodynamics leading to increased glomerular pressure and hyperfiltration has been suggested as the mechanism (63), and adiponectin was suggested to link obesity to podocyte damage (64). Weight reduction from bariatric surgery (65) or pharmacological treatment (66) has been associated with improved renal outcomes, although large weight reductions will improve estimated GFR (eGFR) and not true GFR because of loss of muscle mass and then decline in serum creatinine (67).

Other Metabolic Factors

Blood lipids, including triglycerides (68,69), contribute to the development and progression of CKD, although the lipid phenotype alters as kidney disease progresses (70–72). Insulin resistance increases the risk of albuminuria in type 2 diabetes (73). Individuals with type 1 or type 2 diabetes and CKD are more likely to have the metabolic syndrome (74–76). Multifactorial intervention targeting lifestyle, glucose, blood pressure, and lipids has a beneficial impact on both cardiovascular and kidney outcomes (77).

Genetic Factors

Genetic factors influence susceptibility to CKD in both type 1 and type 2 diabetes (78,79). If one sibling with type 1 diabetes has nephropathy, the risk to a second sibling is increased four- to eightfold compared to sibling sets in which neither has nephropathy (80). Similar familial clustering has been described in type 2 diabetes (81). Despite these findings, strong and clinically useful genes for CKD in diabetes are still lacking.

The clustering of conventional cardiovascular risk factors and cardiovascular disease (CVD) in people with diabetes and CKD also occurs in their parents (82,83). This finding suggests that the genetic susceptibility to nephropathy also influences the associated CVD. Multiple genes, either protective or deleterious, are involved. Different loci may influence albuminuria and GFR separately (84). Epigenetic modification may also be important (85).

Ethnicity

Albuminuria and CKD stages 4 and 5 are more common in U.K. Afro-Caribbean and South Asian individuals than White European people (86,87). The prevalence of early CKD (defined as moderately elevated or greater albuminuria and eGFR<60 mL/min/1.73 m^2) is also higher in Latino and African American individuals than in White people (88). Albuminuria and CKD are also more common in Pima Indians (89) and in Māoris and Pacific Islanders (90,91) than in White Europeans. Reasons for this varying prevalence may include differing genetic influences and altered response to, or poorer access to, treatments.

Type 2 Diabetes Developing in Young People

Individuals who develop type 2 diabetes at a young age have a high prevalence of hypertension and moderately elevated albuminuria (92). ESRD and death are particularly common in young people from ethnic minorities (93–95). However, in some of these populations, there is a high prevalence of kidney disease unrelated to diabetes (96).

Albminuria and eGFR

Baseline albuminuria and eGFR independently influence the development and rate of progression of CKD (97,98). Baseline albuminuria strongly predicts ESRD (99). Higher levels of normoalbuminuria (100) and lower eGFR (101) predict a faster decline in eGFR. Conversely, a short-term reduction in albuminuria with intervention is associated with reduced progression of kidney and cardiovascular complications (102,103).

Other Risk Factors

Other risk factors for nephropathy include smoking (98), pre-eclampsia (104), periodontitis (105), obstructive sleep apnea (106), and nonalcoholic fatty liver disease, all of which are independently associated with diabetic nephropathy (107,108).

Symptoms of CKD

Whereas albuminuria is often an early sign of CKD, there is a paucity of symptoms related to CKD in diabetes until late stages, making systematic screening mandatory to detect CKD as early as possible. Edema is often the first symptom, followed by fatigue and other uremic symptoms with pruritus, and then nausea, but this usually does not occur until CKD stage 4 or 5 (**Figure 2**) (109).

Other symptoms relate to complications, including angina from ischemic heart disease, dyspnea resulting from heart failure, aching from painful neuropathy, or typical symptoms of urinary tract infection. Although these complications are frequent, the symptoms may be atypical or weak because of the presence of neuropathy.

FIGURE 2 Stages and prognosis of CKD based on albuminuria and GFR from the KDIGO (Kidney Disease: Improving Global Outcomes) 2012 clinical practice guideline (109). The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst. Green indicates low risk (if no other markers of kidney disease and no CKD), yellow indicates moderately increased risk, orange indicates high risk, and red indicates very high risk. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl 2013;3:1–150.

				Persistent Albuminuria Categories, Description and Range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30–300 mg/g	>300 mg/g
GFR Categories (mL/min/1.73 m^2), Description and Range	G1	Normal or high	>90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Markers from Different Pathways Predict Kidney Outcomes

Progression of CKD is related to increased activity in different pathophysiological pathways that is reflected in biomarkers of these processes (**Figure 3**) (110).

Vascular Damage

Elevated urinary albumin excretion reflects widespread vascular damage and predicts development of kidney failure and cardiovascular events. In addition, treatment-induced reductions are associated with improved kidney and cardiac prognosis, as initially demonstrated in smaller studies (102,111) and recently documented in meta-analyses of observational (112) and intervention (103) studies.

Troponin T, in addition to its use in acute settings as a marker of myocardial damage, has been used to demonstrate vascular, cardiac, and kidney risk and could be a marker of increased risk for atherosclerosis (113,114).

Fibrosis

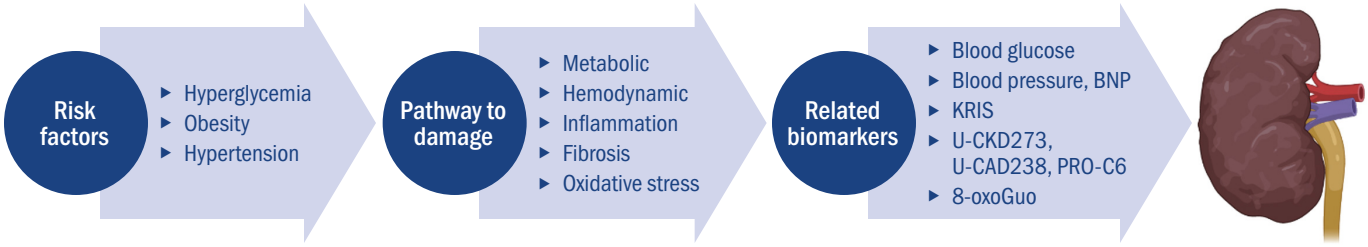
Different markers of fibrosis have been studied such as serum and urine PRO-C6, a C-terminal pro-peptide generated during collagen VI formation. In people with type 2 diabetes and microalbuminuria, a doubling of serum PRO-C6 increased hazards for cardiovascular events (hazard ratio [HR] 3.06, 95% CI 1.31–7.14), all-cause mortality (HR 6.91, 95% CI 2.96–16.11), and reduction of eGFR of >30% (HR 4.81, 95% CI 1.92–12.01).

Applying urinary proteomic analysis with capillary electrophoresis coupled to mass spectrometry, Good et al. (115) described a high-dimensional urinary biomarker pattern composed of 273 peptides associated with overt kidney disease: CKD273. The original studies included people with CKD on a mixed background compared to healthy control subjects. The components of CKD273 include collagen fragments and are assumed to relate to early fibrosis in the kidney. In retrospective studies, this proteomic classifier identified subjects at risk for CKD and progression in albuminuria class earlier than the indices currently used in clinical practice (116). In a prospective study including people with type 2 diabetes and normoalbuminuria, it was also demonstrated that CKD273 was associated with development of microalbuminuria and impaired kidney function (117).

Inflammation

Multiple markers have been investigated related to inflammation. These include fibrinogen, interleukin 6, and tumor necrosis factor-α (TNF-α), which were found to be associated with risk of CKD progression (118). Some of the most widely studied markers have been tumor necrosis factor receptors (TNFRs) 1 and 2. Recently, a Kidney Risk Inflammatory Signature was developed with 17 inflammatory markers, including TNFR superfamily members (119). The signature was tested in two cohorts as a marker of ESRD in both type 1 and type 2 diabetes. All components of the signature had a systemic, non-kidney source and may guide therapy to new targets. Interestingly, the signature was improved with the anti-inflammatory agent baricitinib, but not with RAS blockade (119).

FIGURE 3 Pathways and biomarkers of CKD. BNP, brain natriuretic peptide; KRIS, kidney risk inflammatory signature; U-CAD238, urinary proteome-based classifer for coronary artery disease 238 ; U-CKD273, urinary proteome-based classifer for chronic kidney disease 273. Adapted from Rossing P, Persson F, Frimodt-Moller M, Hansen TW. Diabetes 2021;70:39–50.



Oxidative Stress

It has been proposed that elevated levels of uric acid induce vascular and kidney damage, hypertension, and atherosclerosis due to inflammation and oxidative stress. Elevated uric acid levels were associated with cardiovascular events and progression of kidney disease in type 1 diabetes (120). The PERL (Prevention of Early Renal Function Loss) study (121) tested whether lowering uric acid with allopurinol in people with type 1 diabetes and early CKD with albuminuria or declining eGFR could prevent loss of measured GFR over 3 years. Mean serum urate level decreased from 6.1 to 3.9 mg/dL with allopurinol and remained at 6.1 mg/dL with placebo. Despite this lowering, the trial found no evidence of a kidney protective effect on albuminuria or decline in GFR. These results suggest that uric acid is not a target, in line with a Mendelian randomization study in type 1 diabetes (122). However, a study was presented in 2019 with greater reduction of uric acid in a small group of people with type 2 diabetes who were followed for 24 weeks taking the urate reabsorption inhibitor verinurad and the xanthine oxidase inhibitor feboxustat in combination, resulting in a 49% reduction in urine albumin-to-creatinine ratio (ACR) compared to placebo (123).

Other markers of oxidative stress are oxidatively modified guanine nucleosides 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine (8-oxoGuo) excreted in the urine. The level of 8-oxoGuo was associated with mortality and CVD in type 2 diabetes (124).

Transcriptomics

Tissue from kidney biopsies may provide diagnostic information with typical histological findings. More recently, it has been suggested that histological and transcriptomic analysis of kidney tissue may be relevant to characterize fast CKD progressors and select optimal treatments (125). Transcriptomic profiles in kidney tissue from patients with DKD and animal models of DKD have suggested the importance of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway as a key pathway in DKD. A clinical study in diabetes intervening with a JAK-STAT inhibitor subsequently demonstrated reduced albuminuria (126).

Metabolomics

Metabolites have been investigated in blood and urine using platforms that capture hundreds or even thousands of metabolites. So far, there have only been a few studies in people with type 2 diabetes and CKD. Pena et al. (127) demonstrated that a few metabolites in serum and urine could improve prediction of progression in albuminuria status in type 2 diabetes, and Solini et al. (128) demonstrated in patients with type 2 diabetes that serum, but not urine, metabolites could improve prediction of progression of albuminuria and decline in GFR. Sharma et al. (129) described a signature of 13 metabolites in urine that pointed toward mitochondrial dysfunction as a key feature in progression of CKD in diabetes. Niewczas et al. (130) demonstrated that uremic solutes were associated with the development of ESRD in people with type 2 diabetes. Both the metabolome and lipidome were recently studied in type 1 diabetes (72,131). A number of markers of progression of CKD were identified but await confirmation, which is often a problem, as different studies use diverse platforms.

Stages of CKD

CKD in diabetes is defined as the presence of persistently elevated albuminuria of >30 mg/24 hour or a urinary ACR >30 mg/g creatinine, confirmed in at least two out of three samples (132). As such, its diagnosis is clinical, requiring little more than basic clinical and laboratory evaluations. The normal range for albuminuria is <30 mg/g. The presence of moderately elevated albuminuria (microalbuminuria) (30–299 mg/g) is widely regarded as a precursor of more advanced stages of CKD and a marker of vascular damage. However, in some cases, elevated albuminuria can display remission either spontaneously or as a result of treatment (133–135). Remission indicates lower kidney risk compared to progression of albuminuria. The Italian RIACE (Renal Insufficiency and Cardiovascular Events) study (136) of >15,000 people with type 2 diabetes suggested that patients with elevated albuminuria display the typical microvascular phenotype, whereas nonalbuminuric subjects with impaired kidney function had a more cardiovascular or macrovascular phenotype.

For CKD in general, including in people with diabetes, it has been recommended to stage the severity using a combination of etiology (if known), level of urinary albumin excretion, and eGFR (**Figure 2**) (109).

Conclusion

Advances in diagnosis and treatment have provided new options and potential for better outcomes for CKD in diabetes. As treatment opportunities continue to expand, biomarkers and, most likely, combinations of biomarkers will help us select the optimal treatment or combination of treatments for each patient. This ability will ensure better outcomes and reduce adverse events and unnecessary polypharmacy. A more detailed approach applying multiple biomarkers to select the right treatment for the right person may seem complicated and costly initially but has the potential to save both patients and the health care system considerable costs (137). Integrating multiple "-omics" platforms may lead to a much deeper understanding of the disease. Hopefully, such an approach will help to prevent CKD in diabetes and improve kidney outcomes in the future. For now, much can already be achieved if we ensure full integration of the use of simple biomarkers such as albuminuria and eGFR (138).

See references starting on p. 34.

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The Interplay Between Diabetes, Cardiovascular Disease, and Kidney Disease

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Burden of Diabetes and Associated Cardiorenal Disorders

The Global Burden of Disease Study estimates that there are currently 476 million patients with diabetes worldwide, the large majority of whom suffer from type 2 diabetes. In the United States, the prevalence of type 2 diabetes is 32.6 million, or ~1 in 10 people. These numbers are expected to continue to rise (139).

The metabolic system is closely interrelated with the cardiac and renal systems, and these three systems share a symbiotic relationship that helps maintain homeostasis. The heart is one of the most metabolically demanding organs and is sensitive to changes in energy and volume status. Thus, it relies on the liver, pancreas, and fat for optimal energy metabolism and on the kidneys for volume maintenance. Similarly, the kidneys rely on the heart for adequate perfusion and on the metabolic system for the appropriate hormonal milieu, both of which are necessary to maintain their function. The metabolic system depends on functioning heart and kidneys to prevent neurohormonal activation, which keeps metabolic derangements such as insulin resistance, glucose dysregulation, and dyslipidemias at bay (140).

