Diabetic Kidney Disease and the Cardiorenal Syndrome
Old Disease, New Perspectives

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KEYWORDS

- Diabetes • Cardiorenal syndrome • Diabetic nephropathy • Chronic kidney disease
- Blood pressure variability • Albuminuria • Proteinuria

KEY POINTS

- Diabetic nephropathy should be studied and treated in the context of cardiorenal syndrome, with a focus on the complex intertwined metabolic changes, which increase risk for chronic kidney disease and cardiovascular disease.
- Blood pressure and glycemic control are crucial for prevention and treatment of diabetic kidney disease.
- Newer drugs for achieving glycemic control have an important role in the treatment of type 2 diabetes mellitus in patients with cardiorenal syndrome.
INTRODUCTION

Prevalent chronic kidney disease (CKD) in the United States has increased over last few decades and comprises an alarming 13% of the US general population. Diabetes is recognized as the leading cause of CKD and end-stage renal disease (ESRD), and accounts for about 40% of ESRD cases in the United States. It is estimated that CKD affects more than 35% of adults with diabetes and nearly 20% of adults with hypertension. The expansion of CKD can be explained, in part, by the increased prevalence of obesity and diabetes, thus raising concerns for even more pronounced trends in the future. Regardless of cause, CKD is prevalent enough to be considered a critical public health concern, especially with the associated increased morbidity and mortality from cardiovascular disease (CVD). In this context, diabetic kidney disease (DKD) is a clinical syndrome characterized by early glomerular hyperfiltration and albuminuria, followed by increasing proteinuria and a decline in glomerular filtration rate (GFR), blood pressure increase, and high risk of CVD morbidity and mortality. The cause of this disease, although it is increasingly common because of the global expansion of diabetes and obesity, is poorly understood.

PATHOLOGY OF DKD

DKD has been studied extensively over the years, but our understanding of this complex disease process is far from complete. It is generally accepted that diabetes is associated with diverse structural changes in the kidney; all structural compartments are affected, leading to functional impairments at all levels of the nephron. Three basic steps have been described in progression of DKD: (1) glomerular hypertrophy and hyperfiltration, (2) inflammation of the glomeruli and tubulointerstitial area, and (3) apoptosis of cells and accumulation of extracellular matrix.

The hyperglycemia observed in diabetes contributes to a microinflammatory, oxidative stress milieu and extracellular matrix expansion within the kidney. There are 3 critical abnormalities including intracellular metabolism, formation of advanced glycation end products, and intraglomerular hypertension implicated in development of glomerular endothelial and mesangial cell injury. These pathologic changes are associated with cellular injury, expression of adhesion molecules, and macrophage infiltration in kidney tissue.

Expansion of the mesangium, thickening of the glomerular basement membrane (GBM), and hyalinosis of afferent and efferent arterioles are the characteristic lesions of DKD. It is generally believed that thickening of GBM and expansion of mesangium occur early in the course of diabetes. Diffuse global mesangial expansion is seen in diabetes, and it is primarily caused by an increase in extracellular matrix, with limited contribution from increase in mesangial cell volume. Kimmelstiel-Wilson nodules (acellular to paucicellular nodular accumulations of mesangial matrix) have been described in DKD. These nodular sclerotic lesions occur in patients with advanced DKD, and their presence is considered to mark the transition from early to more advanced stages of DKD. Kimmelstiel-Wilson nodules are not pathognomonic of DKD, because these lesions can be seen in other conditions like monoclonal immunoglobulin deposition disorders, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, and amyloidosis. In parallel, hyaline deposition in the glomerular arterioles is another typical histologic feature of DKD. Hyalinosis and the resultant hyaline appearance (homogeneous and glassy) is caused by insinuation of plasma proteins into the vascular wall.

Alternatively, loss of integrity of the filtration barrier and podocyte injury with effacement of foot processes and loss of podocytes are other microscopic changes evident in DKD.
in DKD that play important roles in the development of progressive sclerosis and proteinuria.9

Recently, DKD in type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM) has been classified based on severity of glomerular lesions. Classification based on glomerular lesions has been chosen over interstitial or vascular lesions, because of ease of recognition and good interobserver reproducibility. In addition, it has been suggested that severity of chronic interstitial and glomerular lesions correlate closely. The pathologic classification of DKD as proposed by the Renal Pathology Society10 is: class 1, diabetic injury with GBM thickening (>2 standard deviations from normal); class 2, mesangial expansion; 2a, mild mesangial expansion; 2b, severe mesangial expansion; class 3, nodular sclerosis (Kimmelstiel-Wilson lesion); class 4, advanced diabetic glomerulosclerosis: global sclerosis involving more than 50% of glomeruli in addition to the changes described earlier. Ongoing basic science and clinical research is helping shape our understanding of DKD pathogenesis and correlation between histologic lesions of DKD and progression of clinical DKD.