Given the close-knit physiology of the metabolic, cardiac, and renal systems, it is not surprising that type 2 diabetes frequently coexists with cardiovascular disease (CVD) and chronic kidney disease (CKD). A 2018 study of >500,000 adults living with type 2 diabetes in the United States demonstrated that <10% had isolated type 2 diabetes with no associated cardiovascular or kidney disorder (141). CVD and CKD in the presence of type 2 diabetes worsen each other, leading to an increase in morbidity and mortality (142). This article focuses on the epidemiology and pathophysiology of CVD and CKD in relation to diabetes and provides an overview of current management.

Effect of Diabetes on a Molecular and Cellular Level

The mechanism behind the clinical manifestations of type 2 diabetes and its complications are rooted in molecular and cellular derangements.

Oxidative Stress

Oxidative stress is a state in which the generation of reactive oxygen species (ROS) exceeds the capacity of the antioxidants to neutralize them. In hyperglycemic states, the increased flux of glucose increases ROS production in mitochondria. Oxidative stress–induced cellular injury plays a central role in the pathology of diabetes-related CVD and CKD, as discussed in more detail in the subsequent sections (143).

Advanced Glycation End Products

Oxidative stress and hyperglycemia drive a nonenzymatic reaction that causes excessive covalent binding between glucose and substrates such as proteins, lipids, and nucleic acid, a process known as nonenzymatic glycation. The resulting compounds are termed advanced glycation end products (AGEs). AGEs can increase the production of ROS, causing increased intracellular oxidative stress. This increased oxidative stress, in turn, promotes the formation of more AGEs, thus resulting in a vicious cycle. AGEs and associated oxidative stress can result in inflammation, cellular dysfunction, and cell death. In the context of CVD and CKD, the effect of AGEs on the endothelium of blood vessels is important (143).

Endothelial Dysfunction

Endothelial dysfunction in patients with type 2 diabetes results from nonenzymatic glycation of the endothelium and oxidative damage. Endothelial dysfunction subsequently drives the development of microvascular and macrovascular disease. Hypertension, a common comorbidity in patients with type 2 diabetes, is also a potent risk factor for endothelial dysfunction (143).

Hypercoagulability

The first line of defense against a thrombotic event is an intact and functioning vascular endothelium. The endothelium releases antithrombotic factors and prevents contact of blood with collagen, which has a prothrombotic effect. Diabetes results in endothelial dysfunction and enhanced activation of both platelets and coagulation factors. On the other hand, anticoagulation mechanisms are relatively diminished in patients with diabetes. A hypercoagulable state inevitably increases the risk of thrombotic events such as myocardial infarction and stroke (143).

Diabetes and Complications of the Cardiovascular System

The link between type 2 diabetes and CVD has been known for decades. Compared to patients without diabetes, those with type 2 diabetes are two to four times more likely to experience cardiovascular events and are more likely to have worse outcomes after these events (144,145). About half of all diabetes-related fatalities can be attributed to cardiovascular causes (145).

Macrovascular and Microvascular Complications

Macrovascular complications such as coronary artery disease (CAD), stroke, and peripheral vascular disease are largely a consequence of atherosclerosis. Several diabetes-specific factors

promote atherosclerosis. Dysfunctional endothelial cells within large arteries are a fertile ground for the initiation of atherosclerosis (143). Dyslipidemia is prevalent in ~80% of patients with type 2 diabetes and is associated with atherosclerosis. Insulin deficiency and insulin resistance activate the enzyme hormone-sensitive lipase, which releases free fatty acids (FFAs) into the blood. This release leads to increased lipoprotein generation and release by the liver and, ultimately, increased circulating levels of triglycerides and LDL cholesterol. Lipoprotein lipase, the enzyme that clears LDL cholesterol, is downregulated, which aggravates dyslipidemia. HDL cholesterol levels are decreased in diabetes (143).

Diabetes also affects the microvasculature. Microvascular damage can lead to complications such as nephropathy, retinopathy, and neuropathy. Microvascular damage is often initiated by nonenzymatic glycation of endothelial cells. This process leads to formation of glycated proteins that trigger a range of effects on surrounding tissues, the most prominent ones being, *1*) thickening of endothelium and collagen, leading to local ischemia; *2*) overproduction of endothelial growth factors and pathologic angiogenesis; and *3*) vascular inflammation and generation of ROS (146). In tandem, these changes increase the risk of endothelial cell apoptosis, vascular remodeling, capillary blockage, capillary hemorrhage, and formation of microthrombosis (146). Depending on the site of involvement, these changes can lead to organ dysfunction and failure. The vascular remodeling and endothelial cell damage increase arterial stiffness and also lead to the loss of local nitric oxide, a potent vasodilator released by the endothelium (143), leaving the vasculature in a predominantly constricted state. Type 2 diabetes contributes to the development of hypertension by this major mechanism. Damage to microvasculature of the kidney can lead to CKD. Hypervolemia secondary to CKD is also an important mechanism by which type 2 diabetes leads to hypertension.

Damage to microvasculature of autonomic nerves (vasa nervorum) is responsible for the characteristic autonomic neuropathy of type 2 diabetes. Autonomic neuropathy further impairs autoregulation of blood flow in the vascular beds of a variety of organs, including the heart. Patients with diabetic autonomic neuropathy lack the normal cardiac flow reserve recruited in conditions that require increased myocardial perfusion. This could, in part, explain the increased rates of sudden cardiac death and overall cardiovascular mortality seen in patients with diabetic autonomic neuropathy (143). Autonomic neuropathy also predisposes patients with diabetes to fatal arrhythmias and sudden cardiac death (147).

Heart Failure

The prevalence of heart failure (HF) in patients with diabetes is ~15–20%, which is multiple-fold higher than the prevalence in age- and sex-matched control subjects without type 2 diabetes (4.5%) (148). The converse is concerning as well, with the prevalence of diabetes ranging from 40–50% in patients with HF. Moreover, in patients with HF, mortality is higher in those with versus those without concomitant diabetes (148).

HF with preserved ejection fraction (HFpEF) is emerging as an especially significant problem among patients with type 2 diabetes. Many of these patients have asymptomatic diastolic dysfunction, and HFpEF, a disease without known mortality-modifying therapies, is the predominant form of HF in type 2 diabetes (143,149). It is important to note that type 2 diabetes has distinct myocardial effects in HFpEF and in patients with HF and reduced ejection fraction (HFrEF), with different biomarker profiles. In HFpEF, the systemic inflammation is associated with higher serum levels of inflammatory biomarkers such as soluble interleukin-1 receptor-like 1 and C-reactive protein; biomarkers of myocardial injury and stretch such as troponins and natriuretic peptides are higher in HFrEF than in HFpEF.

In patients with type 2 diabetes, HF can occur as a result of ischemia or a thrombotic event secondary to CAD. In many cases, however, pathophysiological factors unrelated to CAD are at play. Cardiac disease in patients with type 2 diabetes that is not be attributed to any other known CVD such as CAD or hypertension is sometimes labeled as "diabetic cardiomyopathy," although the exact mechanism and identity of this entity is not fully understood (150). The mechanism behind diabetic cardiomyopathy is attributed to two-pronged abnormalities involving metabolic derangements and microvascular injury (143).

Analysis of the UK Prospective Diabetes Study demonstrated that every 1% increase in A1C was associated with a 12% increase in the risk of HF (43). In states of chronic hyperglycemia and insulin deficiency/insulin resistance, cardiac glucose metabolism is impaired, and the heart in patients with type 2 diabetes switches to FFA oxidation. As discussed earlier, hyperglycemia also induces generation of ROS. FFA oxidation also contributes to oxidative stress. Increased ROS-mediated cell death may drive cardiac remodeling and subsequent morphological and functional abnormalities. In addition, hyperglycemia-induced nonenzymatic glycation of cardiac tissue is another factor that can contribute to myocardial cell damage and remodeling (143).

Hyperinsulinemia plays a role in the development of HF (151). Animal studies show that excessive insulin signaling exacerbates cardiac dysfunction. Insulin use has also been shown to be independently associated with development of HF (151). Moreover, use of drugs that promote insulin signaling (e.g., thiazolidinediones) and those that increase insulin secretion is associated with increased risk of HF. In contrast, drugs that ameliorate hyperinsulinemia such as SGLT2 inhibitors and metformin demonstrate a reduced risk of HF (143,151).

Microvascular injury, particularly hyaline arteriolosclerosis and angiopathy of the small blood vessels, is a common finding in the myocardium of patients with type 2 diabetes. Microvascular disease results in local ischemia and subsequent morphological

and functional derangement. Cardiac autonomic neuropathy, also a complication of microvascular disease within nerves, correlates with systolic and diastolic dysfunction (151). Regardless of whether the mechanism of injury is via ischemia, hyperglycemia, or microvascular disease, the ultimate result is morphological and functional impairment of the heart. Under a microscope, ultrastructural changes such as myocardial injury, hypertrophy, and fibrosis are characteristic of the heart structure of patients with diabetes (152) and inevitably lead to reduced cardiac function. Metabolic derangement and abnormal energy utilization further add to the cardiac dysfunction (151).

Diabetes and Complications of the Kidney

Diabetic kidney disease (DKD) affects almost 40% of patients with diabetes (153), and its prevalence is rising in parallel to the prevalence of type 2 diabetes. DKD remains the leading cause of end-stage renal disease (ESRD) (153). Similar to diabetes-related cardiac disease, the major burden of DKD results from preceding microvascular and macrovascular injury. It is diagnosed based on estimated glomerular filtration rate (eGFR) and presence of albuminuria, along with clinical characteristics of diabetes that increase the likelihood of renal involvement, such as duration of diabetes and presence of diabetic retinopathy (140,154).

The term "DKD" is not synonymous with "diabetic nephropathy." DKD is a broad term encompassing all possible renal complications of diabetes. Diabetic nephropathy, on the other hand, is a progressive glomerular nephropathy secondary to diabetes. As such, diabetic nephropathy is one component that contributes to DKD (154). Diabetic nephropathy generally progresses in five stages, culminating in ESRD (**Table 1**).

Diabetes promotes the development of atherosclerosis. Involvement of the main renal arteries and their branches is common in patients with diffuse atherosclerosis but is frequently overlooked. Most patients with renal artery stenosis do not have the unstable or severe hypertension that is usually considered classic for the disease. Renal artery stenosis is likely underdiagnosed in patients with type 2 diabetes because of its variable presentation and a lack of clinical suspicion. Overzealous use of diuretics, ACE inhibitors, and angiotensin receptor blockers (ARBs) should be avoided in patients with renal artery stenosis (154). Apart from renal artery stenosis, other relatively rare macrovascular complications of the kidney include renal infarction and cholesterol emboli syndrome. People with diabetes are also at increased risk for upper and lower urinary tract infections (154).

Interaction Among Disease Processes

It is clear that type 2 diabetes contributes to both CVD and CKD; both of these diseases have the propensity to initiate and perpetuate each other, leading to a phenomenon termed "cardiorenal syndrome" (CRS). Ronco et al. (142) have classified CRS into five different subtypes, based on etiology (**Figure 1**).

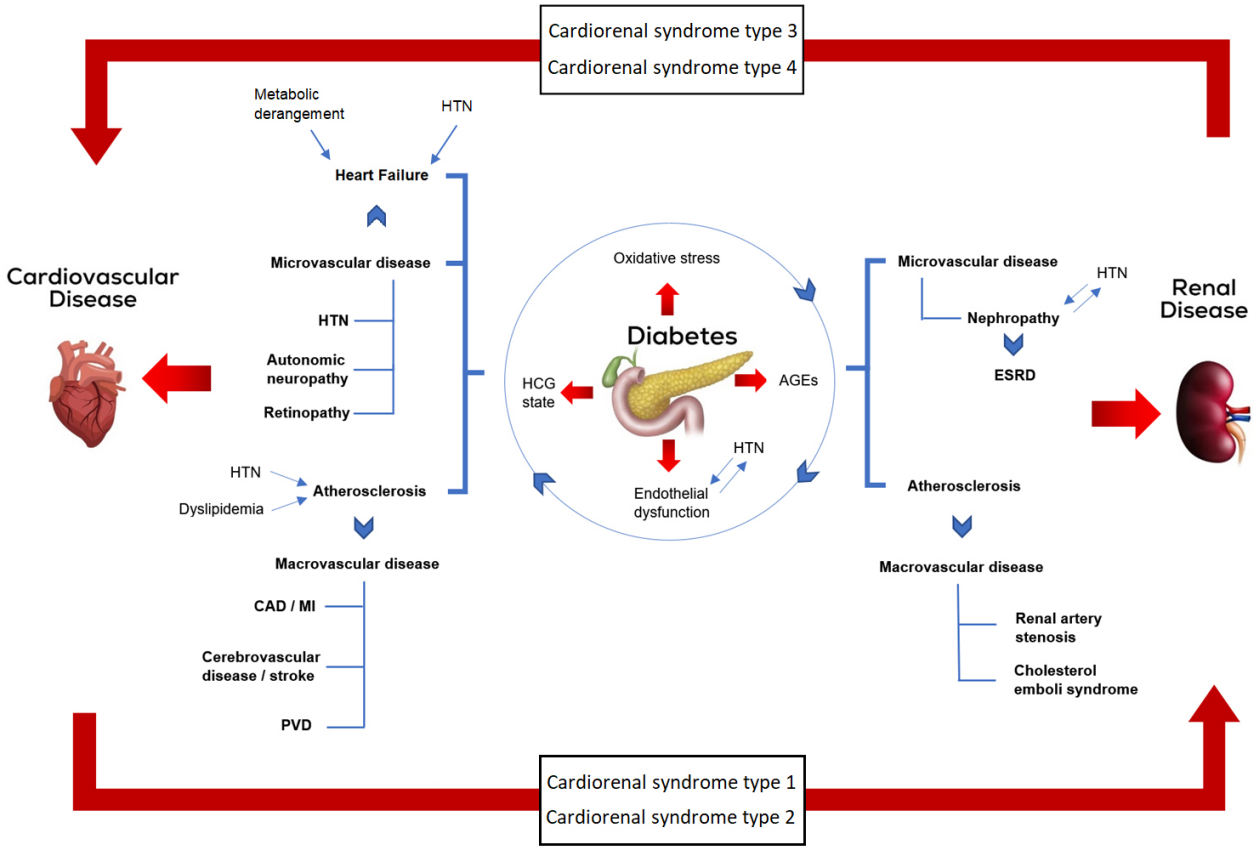
Type 1 CRS is characterized by acute cardiac dysfunction–related kidney dysfunction. Acute cardiac dysfunction may be the result of ischemia or HF, both of which are prevalent in diabetes, resulting in acute hypoperfusion, kidney ischemia, and subsequent necrosis/apoptosis of renal tubular cells. Type 1 CRS may further accelerate cardiovascular injury via activation of neurohormonal and inflammatory pathways (142).

Type 2 CRS is defined as chronic cardiac dysfunction leading to CKD. HF leads to chronic hypoperfusion of the kidney, resulting

TABLE 1 Stages of Diabetic Nephropathy

Stage	Onset (Time After Diabetes Diagnosis)	Key Microscopic Features	Clinical Features	Notes
1 (hyperfiltration)	At diagnosis	▸ Glomerular hypertrophy	▸ Increased GFR	▸ This stage is at least partially reversible.
2 (silent)	2–5 years	▸ Glomerular basement membrane hypertrophy	▸ Increased GFR and intermittent microalbuminuria	▸ Microalbuminuria is only seen when blood glucose is uncontrolled. A large proportion of people with diabetes stay in this stage throughout their life.
3 (incipient)	5–15 years	▸ Mesangial expansion, glomerular basement membrane thickening, and arteriolar hyalinosis	▸ Normal or supranormal GFR, progressive microalbuminuria, and hypertension	▸ This stage heralds the eventual onset of overt diabetic nephropathy.
4 (overt)	>25 years	▸ Mesangial nodules (Kimmelstiel-Wilson lesions) and tubulointerstitial fibrosis	▸ Progressively declining GFR and overt proteinuria (>0.5 g/24 hours)	▸ The decrease in GFR in this stage is particularly steep when comorbid hypertension is not treated.
5 (ESRD)	>25 years	▸ Global glomerular sclerosis in >50% of glomeruli	▸ GFR <15 mL/min/1.73 m^2, uremia, anemia, and other renal failure complications	▸ Renal replacement therapy is essential at this stage.

FIGURE 1 Cardiorenal syndrome.



in subclinical inflammation, endothelial dysfunction, atherosclerosis, renal cell damage, and sclerosis/fibrosis. The reduced GFR results in salt and water retention and in activation of the renin-angiotensin-aldosterone system (RAAS), which exacerbates water retention and systemic vasoconstriction. This process results in hypertension and worsening of chronic HF, thus forming a vicious cycle (142).

Type 3 CRS is defined as acute kidney dysfunction leading to cardiac dysfunction. Patients with diabetes are prone to renal artery stenosis, which increases the risk of acute kidney injury (AKI), especially when ACE inhibitors are used. Renal infarction secondary to distal emboli and acute pyelonephritis are also potential causes of acute kidney dysfunction in diabetes. Abrupt worsening of renal function can affect the heart by fluid overload, hyperkalemia, and the negative effects of uremia on myocardial contractility (142).

Type 4 CRS is characterized by primary CKD, leading to risk of CVD. DKD often progresses to CKD; in fact, up to 23% of patients with diabetes live with CKD. Patients with CKD are 10–20 times more likely to die of cardiovascular causes. CKD can exacerbate hypertension, activate the RAAS, and cause fluid retention. Hypertension increases the incidence of CVD in patients with CKD more than in those with normal renal function. Disturbed mineral and vitamin D metabolism increases vascular calcification risk. Left ventricular hypertrophy is increased in CKD, which may partially explain the risk of sudden cardiac death in this population. Patients with CKD are often undertreated for CVD due to concerns about kidney dysfunction with medication use; also, most drugs used to treat CVD have limited data in CKD (142).

Type 5 CRS is defined as simultaneous cardiac and renal dysfunction resulting from an acute or chronic systemic disorder (e.g., sepsis, amyloidosis, and diabetes). Whereas types 1–4 CRS refer to interactions between disease processes in the heart and kidneys, type 5 CRS refers to other diseases that affect both the heart and the kidney (142).

Several diagnostic tools such as assessment of biomarkers and volume measurement techniques can be used to discriminate among the different CRS phenotypes. While cardiac biomarkers such as troponins and natriuretic peptides are routinely used in clinical practice, kidney biomarkers are being studied to aid in diagnoses. Cystatin C and albuminuria are reflective of glomerular filtration and integrity in CRS, whereas NGAL (neutrophil gelatinase-associated lipocalin) and combination of TIMP-2 (tissue inhibitor of metalloproteinase-2) and IGFBP7 (insulin-like growth factor-binding protein 7) may represent biomarkers of acute tubular injury. These novel kidney biomarkers may have negative predictive value in distinguishing creatinine fluctuations from true AKI (142).

Management Strategies

The protective effects of ACE inhibitors on the heart and kidneys of patients with type 2 diabetes are well known. Certain novel medications such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and selective nonsteroidal mineralocorticoid receptor (MR) antagonists have also shown cardiac and kidney protective effects in populations with type 2 diabetes (**Figure 2**). This supports the idea of integrated multi-organ physiology and pathophysiology leading to benefits with medications across organ systems.

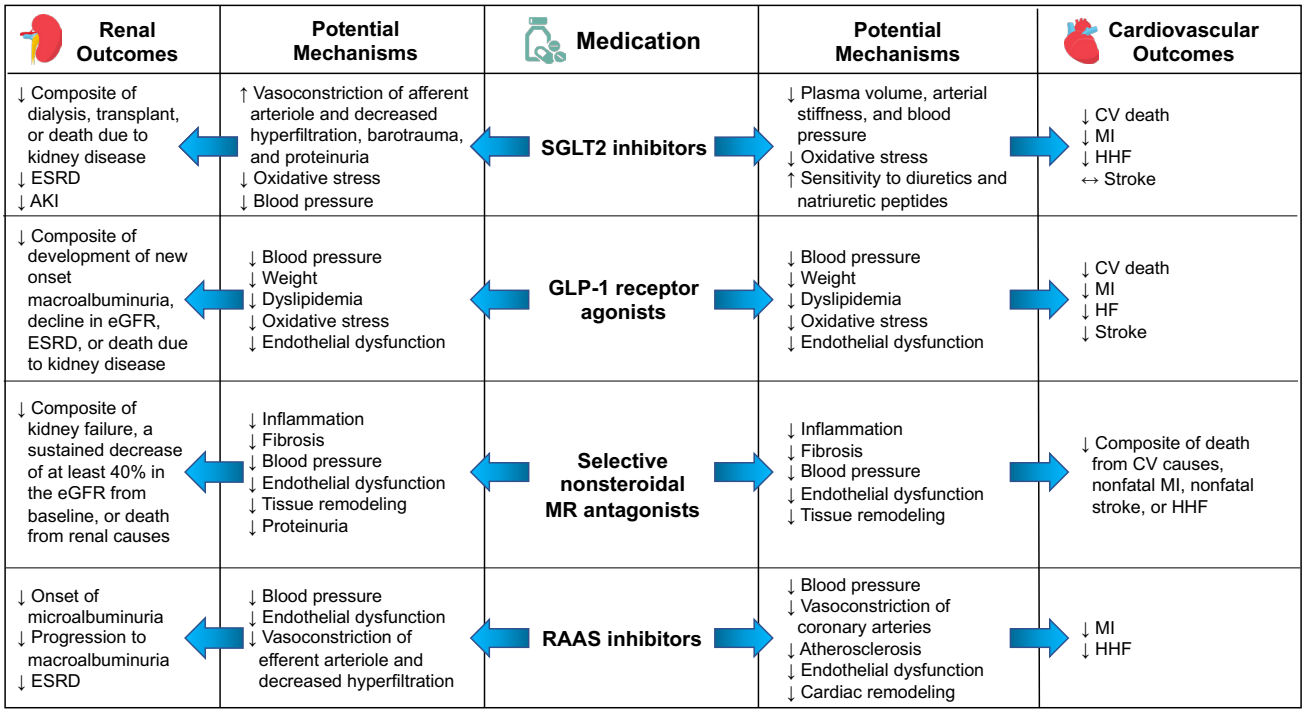
Prevention of Cardiovascular Disease

Blood glucose control may seem like the natural option to prevent diabetes-related cardiovascular events. However, traditional glucose-lowering agents such as metformin, sulfonylureas, and insulin have not demonstrated a convincing relationship between blood glucose control and reduction in macrovascular cardiovascular events. Furthermore, some hypoglycemic agents paradoxically have been associated with an increase in cardiovascular events (e.g., thiazolidinediones are associated with an increased risk of HF). In response to concerns of increased cardiovascular risk, the U.S. Food and Drug Administration (FDA) mandated in 2008 that cardiovascular safety be demonstrated with all new diabetes drugs (155).

Drugs in the dipeptidyl peptidase 4 (DPP-4) inhibitor class in general have good cardiovascular safety from a vascular disease perspective. However, saxagliptin did raise concerns about an increased risk of hospitalization for HF (HHF). Impressively, SGLT2 inhibitors have been shown to reduce the risk of major adverse cardiovascular events (MACE) (hazard ratio [HR] 0.90, 95% CI 0.85–0.95), HHF (HR 0.68, 95% CI 0.61–0.76), and kidney outcomes (HR 0.62, 95% CI 0.56–0.70) (156). The presence or absence of atherosclerotic cardiovascular disease (ASCVD) did not modify the association for any of these outcomes. GLP-1 receptor agonists have also demonstrated improved cardiovascular outcomes, with lower rates of MACE and cardiovascular death compared to placebo. However, no consistent reductions in HF or kidney risk have been observed with agents in this class (155). Finerenone, a selective nonsteroidal MR antagonist, has also exhibited improved cardiovascular outcomes in patients with type 2 diabetes and CKD. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial, finerenone use (versus placebo) resulted in a significantly lower incidence of the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and HHF (9).

Apart from selecting appropriate antihyperglycemic drugs, other relevant steps are required to prevent or treat CVD. Aspirin therapy is recommended as a primary prevention strategy in patients with type 2 diabetes who are at increased cardiovascular risk. Lipid levels should be measured annually, and appropriate treatment should be given to meet guideline-directed goals. Statin therapy should be initiated if the patient has a history of ASCVD or other risk factors (157). Blood pressure control is recommended for patients with comorbid hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg). The target systolic and diastolic blood pressure should be <130 and <80 mmHg, respectively. Potential therapeutic options include ACE

FIGURE 2 Medications with cardiorenal protective effects and their respective potential mechanisms and outcomes. CV, cardiovascular; MI, myocardial infarction.



inhibitors, ARBs, beta-blockers, and calcium channel blockers. Most patients with type 2 diabetes eventually need combined therapy with multiple drugs for adequate blood pressure control. Importantly, lifestyle modifications play a central role in the management of type 2 diabetes and prevention of CVD. These include increased exercise, weight reduction, smoking cessation, and adherence to dietary recommendations (157).

Prevention of Kidney Disease

Blood glucose control is associated with a reduced incidence of microvascular complications, including diabetic nephropathy. The target A1C level to prevent diabetic nephropathy is <7% (158). SGLT2 inhibitors have a particularly strong renoprotective effect. In the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial, patients with diabetes taking dapagliflozin had a 47% reduction compared with placebo in the relative risk of a composite renal outcome, which included ESRD, renal death, and sustained ≥40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2. In the CANVAS Program (Canagliflozin Cardiovascular Assessment Study), canagliflozin also demonstrated significant reduction in a similar composite renal outcome (159–162). The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (8) targeted patients with type 2 diabetes and an eGFR ≥30 to <90 mL/min/1.73 m^2 with a urine albumin-to-creatinine ratio (UACR) >300 mg/g creatinine. Canagliflozin compared to placebo was shown to reduce the risk of a composite kidney outcome, including ESRD, doubling of serum creatinine, or death from renal or cardiovascular causes (HR 0.70, 95% CI 0.59–0.82). A recent meta-analysis of major clinical trials (159) also consolidated the above findings regarding the renoprotective effects of SGLT2 inhibitors in patients with diabetes. These findings strongly favor the idea that SGLT2 inhibitors should be routinely offered to individuals with type 2 diabetes who are at risk of progressive kidney disease.

The benefit of SGLT2 inhibitors was shown in patients with kidney disease with or without diabetes in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial (53). Dapagliflozin was shown to improve the primary composite kidney outcome (HR 0.61, 95% CI 0.51–0.72) in patients with an eGFR ≥25 to <75 mL/min/1.73 m^2 and a UACR ≥200 mg/g, irrespective of diabetes status. Based on this evidence, the FDA recently approved a new indication for dapagliflozin to reduce the risk of sustained eGFR decline, ESRD, cardiovascular death, and HHF in adults with CKD at risk of progression, with or without type 2 diabetes (162a). The ongoing EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin; NCT03594110) trial will investigate the effects of empagliflozin in patients with an eGFR ≥20 to <45 mL/min/1.73 m^2 irrespective of UACR or ≥45 to <90 mL/min/1.73 m^2 with UACR >200 mg/g, irrespective of diabetes status.

GLP-1 receptor agonists also have a renoprotective effect, albeit to a lesser extent than SGLT2 inhibitors (158). There is sufficient evidence that GLP-1 receptor agonists and DPP-4 inhibitors can be used safely in patients with impaired renal function (158).