THE CARDIORENOAL SYNDROME AND DKD

Involvement of both kidneys and the cardiovascular system is common in conjunction with overweight/obesity, metabolic abnormalities, hypertension and early T2DM. Thus, it is important to understand how involvement of 1 organ system contributes to the dysfunction of the other, and these complex interactions have been captured with the emergence of the concept of cardiorenal syndrome (CRS).7,11–13 Risk factors that influence heart and kidney disease like overweight or obesity, hypertension, insulin resistance, and metabolic dyslipidemic function are the defining components of CRS (Fig. 1).11 The presence of hypertension, obesity, and hyperinsulinemia are independently associated with reductions in kidney function.12 The interaction of these factors and their metabolic and immunologic effect should be referred to as the CRS. Obesity is associated with altered intrarenal physical forces, inappropriate activation of the renin-angiotensin system (RAS) and sympathetic nervous system, and decreased activity of endogenous natriuretic peptides, which contribute to increases in blood pressure and altered responses to handling of glucose in individuals with insulin resistance.14 Thus, the various components of CRS interact via complex intertwined pathways and result in the loss of renal structure and function.

IMPACT OF HYPERTENSION ON DKD

There have been several seminal studies describing the importance of hypertension to cardiovascular mortality in individuals with DKD. In this context, approximately 66% of individuals with an estimated GFR (eGFR) less than 60 mL/min/1.73 m² have hypertension and as eGFR diminishes over time, the prevalence rates increase from 36% in stage 1 to 84% in stages 4 to 5 CKD.15 Because increases in blood pressure dictate cardiovascular mortality to some extent, it has been noted that mortality caused by CVD is 10 to 30 times higher in individuals with kidney disease compared with the general population: a relationship that extends into earlier stages of DKD.16 This relationship has been described as a continuous relationship: with reductions in GFR and increases in proteinuria comes a graded increase in CVD.17 Moreover, recent studies support the notion that even early stages of CKD pose a significant risk of CVD.18

Control of blood pressure in diabetes has been studied extensively, and stricter blood pressure targets have been tested over time. Many studies have shown the beneficial effects of blood pressure control on various outcomes in patients with diabetes; however, blood pressure targets have been a source of debate for several
years. There are sufficient data to support blood pressure control in T2DM, because this control reduces proteinuria and progression of DKD. The United Kingdom Prospective Diabetes Study (UKPDS) suggests the potential microvascular benefits of blood pressure control in patients with diabetes, wherein 758 patients with T2DM were randomized to tight blood pressure control (<150/85 mm Hg) and 390 to less tight control (<180/105 mm Hg). Mean blood pressures of 144/82 mm Hg and 154/87 mm Hg were achieved in the 2 groups, respectively. Fewer patients in the tight control group had urine albumin concentration greater than 50 mg/L than in the less tight control group at 6 years, although these differences were not significant at 9 years of follow-up. Data from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial along with the AASK (African American Study of Kidney Disease and Hypertension) trial suggest that tight blood pressure control (<120/70 mm Hg) in the context of diabetes and proteinuria improves kidney-specific outcomes. In the ADVANCE trial, there were
11,140 enrolled patients with T2DM, who were randomly assigned to blood pressure treatment with fixed combination perindopril-indapamide or placebo. During the follow-up, mean systolic blood pressure (SBP) 134.7 and 140.3, and mean diastolic blood pressure (DBP) 74.8 and 77.0 mm Hg was attained in the active treatment and placebo groups, respectively. Active treatment not only decreased the risk for onset and progression of microalbuminuria, it also increased the chance of regression of microalbuminuria.20

Over time, evidence has accumulated to suggest renal benefits of tight blood pressure control in hypertensive patients with diabetes, and has raised questions about treatment threshold. This question was addressed in the Appropriate Blood Pressure Control in Diabetics (Normotensive ABCD) study. Normotensive ABCD is a prospective randomized trial designed to study the effects of decreasing blood pressure in normotensive (blood pressure <140/90 mm Hg) patients with diabetes. A total of 480 patients were randomly assigned to intensive DBP control (target DBP of 10 mm Hg < baseline) and moderate DBP control (target DBP 80–89 mm Hg). The intensive treatment group was treated with nisoldipine or enalapril, and the moderate-treatment group with placebo. Over a 5-year follow-up period, intensive blood pressure control (mean blood pressure 128/75 mm Hg) was associated with decreased risk for progression to incipient nephropathy and diabetic nephropathy in patients who were normotensive at baseline.22

The importance of blood pressure control in patients with diabetes cannot be overemphasized. Blood pressure control is paramount for preservation of kidney function in patients with diabetes, especially because risk for progression to ESRD is increased up to 7-fold in patients with concomitant T2DM and hypertension.23