Adequate blood pressure regulation also plays a key role in the primary prevention of diabetic nephropathy. Blood pressure control in type 2 diabetes is associated with a reduction in the incidence of microalbuminuria, particularly with the use of ACE inhibitors or ARBs. Agents in these two drug classes have a renoprotective effect via both reduction in blood pressure and direct effects on the kidney (158).

In the FIDELIO-DKD trial (9), treatment with finerenone resulted in lower risks of CKD progression, evaluated as a composite of kidney failure, a sustained decrease of ≥40% in eGFR from baseline, or death from renal causes.

Conclusion and Future Direction

CKD, HF, and type 2 diabetes are commonly associated with each other and lead to worse outcomes. Multidirectional relationships among all three comorbidities are well established. Data from trials of SGLT2 inhibitors, renin-angiotensin inhibitors, and selective MR antagonists provide support for the dual cardio- and renoprotective effects of these agents and the notion that the pathophysiologies of heart and renal disease are interconnected. Both SGLT2 inhibitors and MR antagonists have been shown to improve outcomes in patients with HFrEF who have diabetes (and in those without diabetes). The FIGARO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; NCT02545049) will provide further evidence regarding the use of finerenone in patients with type 2 diabetes and DKD. The use of SGLT2 inhibitors in patients with HFpEF is being studied in two ongoing trials: the EMPEROR-Preserved (Empaglifozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; NCT03057951) and the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; NCT03619213) trials. Although steroidal MR antagonists did not show definitive benefit in HFpEF patients in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial (163), a re-analysis of the trial taking into account regional differences and potential of nonadherence to trial procedures found that spironolactone use was associated with benefit in HFpEF as well (164). Finerenone is being studied in the HFpEF population in the FINEARTS (Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity & Mortality in Participants With Heart Failure and Left Ventricular Ejection Fraction Greater or Equal to 40%; NCT04435626) trial. Several ongoing trials are studying this issue further.

See references starting on p. 34.

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Socioeconomic and Racial Disparities Related to Chronic Kidney Disease and Type 2 Diabetes

Keith C. Norris, MD, PhD

Diabetes and chronic kidney disease (CKD) are growing public health problems that have become recognized globally as important causes of premature morbidity and mortality (165). According to the Centers for Disease Control and Prevention's National Diabetes Statistics Report, 2020, the overall estimated prevalence of diabetes (both diagnosed and undiagnosed) among U.S. adults is 13%, with higher rates noted for non-Hispanic Asian (14.7%), Hispanic (14.9%), and non-Hispanic Black Americans (16.9%) (166). Type 2 diabetes accounts for as many as 90–95% of diabetes cases, and among people with type 2 diabetes, an estimated 40% will develop microvascular evidence of diabetic kidney disease (DKD) (165). DKD is defined as urinary albumin excretion >30 mg/g creatinine and/or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for at least 3 months in the setting of longstanding diabetes and absence of other causes of CKD (167,168). Furthermore, type 2 diabetes is the leading cause of end-stage renal disease (ESRD) in the United States and worldwide (165). DKD disproportionately affects many racial and ethnic minority populations, as well as those with the lowest levels of education and income (169).

A poor social environment has been cited as a key factor in the historic and contemporary health inequities in the United States. Despite its recognized world leadership in health technology and medical care, the United States continues to rank last or near last among developed nations in preventable deaths (170). Steven A. Schroeder, MD, former president of the Robert Wood Johnson Foundation, has remarked that "Since all the actionable determinants of health—personal behavior, social factors, health care, and the environment—disproportionately affect the poor, strategies to improve national health rankings must focus on this population" (171). This serves as a clear directive to establish greater social equity and justice as part of a broad strategy to improve health outcomes and reduce health disparities.

Theoretical Framework for Adverse Socioeconomic Status and DKD

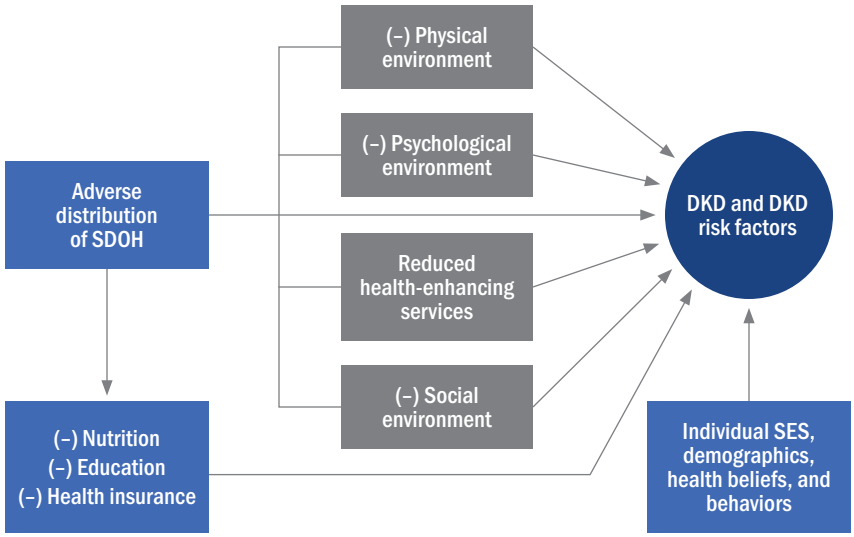
The major social determinants of health (SDOH) are societal resources such as education, employment, housing, health insurance, access to quality foods, access to quality health care, and more that occur in the setting in which people are born, grow up, live, work, and age (172–174). Inequities in the distribution of these structural and system-level resources with disinvestment in many racial and ethnic minority communities contribute to disparities in DKD incidence, progression, and complications. In the United States, this maldistribution of resources was established through historic discriminatory laws, policies, and practices specifically designed to disinvest in racial and ethnic minority communities and is termed "structural racism" (175,176). Many of these biased systems and practices continue today, and, with rare exceptions, there have been no efforts to establish equity in the distribution of SDOH to correct for longstanding deficits. This situation perpetuates health inequities and their downstream effects for racial and ethnic disparities for people with or at risk for DKD, as well as many other related medical conditions (175–177). Lack of access and exposure to high-quality SDOH can lead to a cascade of health risks for conditions such as DKD that include, but are not limited to, poor nutrition, being un- or underinsured, psychosocial stress, and depression (172–174,178,179), as well as what is called "weathering"—the health disadvantage resulting from cumulative lifetime exposure to adverse socioeconomic conditions and discrimination (180).

The World Health Organization has identified three key elements to improving health at a global level that are highly relevant for reducing disparities: *1*) improve the conditions of daily life, *2*) tackle the inequitable distribution of power, money, and resources—the global, national, and local structural drivers of those conditions of daily life, and *3*) develop a workforce trained in and raise public awareness about SDOH (181). To this end, a conceptual framework capturing key pathways through which socioeconomic disinvestment mediates DKD development, progression, and complications is presented in **Figure 1** (182).

Socioeconomic Status and Key Determinants of Health Values

The World Health Organization's Commission on Social Determinants of Health has found that poor health of low-income individuals is directly related to the social gradient in health within and across countries that is caused by the unequal distribution of power, income, goods, and services, both globally and nationally (181). Importantly, the commission has noted that unequal and unfair social policies, poor economic arrangements, and bad politics conspire to cause much of the health inequity in the world. This has been seen dramatically for many years in infectious disease morbidity and mortality and now more recently in chronic diseases such as cardiovascular disease, diabetes, and DKD (171,181). Socioeconomic status (SES) may considerably affect one's perception and values of seemingly mundane matters such as food, education, language, and worldview (183). These

FIGURE 1 SDOH and DKD. (–) indicates negative or adverse impact. Adapted from Wen M, Browning CR, Cagney KA. Soc Sci Med 2003;57:843–860.



perceptions can influence how patients prioritize many competing risks, and providers need to be cognizant of how these competing risks may affect health care recommendations. Key SDOH that most directly affect patients with or at risk for DKD are discussed below.

Nutrition

Low-income and minority communities face disparities in access to quality food caused by what are often described as "food deserts" (184). There are fewer supermarkets and more liquor stores and small convenience stores that sell little fresh produce or nutrient-dense foods and instead sell mostly high-fat, high-sugar, and energy-dense foods (184). Poor nutrition can adversely affect glycemic control and DKD progression.

Green Space Exposure

Low-income and minority communities suffer from reduced green spaces and reduced safety to use such spaces for exercise, a crucial component of DKD care. People who are exposed to more green spaces, especially within their own neighborhood, have been found to have an increased likelihood of physical activity and reduced risks of developing obesity and type 2 diabetes (185). Access to and use of green spaces can increase physical activity levels and thereby moderate the onset and progression of type 2 diabetes and DKD (185).

Education

Level of educational attainment has been shown to be associated with barriers to care in people with DKD. A variety of studies have demonstrated that level of education is related to control of DKD risk factors, as well as progression of DKD (184). Because educational attainment is not uniformly distributed across racial and ethnic groups, the adverse effects of limited education on DKD development and progression are more heavily levied on racial and ethnic minority populations.

SES

SES has also been shown to be associated with barriers to care for people with DKD. Several studies have demonstrated that higher income level is related to enhanced control of DKD risk factors and reduced progression of DKD (184). Because SES also is not uniformly distributed across racial and ethnic groups, the effects of low SES also have a greater impact on DKD in racial and ethnic minority populations (186).

Health Care Literacy

Health care literacy is commonly recognized as the cognitive skills needed to function effectively in the health care environment. Health care literacy is strongly associated with, but does not necessarily follow, an individual's level of educational attainment. In general, poor health literacy is associated with increased hospitalizations and emergency room use, reduced use of preventive services, and lower rates of medication adherence (184). Thus, low health care literacy may also contribute to racial and ethnic disparities in health service utilization and health outcomes for patients with DKD (184).

Health Insurance and Access to Care

In the United States, people with DKD who are un- or underinsured are less likely to receive adequate treatment for DKD risk factors such as hypertension, diabetes, and obesity and are also less likely to receive quality DKD care compared to individuals with DKD who have adequate health insurance (184). Racial and ethnic minorities in the United States are more likely to be un- or underinsured,

which contributes to DKD disparities (184). Lack of insurance can affect the affordability of medications and other aspects of care and delay timely nephrology referral for cases in which DKD is progressing, and these delays can contribute to earlier progression to kidney failure (169).

Special Considerations

Several unique aspects of racial and ethnic disparities have received more attention since the beginning of the coronavirus 2019 pandemic, highlighting social injustices and spurring global racial justice protests. In medicine, these events have prompted a closer examination of how race and ethnicity are used in research and clinical care. In the United States, race generally refers to someone's socially assigned phenotypic appearance, whereas ethnicity is commonly defined by culture and language (187). In a racially stratified society, race is a risk factor for racism, and it is racism that is the risk factor for poor health and disease. Race is who society says you are, and racism is what society does to you based on how it has categorized you.

By contrast, ancestry usually refers to one's homeland and, in medicine, the genetic variation within one's homeland. Importantly, ancestry is not directly related to race, although there may be some association, and even ancestry is difficult to ascertain given the tremendous admixture of racial and ethnic groups in the United States. This concept is important in understanding the genetic risk for CKD related to two relatively recently identified independent coding variants in the apolipoprotein L1 gene (APOL1), G1 and G2, which are found almost exclusively in people with recent West African ancestry (188,189). An estimated 13% of Black individuals in the United States have two APOL1 alleles, placing them at high risk for CKD (190), but racial group is a very poor surrogate for trying to identify the presence of APOL1 alleles associated with high risk for CKD. Although the majority of people with a high-risk APOL1 genotype will not develop CKD, there is presently no way to predict who and will not be affected. A two-hit hypothesis has been proposed that suggests that a high-risk APOL1 genotype alone does not lead to CKD, but a second hit, such as activation of a disease state or modifier genes, is required to initiate nephropathy (191). However, people with type 2 diabetes and APOL1 alleles associated with high risk for CKD do not appear to have an increased likelihood of developing DKD (191).

Another contentious issue that is relevant for people with DKD is the use of race in the formula for determining eGFR. The commonly used CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and MDRD (Modification of Diet in Renal Disease) study equations apply a race modifier of 1.16 and 1.21, respectively, for Black individuals (192,193). The increased value resulting from the modifier may delay care for Black Americans, who are at highest risk for progression to kidney failure (194). In addition, unlike age, race is a social construct and is not a biological variable. The use of race as a biological variable in individual-level formulas or algorithms is methodologically flawed and termed an "ecological fallacy" (195). Also, because there is a large degree of social and genetic heterogeneity within and across racial groups, assigning a single value to each Black individual represents a substantial aggregation bias (195). This is why we do not add or subtract a given value to each Black person's blood pressure measurement despite group differences in mean blood pressure levels. One's individual blood pressure level is what is measured. Many institutions have eliminated the use of race from the eGFR calculation, but formal recommendations regarding this issue from the National Kidney Foundation/American Society of Nephrology eGFR Workgroup have yet to be announced.

The Way Forward

In its *Standards of Medical Care in Diabetes—2021*, the American Diabetes Association (ADA) included recommendations for improving care and promoting health at a population level, including *1*) ensuring that treatment decisions are timely, rely on evidence-based guidelines, and are made collaboratively with patients based on individual preferences, prognoses, and comorbidities; *2*) aligning approaches to diabetes management with the Chronic Care Model to emphasize person-centered team care, integrated long-term treatment approaches to diabetes and comorbidities, and ongoing collaborative communication and goal-setting between all team members; *3*) ensuring that care systems facilitate team-based care and utilization of patient registries, decision-support tools, and community involvement to meet patient needs; and *4*) providing diabetes health care maintenance using reliable and relevant data metrics to improve processes of care and health outcomes, with attention to care costs (196). Although these recommendations are not specific to DKD, a multidimensional support program (i.e., one that includes disease knowledge, self-management, and motivation skills) addressing many of these recommendations has been shown to improve A1C, albuminuria, and physical activity in patients with DKD (197). Multidisciplinary care with a team composed of a primary care provider, nephrologist, diabetes educator, dietitian, social worker, pharmacy specialist, and nephrology nurse was also reported to significantly reduce the annual decline in eGFR (to approximately half the rate) compared to patients with usual care (184).

As noted above, multiple barriers to quality DKD care exist at the community level, especially in high-risk communities, and include having low health literacy, being un- or underinsured, and facing difficulty in accessing quality care. Other important barriers include lack of trust in the health system, which is related to poor treatment, and lack of respect as a fellow American, both within and outside of the health care system (172–174). Effective approaches to counter the impact of the maldistribution of SDOH that disproportionately afflicts racial and ethnic minority communities and DKD care are challenging because of the longstanding disinvestment in racial and ethnic minority communities.

Overcoming these barriers requires additional tailoring to the ADA recommendations summarized above to improve care and promote health at a population level in marginalized communities. The use of lay health educators or patient navigators, mobile clinics, and engagement of community-based and allied health professionals in early DKD management may also be effective (184,198,199). Working with social support networks in interventions that include patients' family members or close friends can assist in implementing and increasing adherence to DKD recommendations for lifestyle, nutrition, and pharmacologic therapy (198,199). With recognition that health literacy, educational attainment, and cultural beliefs and behaviors can vary widely across the diverse array of communities in our nation, several efforts to adapt existing educational materials to enhance DKD messaging should be undertaken and can include the use of novel strategies such as novellas or other short stories, brief videos, and social or digital media (198–200).

Conclusion

DKD remains a major health care issue and is beset by significant disparities in its incidence, progression, and complications. DKD disproportionately affects racial and ethnic minorities, as well as individuals with more limited education, lower SES, un- or underinsured status, and reduced access to health care. Because many barriers exist, population strategies are needed to increase DKD awareness, activate multidimensional support, and promote timely, high-quality care. The medical community should leverage its privilege to help advance progressive policy changes needed to address the inequitable distribution of SDOH and to fill gaps resulting from long-term disinvestment in racial and ethnic minority communities. Doing so would further efforts to reduce racial and ethnic health disparities and improve trust in the health care system within marginalized communities, improve health outcomes for all members of society, and assist our nation in manifesting its full potential.

See references starting on p. 34.

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Screening, Monitoring, Prevention, and Treatment Strategies for Chronic Kidney Disease in Patients with Type 2 Diabetes

Sam Dagogo-Jack, MD, DSc

Diabetes is a major risk factor for chronic kidney disease (CKD), and an estimated 20–40% of people with diabetes have evidence of CKD (109,201–205). In people with type 1 diabetes, CKD usually develops ≥10 years after diagnosis of diabetes. Because the exact time of onset of type 2 diabetes is often unclear and many patients may have had the condition for several years before diagnosis, CKD can manifest at diagnosis of type 2 diabetes. There is even evidence that CKD can occur in people with prediabetes (206,207).

CKD does not remit spontaneously; its severity gradually progresses to end-stage renal disease (ESRD) in the absence of intervention. Besides being the leading cause of ESRD, there is a markedly increased burden of cardiovascular morbidity, premature mortality, and health care expenditure associated with CKD (205,208–210). CKD is clinically silent at its early stages, and individuals with even advanced stages may lack pathognomonic symptoms. In some patients, polyuria and polydipsia may be clues to impaired urine concentration from CKD; however, such symptoms lack sensitivity and specificity and are often ignored. Complaints of weakness and lassitude, particularly in the setting of anemia, are other nonspecific symptoms associated with advanced CKD.

The natural history of CKD in patients with type 1 diabetes is characterized by the presence of diabetic retinopathy, albuminuria with an inactive urinary sediment, and progressive decline in estimated glomerular filtration rate (eGFR). People with type 2 diabetes exhibit these same features, with or without the presence of retinopathy (211). Furthermore, many people with type 1 or type 2 diabetes can have reduced eGFR without albuminuria, a pattern that is being increasingly observed (211,212). The corollary is that a person with diabetes with an active urinary sediment (showing cellular casts, red blood cells, or white blood cells), rapidly worsening or massive albuminuria, or sharp decline in eGFR requires evaluation by a nephrologist for alternative or atypical causes of kidney disease.

Unfortunately, owing to its largely asymptomatic nature, most patients in the early stages of CKD are not aware that they have the disease (202,212–214). Even among patients with severely reduced kidney function (glomerular filtration rate [GFR] <45 mL/min/1.73 m^2), ~50% may not be aware that they have CKD (212,213). Given the high morbidity and mortality risks associated with CKD, the enormous costs of managing ESRD, and the treacherously asymptomatic nature of the disease, increased surveillance through regular, targeted screening of at-risk individuals is the dominant strategy for containing the scourge of CKD.

Screening for CKD in People with Diabetes

The current approach to screening individuals for the presence of CKD is based on documentation of elevated urinary albumin excretion (albuminuria) and decline in eGFR (**Table 1**) (109,168,215–217).

Albuminuria

Glomerular hyperfiltration is a cardinal manifestation of incipient nephropathy, and measurement of albumin excretion in a 24-hour urine collection provides significant insight into renal health. Albumin excretion rates of 30–300 mg/24 hours (historically called microalbuminuria) indicate incipient nephropathy and predict progression to higher-grade albuminuria (>300 mg/24 hours, historically called macroalbuminuria) and decline in GFR in the ensuing several years (218,219). Because of challenges in obtaining adequate 24-hour urine collections from patients, the albumin-to-creatinine ratio (ACR) in random spot urine samples has been validated as a convenient and reliable alternative approach (168,220). The simple measurement of a spot urine albumin level alone by dipstick or other methods is inadequate for assessing renal

TABLE 1 Screening for CKD in Patients with Diabetes

Test	Frequency	Values
Albuminuria test in spot urine specimen, mg/g creatinine	▸ Type 1 diabetes: annually from 5 years after diagnosis ▸ Type 2 diabetes: annually from time of diagnosis ▸ More frequently in patients with values >300 mg/g to assess progression and response to treatment	▸ Normal: <30 ▸ Moderately increased: 30–300 ▸ Severely increased: >300
eGFR, mL/min/1.73 m^2	▸ Type 1 diabetes: annually from 5 years after diagnosis ▸ Type 2 diabetes: annually from time of diagnosis ▸ More frequently in patients with eGFR <60 mL/min/1.73 m^2, to assess progression and response to treatment	▸ Normal or high: ≥90 ▸ Mildly decreased: 60–89 ▸ Mildly to moderately decreased: 45–59 ▸ Moderately to severely decreased: 30–44 ▸ Severely decreased: 15–29 ▸ Kidney failure: <15

function, as such measurements are prone to false-negative and false-positive errors resulting from variations in urine concentration and hydration status (168,221). Therefore, a more appropriate approach is simultaneous measurement of albumin and creatinine concentrations in spot urine and derivation of the ACR (168).

A normal value for urinary ACR is <30 mg/g creatinine. Values of ≥30 mg/g indicate elevated ACR (**Table 1**).

The interpretation of ACR requires several careful considerations. First, there is a gradation of renal and cardiovascular risk even within the normal range of urinary ACR; therefore, a patient's full clinical profile must be considered before declaring low ACR values as evidence of normal organ function. Second, because of a high (≥20%) biological variability between urinary ACR measurements, it is recommended that the diagnosis of elevated albuminuria be based on positive results in at least two of three urine specimens obtained within 3–6 months (109,168,201,220,221). Note that urinary ACR has a continuous distribution of values; thus, differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (168,203,209,210). Urine albumin excretion can be affected by recent exercise, febrile illness, infection, heart failure (HF), severe hyperglycemia, uncontrolled severe hypertension, and contamination with menstrual flow, among other factors (**Table 2**). Therefore, care must be taken to avoid spurious results, and the test should be repeated to confirm doubtful values.

TABLE 2 Factors That Increase Urinary Albumin Excretion

- Exercise
- Febrile illness
- Urinary tract infection
- Hematuria
- Menstruation
- HF
- Severe hyperglycemia
- Severe hypertension

eGFR

eGFR is calculated automatically by most laboratories from the serum creatinine level, using well-validated formulas (109,168,211,216,217). Traditionally, the GFR estimation equations have applied a correction factor based on self-described race/ethnicity, but that step is currently under re-evaluation. Values of eGFR ≥90 mL/min/1.73 m^2 are generally normal or high, and decreasing values indicate gradations of decline in kidney function (**Table 1**). However, because of physiological age-related decline in renal function, the eGFR threshold for diagnosis of CKD in older individuals is somewhat imprecise (168). Urinary ACR and eGFR values are useful metrics for the screening, diagnosis, staging, prognostication, and management of CKD (109,168,201,202,211,216,217) (**Table 1**).

Current CKD screening guidelines recommend measurement of spot urinary ACR and eGFR at least annually in patients with type 1 diabetes of ≥5 years' duration and in all patients with type 2 diabetes from the time of diagnosis (168,211,216,217) (**Table 1**). Patients with diabetes whose tests reveal a urinary ACR >300 mg/g and/or an eGFR in the range of 30–60 mL/min/1.73 m^2 should be monitored more frequently to gauge the adequacy of treatment interventions (168).

Approach to Prevention and Treatment of CKD in People with Diabetes

Lifestyle Modification

Adoption of healthy lifestyle habits should be promoted in people with diabetes and CKD. In particular, smoking cessation should be encouraged and supported with proven medical interventions such as prescription of bupropion or varenicline and/or cognitive behavioral counseling (168,216,217,222). Current dietary recommendations for adjunctive CKD management have become less stringent than in the past. The dietary protein intake recommended for people with CKD not yet requiring dialysis treatment is ~0.8 g/kg body weight/day, similar to the daily allowance for healthy people. Dietary protein intake at this level has been shown to delay eGFR decline compared with higher levels of intake (168). Indeed, dietary protein intake >1.3 g/kg/day has been associated with worsening albuminuria and accelerated loss of kidney function (168,223). However, reducing dietary protein intake to <0.8 g/kg/day does not improve renal function or decline in eGFR and is not recommended (223,224). Once dialysis treatment has been initiated, it is prudent to recommend higher levels of dietary protein intake to guard against likely malnutrition from the hypercatabolic milieu of advanced CKD (223,224). Dietary sodium restriction to <2,300 mg/day may improve blood pressure control and decrease cardiovascular risk (225). On an individual basis, restriction of dietary potassium may be appropriate; patients with significant reduction in eGFR may have impaired urinary excretion of potassium with consequent risk of hyperkalemia (**Table 3**) (223,226).

TABLE 3 Approach to Prevention and Treatment of CKD in Diabetes

- Lifestyle modification
  - Appropriate dietary protein intake
  - Sodium restriction
  - Potassium management
- Optimization of blood pressure control
  - Preferential use of angiotensin system inhibitors
  - Consideration of MR antagonists
- Optimization of glycemic control
- Specific use of SGLT2 inhibitors
- Consideration of GLP-1 receptor agonists

Optimization of Blood Pressure and Glycemic Control

There is abundant evidence from randomized controlled trials (RCTs) that control of blood pressure and blood glucose can reduce the risk of CKD and delay its progression in people with diabetes (218,227–230).

Blood Pressure Control

Hypertension is a leading cause of CKD, a risk that can be mitigated by effective antihypertensive therapy (227,228,231–234). Reduction of blood pressure decreases the risk of developing albuminuria, in addition to conferring cardioprotective benefits (227,228,231–235). In patients with type 1 or type 2 diabetes who have already developed CKD (eGFR <60 mL/min/1.73 m^2 and urinary ACR ≥300 mg/g), treatment with ACE inhibitor or angiotensin receptor blocker (ARB) therapy delays the worsening of decline in renal function and progression to ESRD (3,168,236). The generally recommended target blood pressure level for cardiorenal protection in people with diabetes is <140/90 mmHg (168). Lower blood pressure targets (e.g., <130/80 mmHg) may be appropriate to further reduce the risks of cardiovascular disease (CVD) and CKD progression in selected patients (e.g., those with albuminuria ≥300 mg/g) (168). Based on their now well-documented cardiorenal protective benefits, ACE inhibitors and ARBs are the recommended first-line agents for blood pressure control in nonpregnant patients with diabetes, hypertension, an eGFR <60 mL/min/1.73 m^2, and urinary ACR ≥300 mg/g (168,216,217).

Combination therapy with an ACE inhibitor and an ARB has no benefits on CVD or CKD outcomes, may increase adverse events, and is therefore unwarranted (237). The fairly widespread clinical practice of prescribing an ACE inhibitor or ARB for normotensive patients with elevated albuminuria also is not evidence-based, as the benefit of that approach on renal outcomes has yet to be demonstrated in RCTs (168). Currently, treatment with an ACE inhibitor or ARB is not recommended for the primary prevention of CKD in normotensive patients with diabetes who have normal urinary ACR (<30 mg/g) and a normal eGFR (168).

The addition of a mineralocorticoid receptor (MR) antagonist (spironolactone, eplerenone, or finerenone) to background antihypertensive medication, including an ACE inhibitor or ARB, is an established clinical strategy for improving blood pressure control in patients with resistant hypertension (168,238). Preliminary studies have suggested that combination drug regimens that include an MR antagonist may reduce the risks of albuminuria and CVD (239). The findings of a recent, large RCT support the long-term beneficial effects of finerenone, an investigational nonsteroidal MR antagonist, on CKD and CVD outcomes in people with type 2 diabetes (9). Notably, the participants were already receiving treatment with the maximum recommended (or tolerated) dose of an ACE inhibitor or ARB. During a median follow-up of 2.6 years, treatment with finerenone, compared to placebo, resulted in an 18% reduction in the occurrence of the primary outcome (≥40% decline in eGFR from baseline or death from renal causes) and a 14% reduction in a secondary outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF) (9). Thus, patients with CKD and type 2 diabetes already receiving angiotensin system blocking agents experienced significant reductions in CKD progression, major CVD events, and HF after the addition of finerenone to the treatment regimen.

Glycemic Control

Care must be taken in the selection of medications and doses for lowering blood glucose in people with CKD to avoid increased risks of hypoglycemia, increased toxicity from drug accumulation, or loss of efficacy with declining eGFR that may occur with some drugs (240). The doses of certain drugs, including insulin, sulfonylureas, meglitinides, and some dipeptidyl peptidase 4 inhibitors, may require adjustments in patients with CKD (as indicated by serum creatinine or eGFR <60 mL/min/1.73 m^2 [201]).

The use of metformin, the most widely recommended initial drug for people with type 2 diabetes, has had restrictions based on kidney function, principally because of the risk of rare lactic acidosis (241). The 2016 U.S. Food and Drug Administration (FDA) revised guidance for the use of metformin in CKD stipulates that eGFR instead of serum creatinine be used to determine and monitor the safety of metformin therapy (242). According to the FDA guidance, metformin should not be initiated in patients with an eGFR <45 mL/min/1.73 m^2 and is contraindicated in patients whose eGFR decreases to <30 mL/min/1.73 m^2 while taking metformin. Metformin should be stopped temporarily shortly before or on the day of exposure to iodinated contrast media in patients with an eGFR of 30–60 mL/min/1.73 m^2 (242). Thus, metformin remains the first-line treatment for all patients with type 2 diabetes, including those with CKD, once the rubrics in the FDA guidance have been considered (242,243).

Achievement and maintenance of an A1C target of <7% has been shown in landmark clinical trials to reduce the risk of development or progression of CKD in people with type 1 or type 2 diabetes (45,46,49,228,229,244,245). In the Diabetes Control and Complications Trial (DCCT) (244), during a mean follow-up period of 6.5 years, patients with type 1 diabetes on intensive treatment (mean A1C ~7%) versus conventional treatment (mean A1C ~9%) experienced risk reductions of 35% for the development of albuminuria (30–299 mg/day) and 56% for albuminuria (>300 mg/day). Combined data from the DCCT and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) cohort (median follow-up 22 years) showed that intensive glycemic control during the DCCT was associated with a 50% risk reduction in the incidence of CKD (GFR <60 mL/min/1.73 m^2) and ESRD, despite convergence of the mean A1C to ~8% in the two treatment groups (228,229). In the UK Prospective Diabetes Study (UKPDS) (45), patients with newly diagnosed type 2 diabetes who were assigned to intensive treatment (median A1C ~7%) versus conventional treatment (median A1C 7.9%) decreased their risk of albuminuria and had a 67% risk reduction in doubling of plasma creatinine level (45). As was observed post-DCCT, the 0.9% difference in A1C

between groups during the UKPDS disappeared after 1 year of additional follow-up. Despite the glycemic convergence, 10-year post-UKPDS follow-up data showed persistence of the benefits of intensive glucose control on renal and other microvascular endpoints (24% risk reduction) (46).

These results from the UKPDS follow-up and the DCCT/EDIC studies support the concept of "metabolic memory" or "legacy effect" and emphasize the importance of early intervention (245). In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study (49), patients with type 2 diabetes who achieved a mean A1C of 6.5% showed a 21% relative reduction in the development of new or worsening nephropathy compared to a control group (mean A1C 7.3%) during a median follow-up period of 5 years. Note, however, that intensive glycemic control may be associated with a modest initial decline in GFR (possibly resulting from amelioration of hyperfiltration), as was observed in the DCCT. Reassuringly, after 10 years of follow-up (the EDIC phase), intensive glucose control was associated with a slower decline in GFR and higher mean eGFR compared with conventional therapy (228,229). Underscoring the importance of glycemic control, the DCCT investigators reported that the effect of improved glycemic control on GFR remained significant after adjustments for blood pressure, BMI, and the use of antihypertensive agents, including inhibitors of the renin-angiotensin-aldosterone system, and was fully attenuated after adjustment for A1C (228,229).

Together, the results from these landmark clinical trials demonstrate that achieving A1C levels of ~7% early in the course of diabetes is specifically associated with decreased risk of diabetic nephropathy (45,46,49,228,229,244,245). Furthermore, even in the setting of preexisting nephropathy, improved glycemic control can slow the rate of progression of CKD (49,228,229). Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in other large prospective randomized studies to delay the onset and progression of albuminuria and CKD in patients with diabetes (246,247). Despite the demonstrated value of intensive glycemic control, it should be cautioned that the presence of CKD can increase the risk of hypoglycemia, with deleterious consequences including potentially fatal cardiac arrhythmias (240,248,249). Thus, the target A1C should be individualized in patients with CKD, particularly those who harbor cardiovascular and other comorbidities (168).

Role of Antidiabetic Agents with Renoprotective Effects

Beyond general glycemic control and optimization of blood pressure, recent evidence supports the specific benefits of certain antidiabetic medications on renal health. The strongest such evidence pertains to drugs from the sodium–glucose cotransporter 2 (SGLT2) inhibitor class, but there is also limited evidence for the glucagon-like peptide 1 (GLP-1) receptor agonists.

SGLT2 Inhibitors

SGLT2 inhibitors improve blood pressure control by blocking renal tubular glucose reabsorption and inducing glycosuria, but these drugs also block renal sodium reabsorption and decrease body weight, blood pressure, and intraglomerular pressure (250,251). The clinically measurable renal effects of SGLT2 inhibitors include a transient decrease in GFR followed by sustained slowing of decline in GFR along with reduction of albuminuria (5,6,161,250,251). The beneficial effects on albumin excretion and GFR decline do not seem to be related to the glycemic effect of SGLT2 inhibitors, and their exact underlying mechanisms are under investigation. Some proposed mechanisms/mediators include effects of SGLT2 inhibitors on redox state, angiotensinogen expression, inflammation, and the sodium hydrogen exchanger in the kidney, among others (252–255). Significant reductions in various measures of kidney outcomes, including albuminuria, doubling of serum creatinine, decline in eGFR, and occurrence of ESRD or renal death have been observed when comparing SGLT2 inhibitors to placebo in patients with diabetes (5,6,156,161,251,256), including those with preexisting severe CKD or HF (53,257).

The currently approved SGLT2 inhibitors have different cutoff eGFR levels for dosing considerations based on the glycemic efficacy demonstrated in the populations studied in clinical trials (**Table 4**) (258–261). However, it is likely that the eGFR cutoffs might change after ongoing regulatory review of candidate SGLT2 inhibitor drugs

TABLE 4 FDA-Approved SGLT2 Inhibitors and GFR Considerations for Dose Selection for Glycemic Control

eGFR, mL/min/1.73 m^2	Canagliflozin (258)	Dapagliflozin (259)	Empagliflozin (260)	Ertugliflozin (261)
≥60	100 mg once daily with titration to 300 mg once daily	5 mg once daily with titration to 10 mg once daily	10 mg once daily with titration to 25 mg once daily	5 mg once daily with titration to 15 mg once daily
45–60	100 mg once daily	5 mg once daily with titration to 10 mg once daily	10 mg once daily with titration to 25 mg once daily	
30 to <45	▸ 100 mg once daily ▸ Approved down to an eGFR of 30 (Initiation is not recommended; however, patients with albuminuria >300 mg/day may continue.)	Limited glycemic benefit but no dose adjustment needed to decrease the risk of cardiovascular death or hospitalization for heart failure in patients with diabetes down to an eGFR of 30	▸ Do not initiate ▸ Discontinue if GFR falls into this range.	▸ Do not use in patients with an eGFR <30 ▸ Initiation is not recommended in patients with an eGFR of 30–60 ▸ Continued use is not recommended in patients with an eGFR persistently between 30 and <60

specifically for the treatment of patients with CKD. SGLT2 inhibitors are generally well-tolerated oral drugs, and their most notable adverse effects are an increased risk of genital mycotic infection, hypovolemic symptoms, and rare ketoacidosis (5,6,161,251). To minimize the risk of ketoacidosis, it is prudent for patients to withhold SGLT2 inhibitors during periods of prolonged fasting or critical illness or perioperatively. Patients with hypovolemia may benefit from a reduction in the doses of concomitant diuretic medications (217).

GLP-1 Receptor Agonists

In addition to the SGLT2 inhibitors, analysis of cardiovascular outcomes trials of GLP-1 receptor agonists has shown evidence of kidney benefits when assessed as secondary outcomes (7,51). Significant decreases in the composite measures of urinary ACR, new or worsening nephropathy, doubling of serum creatinine, ESRD, or death from ESRD have been reported for GLP-1 receptor agonists (liraglutide: 22% reduction vs. placebo, semaglutide: 36% reduction vs. placebo) (7,51). The GLP-1 receptor agonists significantly reduce the risk of atherosclerotic cardiovascular events and also have direct effects on the kidney that may explain the improved renal outcomes (262). However, pending the results of ongoing evaluations dedicated to patients with CKD, the weight of available evidence accords priority to SGLT2 inhibitors in the overall strategy of preventing progression of CKD in people with type 2 diabetes (**Table 3**) (168,262,263). Thus, consideration of GLP-1 receptor agonists would be most appropriate in patients with suboptimal glycemic control despite the use of metformin and an SGLT2 inhibitor or who cannot tolerate those medications. Based on current evidence, a long-acting GLP-1 receptor agonist is recommended, and the treatment should be initiated at the lowest dose and titrated slowly to minimize gastrointestinal side effects (217).

Monitoring CKD in People with Diabetes and Referring Patients to Nephrologist

Patients with CKD should undergo regular clinical surveillance and measurement of urinary ACR and eGFR to monitor disease progression, adverse drug effects, and other complications. Serum creatinine and potassium levels should be monitored periodically in patients treated with an ACE inhibitor, ARB, or diuretic, as alterations in creatinine and potassium levels may warrant treatment modification (168,216,217). It is prudent practice to document and assess the effects of exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs, aminoglycosides, and iodinated contrasts) as a possible explanation for any unexpected decline in kidney function parameters.

Modest elevations in serum creatinine can occur with exposure to ACE inhibitors and ARBs that should not cause undue clinical concern or necessitate abrupt discontinuation of life-saving treatment (168,264). Increases in serum creatinine up to 30% above baseline values after intensification of blood pressure control with these agents have been shown to be clinically benign and not associated with any increase in biomarkers of acute kidney injury (AKI) or risks of CKD progression or mortality (264,265). Thus, after careful evaluation and elimination of other factors, an increase ≤30% in serum creatinine in an otherwise stable and well-hydrated patient treated with an ACE inhibitor or ARB does warrant cessation of therapy (168,264,265).

The typical findings in diabetes-related CKD include long duration of diabetes (usually ≥10 years), presence of diabetic retinopathy, albuminuria, inactive urinary sediment, and gradual decline in eGFR (168,201,216,217). Patients who present with atypical findings, massive proteinuria, a rapidly declining eGFR, or other unusual features would benefit from referral to a nephrologist (168,216,217). Referral is also prudent whenever there is uncertainty about the diagnosis or etiology of kidney disease in a patient with diabetes. Other candidates for management in consultation with a nephrologist include patients with complex comorbidities (e.g., anemia of CKD, secondary hyperparathyroidism, and metabolic bone disease) and those with advanced CKD (eGFR <30 mL/min/1.73 m^2), who would require planning for renal replacement therapy for ESRD (**Table 5**) (109,168,201,216,217).

TABLE 5 Some Indications for Referral to a Nephrologist

- Clinical findings inconsistent with typical diabetic nephropathy
- Massive proteinuria
- Hematuria, casts, and/or active urinary sediment
- AKI or rapidly declining eGFR
- Anemia of CKD
- Complex comorbidities (e.g., hyperparathyroidism or bone disease)
- Advanced CKD (eGFR <30 mL/min/1.73 m^2)

The discovery of AKI, as evidenced by a sustained increase of ≥50% in serum creatinine over a relatively short time, along with a rapid decrease in eGFR, warrants immediate evaluation and action (266,267). The risk of AKI is higher in people with diabetes than in the general population (266,267). Risk factors for AKI include nephrotoxic drugs, medications that alter renal hemodynamics, and intravascular volume reduction from medical conditions (e.g., hemorrhage, diarrhea, and emesis), diuretics, and antihypertensive medications. Decreased fluid intake and volume loss from nausea and vomiting in patients with adverse reactions to GLP-1 receptor agonists also pose a risk for AKI. The transient decrease in eGFR within days of initiating treatment with an SGLT2 inhibitor is not a manifestation of AKI, and evidence from RCTs confirms the renoprotective effects of these agents (5,6,53,156,161,251,256,257). All patients at risk for AKI should undergo appropriate assessment and prompt referral to a nephrologist for proper care (168,216,217,268).

See references starting on p. 34.

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Slowing Diabetic Kidney Disease Progression: Where Do We Stand Today?

Sandra C. Naaman, MD, PhD, and George L. Bakris, MD, MA

Despite increasing awareness and great strides in treatment options, diabetes continues to be a global epidemic currently affecting well above 400 million individuals worldwide. This figure is expected to reach 600 million by 2035, affecting one in 10 individuals (269). Diabetes is the chief contributor to chronic kidney disease (CKD), followed by hypertension and prediabetic hyperglycemia (1), which, when taken together, capture close to 75% of CKD causes (138). Defined by the presence of diabetes and reduced estimated glomerular filtration rate (eGFR) to <60/mL/min/1.73 m^2, increased albuminuria (>300 mg/24 hours) or both, diabetic kidney disease (DKD) is a progressive disease that affects one in seven individuals worldwide eventuating renal replacement therapy (RRT) and premature death secondary to cardiovascular causes (2,270).

In 2010, the number of RRT recipients worldwide was 2.618 million, 78% of whom were on dialysis. This figure is expected to burgeon by more than twofold by 2030, reaching 5.435 million, based on demographic projections of "unhealthy" aging populations (271). Although lifesaving, RRT expansion is not economically sustainable for health care systems in developed nations and remains largely inaccessible to many low- to middle-income countries. Thus, several organizations launched by a U.S. government executive order have called for the development of novel approaches to identify therapeutic options to prevent or slow DKD progression, with the overarching goal of reducing the incidence of end-stage renal disease (ESRD) by 25% by 2030 (272). This article aims to provide an overview of the major clinical trials conducted within the past 20 years, addressing this critical clinical need. Specifically, we will review several therapeutic drug classes that have demonstrated renoprotective potential by halting the progression of DKD.

Angiotensin II Receptor Blockers

Albuminuria levels >30 mg/day are an established continuous variable associated with adverse cardiovascular outcomes, while levels >300 mg/day indicate established kidney disease associated with faster DKD progression (273,274). Two early randomized trials—RENAAL (Reduction of End Points in Non-insulin Dependent Diabetes With the Angiotensin II Antagonist Losartan) (3) and IDNT (Irbesartan Diabetic Nephropathy Trial) (4)—support the renoprotective effects of the angiotensin receptor blockers (ARBs) losartan and irbesartan in people with type 2 diabetes who have albuminuria >300 mg/day. In comparison to placebo, losartan achieved a 25% relative risk reduction in time to doubling of serum creatinine, a 28% risk reduction in time to ESRD, and a 35% decline in proteinuria. In a trial using the same endpoints, irbesartan showed a similar benefit pattern, with a 33% lower risk of doubling of creatinine and a 23% lower relative risk of glomerulopathy progression relative to the comparator groups. Notably, the renoprotective effects conferred by both ARBs in these separate trials were not attributable to any blood pressure differences observed between the active and control arms. This conclusion was confirmed by statistically correcting for any small blood pressure differences (275). The beneficial effects of ARBs on the kidney seem to extend to individuals with diabetes without overt proteinuria, as shown in the MARVAL (Microalbuminuria Reduction with Valsartan) trial (276), which showed a significant protein-lowering effect of valsartan, again independent of blood pressure effects.

Because ARBs curtailed CKD progression to some degree via mechanisms apart from significant blood pressure-lowering, they were integrated into the standard of care (277). Although these ARB trials reduced DKD progression to about a 4–5 mL/min/year loss, we still did not have a way to normalize the rate of decline to normality (i.e., 0.8 mL/min/year), as shown in **Figure 1** (3,4,9,53,236,278–281). Thus, the significant residual risk that remained in DKD patients drove the development of a spectrum of agents, all of which unfortunately failed to further slow nephropathy progression (**Figure 2**) (237,282–287).

The subsequent renal outcomes trials examined agents addressing mechanisms such protein kinase C (PKC)-ß inhibition, dual ACE inhibition/ARB blockade, transforming growth factor (TGF)-ß production inhibition, renin inhibition, and activation of the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway while inhibiting the nuclear factor-κB pathway; however, none of them successfully further slowed DKD progression, and

FIGURE 1 Historical perspective on slowing CKD progression associated with type 2 diabetes (3,4,9,53,236,278–281).

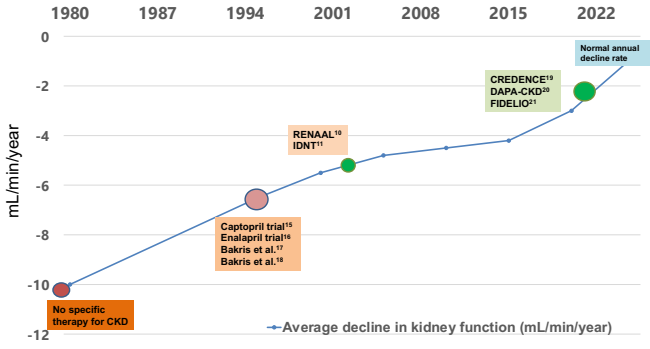
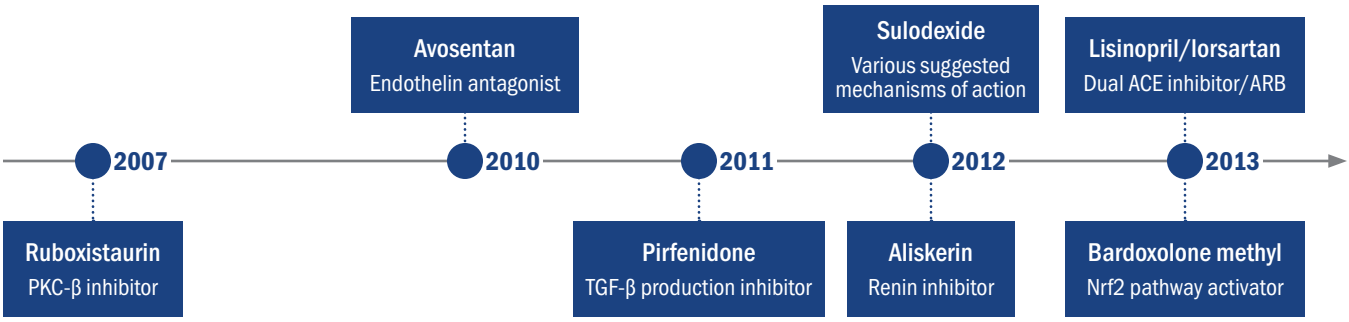


FIGURE 2 Summary of clinical outcomes trials focused on slowing DKD progression after the RENAAL and IDNT trials (237,282–287). These new therapeutic strategies largely failed to further slow nephropathy progression.



some were associated with even higher morbidity and mortality (237,285,288). The development of sodium–glucose cotransporter 2 (SGLT2) inhibitors for hyperglycemia management and the subsequent results of their cardiovascular outcomes trials (CVOTs) led to a marked paradigm shift in DKD management from a cardiorenal perspective.

SGLT2 Inhibitors

Although initially designed to manage hyperglycemia, SGLT2 inhibitors proved to possess pleiotropic effects that extend well beyond their glucose-lowering effects. They have been clearly shown to be cardiorenal risk–reducing agents irrespective of glycemic control and level of kidney function down to an eGFR of 25 mL/min/1.73 m^2 (53,281,289). In people with relatively healthy kidneys (i.e., an eGFR >60 mL/min/1.73 m^2), they aid in glycemic control by blocking SGLT2 receptors in the proximal tubule. Hence, renal absorption of glucose is withheld independent of insulin action. This mechanism results in osmotic diuresis, natriuresis, and reduction in intraglomerular pressure, often observed as a rapid decline in eGFR during the first weeks of treatment, followed by a slight increase toward baseline, then stabilization reflecting long-term renoprotection (290,291). Also, note that this initial reduction in eGFR does not occur among individuals with an eGFR well below 40 mL/min/1.73 m^2, yet renal and cardiovascular benefits are still seen (281,292). Moreover, the magnitude of blood pressure reduction is independent of glucose-lowering and eGFR, as similar levels of reduction are seen throughout the eGFR range of 25–80 mL/min/1.73 m^2 (293).

There is no unifying mechanism for how SGLT2 inhibitors reduce cardiovascular risk and preserve kidney and cardiac function; however, potential mechanisms have been reviewed (294–296). For example, blood pressure reduction occurs irrespective of sodium loss with glucose or eGFR level (293) and may relate to sympathetic inhibition of this class, as SGLT2 inhibition has been nicely shown to have effects such as renal denervation in an animal model (297). Extrarenal metabolic effects include reductions in body weight (specifically, in visceral fat); lower systolic and diastolic blood pressure, serum uric acid, and albuminuria; and either neutral or favorable effects on lipid fractions (292,298,299). **Figure 3** summarizes the panoply of mechanisms found to relate to changes seen with SGLT2 inhibitors.

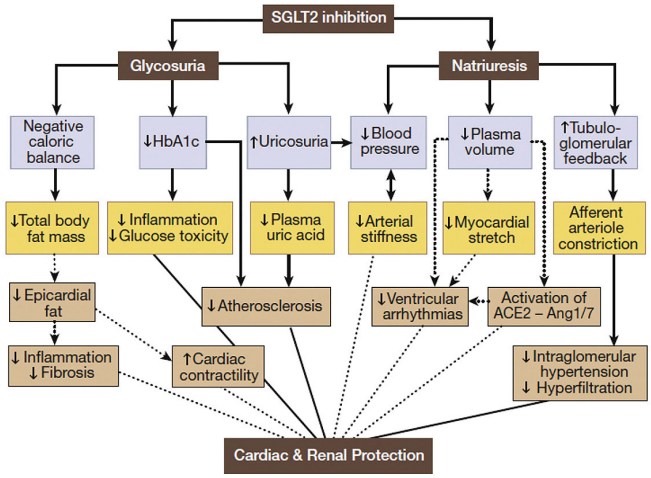
There are currently four U.S. Food and Drug Administration (FDA)–approved SGLT2 inhibitors that have been studied in large and appropriately statistically powered CVOTs and two renal outcomes trials. All have converged on favorable cardiovascular and renal outcomes. The most recent meta-analysis, by McGuire et al. (156) included the six trials that, despite heterogeneity across the different SGLT2 inhibitor agents concerning cardiovascular outcomes, found consistent reduction of hospitalization for heart failure (HHF) and progression of kidney disease. On closer examination of the individual trials included in this meta-analysis, patients in four of the six trials had baseline eGFRs between 60 and 90 mL/min/1.73 m^2, with high or moderately increased albuminuria (<300 mg/day). This argues for a relatively healthier subgroup of patients at lower risk for kidney failure. Moreover, these trials looked at kidney disease progression through secondary data analyses that were generally limited by smaller numbers of patients with ESRD (160,300–302).

These shortcomings were addressed in two dedicated trials examining renal outcomes with canagliflozin and dapagliflozin in patients with stage 3 CKD with macroalbuminuria at study entry (293,294).

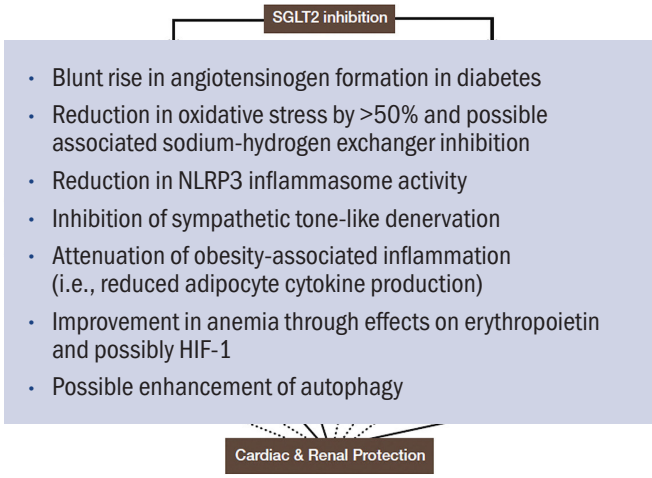
In the landmark CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (8), canagliflozin was compared to placebo in patients with type 2 diabetes, with the primary endpoint encompassing ESRD or a sustained eGFR of <15 mL/min/1.73 m^2), doubling of creatinine level, or death from renal or cardiovascular causes. The trial was terminated early due to clear renal benefits of canagliflozin. It showed a 30% lower relative risk of reaching the primary endpoint, a 32% lower relative risk of progressing to ESRD, and a significantly lower risk of cardiovascular death and HHF. Importantly, amputation and fracture risks were similar between canagliflozin and placebo. This result led to the FDA lifting its "black box" warning labeling requirement regarding these risks.

FIGURE 3 Contributing mechanisms to the panoply of effects of SGLT2 inhibitors. NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; HIF-1, hypoxia-inducible factor. Adapted from Rajasekeran H, Lytvyn Y, Cherney DZI. Kidney Int 2016;89:524–526 and Packer M. Am J Nephrol 2020;51:289–293.

Multidimensional effects with **eGFR >45 mL/min/1.73 m²**



Multidimensional effects that persist at **eGFR >45 mL/min/1.73 m²**



In another landmark study, DAPA-CKD (Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease) (303), participants, of whom about two-thirds had type 2 diabetes and about one-third did not, were randomized to receive either dapagliflozin or placebo against a background ACE inhibition/ARB treatment. Dapagliflozin resulted in a significant reduction in risk of a sustained decline in eGFR, progression to ESRD, or death from renal or cardiovascular causes and a 29% reduction in risk of death from cardiovascular causes or HHF irrespective of diabetes status. As a result, dapagliflozin is now also indicated to reduce the risk of sustained eGFR decline, ESRD, cardiovascular death, and HHF in adults with CKD at risk of progression, with or without type 2 diabetes (162a). Additionally, dapagliflozin is the only SGLT2 inhibitor to demonstrate 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, $P = 0.0035$). Safety outcomes data and adverse events were similar across both arms, with no reports of hypoglycemia or diabetic ketoacidosis in patients without diabetes, a concern that had been raised in the literature.

Taken together, all six trials add to the unequivocal benefits of SGLT2 inhibitors in both primary and secondary kidney disease prevention, even in patients with lower eGFRs. This is reflected in the American Diabetes Association's *Standards of Medical Care in Diabetes—2021*, which supports the use of an SGLT2 inhibitor if CKD or heart failure is present irrespective of glucose level or metformin use (168,277).

Glucagon-Like Peptide 1 Receptor Agonists

Glucagon-like peptide 1 (GLP-1) receptor agonists, another novel class of injectable antidiabetics and more recently available in an oral formulation, are glucose-dependent insulinotropic medications, the mechanisms of which involve enhancing both peripheral glucose uptake and glycogen synthesis, delaying gastric emptying, and promoting satiety (304). The myriad clinical effects beyond glycemic control have placed this drug class at center stage with endocrinologists, cardiologists, and nephrologists. In addition to reductions in weight, small reductions in systolic blood pressure, and improved lipid profiles, this incretin-based drug class has proved to have a role in curtailing CKD progression and reducing cardiovascular morbidity and mortality (305).

An analysis of renal outcomes of CVOTs showing a slowing of CKD progression was published recently (306); however, no specific primary renal outcomes trials with GLP-1 receptor agonists have been published. There are data from post hoc analyses and a recent meta-analysis suggesting that drugs in this class slow CKD progression (307–309). The ongoing FLOW (Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease) trial (263) is a randomized controlled trial examining the efficacy of semaglutide compared to placebo in people with type 2 diabetes and CKD that has sufficient statistical power for a primary renal endpoint. Its results are expected in 2024. Nonetheless, the impact of GLP-1 receptor agonists can be readily inferred from several important cardiovascular trials enrolling mixed patient populations with either CKD, coronary artery disease, or a combination of the two, which will be reviewed here.

The first trial to examine the efficacy of dulaglutide, a long-acting GLP-1 receptor agonist, in patients with type 2 diabetes and moderate to severe CKD was AWARD-7 (Dulagulide Versus Insulin Glargine in Patients with Type 2 Diabetes and CKD) (305). At baseline, the average mean eGFR was 38 mL/min/1.73 m², with one-third of patients at stage 4 CKD (eGFR 16–29 mL/min/1.73 m²). Over 1 year, insulin was associated with a steeper decline in eGFR (−3.3mL/min/1.73 m² compared to dulaglutide, which evidenced an eGFR decline of −0.7mL/min/1.73 m² for both low-dose (0.75 mg weekly)

and high-dose (1.5 mg weekly) groups. Notably, the gradients of eGFR decline between dulaglutide and insulin were maintained even among patients with a urine albumin-to-creatinine ratio >300 mg/g creatinine, who are at higher risk of CKD progression, 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. Compared to patients in the insulin group, fewer patients who received high-dose dulaglutide reached the composite renal endpoint of ESRD or >40% decline in eGFR (10.8 vs. 5.2%, P <0.038).

Similar trends were reported in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) (310), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) (7), and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) (52) trials, in which, compared to placebo, liraglutide, semaglutide, and dulaglutide achieved significant risk reductions of 22, 36 and 15%, respectively, in secondary composite renal endpoints (new onset of macroalbuminuria, doubling of serum creatinine, sustained 45% reduction in eGFR, RRT, or renal death), findings that were largely driven by macroalbuminuria reduction (7,52,310). In the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial (311), although secondary renal endpoints were not prespecified, post hoc analyses demonstrated a risk reduction of 40% associated with exenatide in combined renal endpoints, defined similarly to the above studies. The proportion of patients with an eGFR <60 mL/min/1.73 m^2 ranged from 17 to 28% in these four trials. The similarity in outcomes across the different medications argues persuasively for a class effect on DKD.

Collectively, these studies suggest that GLP-1 receptor agonists may be as efficacious as SGLT2 inhibitors for cardiorenal risk reduction, particularly for patients with lower renal reserve who are at higher risk for DKD progression. It would seem intuitive to consider combining GLP-1 receptor agonist and SGLT2 inhibitor regimens, given the absence of overlapping mechanisms of action and side effect profiles, to determine whether they work synergistically to optimize renal outcomes. This is a question being investigated by the EMPA-SEMA (Renal Effects of Treatment With Empagliflozin Alone or in Combination With Semaglutide in Patients With Type 2 Diabetes and Albuminuria) trial (312).

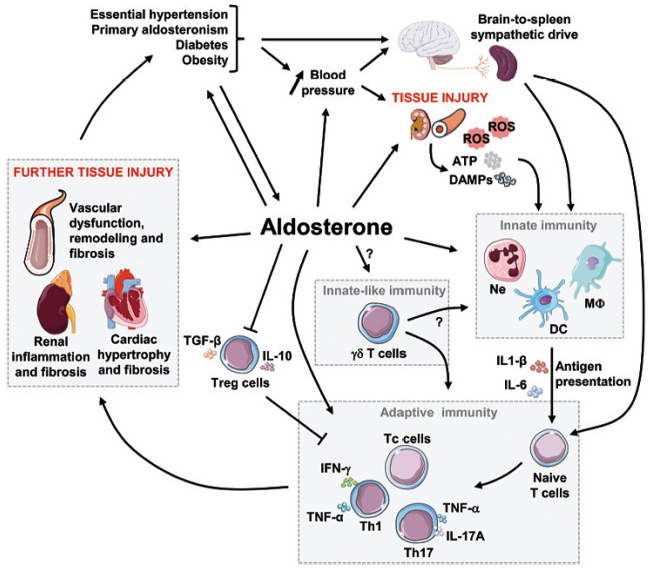
Mineralocorticoid Receptor Antagonists

Early studies establishing the renoprotective effects of renin-angiotensin system (RAS) blockade spurred the investigation of whether maximal inhibition of angiotensin II signaling would further slow DKD progression over either class alone. However, dual inhibition with combined ACE inhibitor and ARB therapy was unsuccessful in improving renal outcomes, as shown in the VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) trial (237) and ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) (288), and there was a notable increase in risk for acute kidney injury and hyperkalemia (237,288). Moreover, this was also seen when renin inhibition was used with an ARB in ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) (286).

Attention then shifted to a downstream target of the RAS, the mineralocorticoid receptor (MR), activated by aldosterone. This was the result of aldosterone's recognized deleterious effects on the heart and kidney and role in CKD pathophysiology (313). Aldosterone is a vital ligand of the MR, the activation of which mediates inflammation and fibrosis beyond blood pressure and sodium retention effects (313). Moreover, patients on long-term ACE inhibitor/ARB therapy evidence increased plasma aldosterone due to incomplete suppression of aldosterone, also known as "aldosterone escape," which is an important contributor to MR activation (314). MR antagonism exerts anti-inflammatory and anti-fibrotic effects on the kidney (313,315), heart, and vasculature that, when combined with ACE inhibitor/ARB therapy can exert sustained declines in proteinuria and blood pressure and better preservation of renal function (316,317), as shown in **Figure 4**.

The use of MR antagonists outside of heart failure has generally been limited because of a lack of data in DKD and important side effects such as hyperkalemia and gynecomastia associated with earlier-generation agents. With finerenone, a third-generation MR

FIGURE 4 Summary schematic of aldosterone's contribution to fibrosis and inflammation in diabetes over time. Excess aldosterone production occurring in diseases such as essential hypertension, primary aldosteronism, diabetes, and obesity contributes to increased blood pressure. Over time, elevated blood pressure and/or aldosterone cause renal and vascular injury, which activates the innate and adaptive immune systems, causing further tissue injury and thereafter exacerbating the detrimental effects of the initial disease. ATP, adenosine triphosphate; DAMP, damage-associated molecular pattern; DC, dendritic cell; IFN, interferon; IL, interleukin; MΦ, macrophage; Ne, neutrophil; ROS, reactive oxygen species; Tc, cytotoxic T cells; TGF, transforming growth factor; Th, T-helper cells; TNF, tumor necrosis factor; Treg, T regulatory cells. Reprinted with permission from Ferreira NS, Tostes RC, Paradis P, Schiffrin E. Am J Hypertens 2021;34:15–27.



antagonist that is a selective nonsteroidal agent with higher MR affinity and potency than eplerenone and spironolactone, respectively (312,313), strong inhibition of renal pro-inflammatory and pro-fibrotic markers has emerged as a promising option.

ARTS-DN (Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy) (239) was an initial tolerability study including patients with diabetes, macroalbuminuria, and an eGFR <60mL/min/1.73 m^2 that demonstrated significant dose-dependent albuminuria-reducing effects of finerenone despite modest nonsignificant blood pressure–lowering.

The largest phase 3 double-blinded randomized renal outcomes trial to date, FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) (9) investigated the efficacy and safety of finerenone in >5,700 participants with type 2 diabetes and moderate to severe CKD who were on a maximally tolerated RAS blocker. Over a median duration of 2.6 years, finerenone was associated with an 18% relative risk reduction (HR 0.82, 95% CI 0.73–0.93, $P = 0.001$) in the primary renal outcome, which was a composite of time to kidney failure, sustained eGFR decrease ≥40% from baseline, or renal death. There was also a 14% relative risk reduction (HR 0.86, 95% CI 0.75–0.99, $P = 0.03$) in the secondary cardiac outcome, which was a composite of time to death from cardiac causes, nonfatal myocardial infarction, nonfatal stroke or HHF (9). Adverse effects were balanced between finerenone and placebo. Of interest was the emergence of cardiovascular benefits as early as the first month in the experimental arm compared to renal benefits, which did not emerge until 12 months but then persisted throughout the study duration. These findings are in line with known underlying mechanisms of finerenone: mild natriuresis translating into a 2.4-mmHg reduction in systolic blood pressure and presumptive anti-fibrotic and anti-inflammatory effects halting progression of renal tissue remodeling. These clinical benefits may take several months to see, and this was especially true in FIDELIO-DKD, in which specific inflammatory and fibrosis markers were not incorporated into the study.

Parallel to FIDELIO-DKD is another phase 3 trial, FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) (318), a trial involving >7,000 people that is expected to be completed in summer 2021 will provide insight into this drug's cardiorenal efficacy and safety in people with type 2 diabetes and less advanced DKD. Readers should note, however, that, as of March 2021, finerenone was under evaluation but not yet approved by the FDA.

Summary

More than 400 million people are living with diabetes worldwide, and that number is projected to continue increasing steadily (269), driven by aging population trends, expanding urbanization, sedentary lifestyles, and rising obesity rates. Diabetes is the leading cause of CKD; combined with hypertension and prediabetes, it accounts for 75% of CKD causality (138). DKD, a "disease multiplier," is associated with significant cardiorenal morbidity and mortality. Treatment of DKD, when previously limited to RAS blockade and management of traditional metabolic risk factors for cardiovascular disease and CKD, did not sufficiently halt kidney disease progression (**Figure 1**). This outlook has changed in recent years with the advent of SGLT2 inhibitors and nonsteroidal MR antagonists, as well as, potentially, GLP1 receptor agonists.

Contemporary standard management of DKD now includes the use of an SGLT2 inhibitor alone or in combination with a GLP-1 receptor agonist if atherosclerotic disease is present, on top of an RAS blocker in individuals with cardiovascular and kidney disease (277). However, even under optimal conditions, there remains residual cardiorenal risk significant enough to spur the search for other therapeutic options. In addition to these drug classes, we have strong evidence from nonsteroidal MR antagonists showing both relative safety and clear efficacy in slowing DKD progression and reducing cardiovascular events (319).

Other agents that remain to be proven but have data supporting a possible role include the endothelin receptor antagonists. For example, atrasentan still holds some promise in a subset of patients whose cardiac status can handle a small increase in volume when it is dosed carefully. With distinct mechanisms of action and non-overlapping side effect profiles, some of these drug classes may even be combined to create additive or synergistic effects. This possibility was illustrated in a post hoc analysis of the SONAR (Study of Diabetic Nephropathy With Atrasentan) trial (320), in which patients with type 2 diabetes and CKD achieved larger reductions in albuminuria and body weight, a surrogate for fluid retention, when they were given an SGLT2 inhibitor in combination with atrasentan compared to those who took atrasentan alone. Finally, praliciguat, a soluble guanylate cyclase stimulator, remains to be tested to determine whether it can offer additional slowing of renal disease beyond relaxing vascular tone and reversing tissue remodeling (321).

These data, when taken together, suggest that nephrologists can finally celebrate the availability of new agents that slow CKD progression in diabetes from eGFR reduction of ~10–12 mL/min/year in 1980 to ~3 mL/min/year today. Unfortunately, the normal rate of kidney function decline is 0.7–0.9 mL/min/year; thus, residual risk remains. Future trials should aim to examine the additive or synergistic effects that may be conferred by using combinations of the therapeutics discussed here.

See references starting on p. 34.

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Conclusion

Matthew R. Weir, MD

This compendium provides an important and timely update for clinicians, reviewing many important considerations for improving clinical outcomes in patients with type 2 diabetes and chronic kidney disease (CKD). It is important to remember that, from an epidemiological standpoint, people with type 2 diabetes and CKD are much more likely to suffer from cardiovascular events than they are to reach end-stage renal disease. In fact, they are five times as likely to succumb from cardiovascular disease than to require renal replacement therapy. With improved opportunities to identify patients earlier in their course of disease and those with increased risk factors for progression, we may be in a better position than ever to implement primary rather than only secondary prevention strategies.

Unfortunately, most of the available data in this arena are from clinical trials focusing on secondary prevention in patients who have already lost more than half of their original kidney function. In large part, secondary prevention studies have been the norm because these studies tend to be shorter and more cost-effective for providing the hard endpoints needed for regulatory approval with specific indications. On the other hand, in clinical practice, primary prevention is a much more important opportunity to make a substantial difference in the quality and duration of our patients' lives. We therefore hope this compendium will be important to readers, not only by describing more precise, evidence-based approaches for disease progression mitigation, but also by helping them adopt and optimally implement both traditional and newer therapeutic options to improve clinical outcomes. Additionally, we hope this opportunity to understand more about risk factors, biomarkers, and phenotyping of patients who are more likely to exhibit kidney disease progression will encourage readers to focus not only on secondary intervention, but also on primary prevention of CKD in their patients with diabetes.

Toward that end, our focus for patients with diabetes and CKD should be on earlier identification, education, and intervention using guidelines-based and carefully individualized approaches. The discussion provided by Dr. Keith C. Norris (p. 19) about the need to correct disparities in clinical care is also a particularly important consideration for diabetic kidney disease treatment. So, too, is the current conversation about the potentially deleterious effect of modifying GFR estimation equations based on patients' race and whether this practice should be halted to reduce bias and inequities in the timely provision of appropriate treatment.

In the meantime, it is encouraging that we now have more therapeutic opportunities. Moving forward, it will be important for our patients to have access to newer therapies and the ability to avoid the pitfalls of prescription regimens that require substantial out-of-pocket copayments and laborious prior authorizations. We hope readers will find the data and practical strategies presented throughout this compendium helpful in their clinical practice and that they will appreciate and embrace the wealth of new clinical options to improve the health and lives of their patients with type 2 diabetes and CKD.

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