NONDIPPING BLOOD PRESSURE/PULSE PATTERN IN DIABETES

A characteristic of diabetes includes a disproportionate increase in SBP, with a loss of nocturnal dipping of blood pressure and heart rate, commonly referred to as nondipping.24 In normotensive patients, there is a circadian regulation of blood pressure wherein there are nocturnal drops in blood pressure of approximately 10% to 15%, commonly referred to as dipping. Alternatively, nondippers have less than the usual 10% decline at night. Nondipping is frequent among diabetic patients, as shown on ambulatory blood pressure monitoring. This nondipping pattern is caused, in part, by dysfunction of the autonomic nervous system, which is often present in individuals with T2DM and is characterized by a reduction in relative parasympathetic activity; it is believed to contribute to the 5-fold to 7-fold increase in sudden death in diabetic patients.24,25 Studies have shown that the nondipping pattern of blood pressure is associated with microalbuminuria, overt proteinuria, and higher morbidity and mortality in patients with diabetes.26 In this context, use of ambulatory blood pressure for measurement of dipping status is superior to office blood pressure in predicting target organ involvement, such as proteinuria and left ventricular hypertrophy.24

BLOOD PRESSURE VARIABILITY AS A RISK FACTOR FOR DKD

There are several modifiable risk factors that predict development of incipient and overt kidney disease in people with obesity and diabetes.27,28 Traditional risk factors for DKD include long-term poor glycemic control, systemic and glomerular hypertension, hypercholesterolemia, urine albumin excretion (UAE) rate, intrauterine growth retardation, and smoking.27–29 With regard to hypertension, attention has traditionally been focused on systolic, diastolic, and mean blood pressure with the assumption that conventional clinic readings depict a patient’s true blood pressure and predict adverse outcomes.30 Blood pressure variability has been considered a random
phenomenon of little clinical significance, although accumulating data suggest that visit-to-visit variability in blood pressure and episodic hypertension might affect cardiovascular and other target organ outcomes.30,31 Emerging data also suggest that different drug classes affect blood pressure variability differently. Calcium channel blockers and nonloop diuretics decrease blood pressure variability, whereas β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) increase the blood pressure variability.32

A post hoc analysis of data from DCCT (Diabetes Control and Complications Trial) shows that a patient with SBP variability of 13.3 mm Hg has a risk 2.34 times higher for kidney disease compared with a patient with variability of 3.7 mm Hg.33 Observational data from a retrospective cohort study involving 354 patients with T2DM suggest that individuals who have greater visit-to-visit SBP variability might be at risk for development and progression of proteinuria.34 Recent data from multiple cohorts involving patients with previous transient ischemic attacks and treated hypertension show a strong predictive value of visit-to-visit variability in SBP and maximum SBP for stroke and coronary events, independent of mean systolic pressures. Data from this study emphasize the risks of episodic hypertension, but do not prove a causal link between stroke and blood pressure variability or maximum SBP.35 Data from a relatively small longitudinal retrospective observational study involving 374 elderly patients with CKD showed association between visit-to-visit blood pressure variability and all-cause mortality. This study failed to show association between blood pressure variability and progression of CKD.36 Data accumulating from other studies points that visit-to-visit SBP variability might be associated with all-cause mortality and progression of vascular disease independent of mean arterial pressures in patients with or without diabetes.34–39

Results of a meta-analysis40 suggest that variability of SBP between arms could be helpful for identification of people at increased risk for vascular disease. These findings have prompted investigators to study the role of blood pressure difference between arms further and to explore its predictive value for other outcomes. Recently, investigators have studied the role of difference in SBP between arms and between lower limbs, in predicting risk for DKD. Initial data suggest that such blood pressure differences could be novel risk markers for DKD.41

Accumulating data challenges the notion that mean arterial pressure or usual blood pressure is a sufficient predictor of vascular events and stresses the need to analyze the available data and to explore the roles of other factors like blood pressure variability. Blood pressure variability is difficult to quantify and it is unclear how to incorporate it in to clinical practice. Further research is needed to better quantify associated risks and treatment parameters.

**USE OF ACE INHIBITORS OR ARBS IN DKD**

The treatment of hypertension in those with DKD includes both nonpharmacologic and pharmacologic approaches. However, in the presence of reduced blood pressure in DKD, use of pharmacologic strategies with interruption of the RAS with ACE inhibitors or ARBs is a primary risk-reduction strategy.23,42–45 Available data suggest that ARBs might have renal benefits independent of the SBP decreasing effect in patients with T2DM.43,44,46 Data from a study that compared the renoprotective effects of telmisartan and enalapril suggest that ARBs and ACE inhibitors are equally effective in preventing loss of kidney function in patients with T2DM and early DKD.47 Data from another large study show that losartan has significant beneficial effects on kidney function in patients with T2DM. Small differences in blood pressure were noted between the losartan and placebo-treated groups, and it remains unclear to what extent
the renal benefits in the group treated with losartan could be attributed to the lower blood pressure. Data from the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) trial also showed that the use of olmesartan was associated with delay in onset of microalbuminuria, but again there were subtle differences in blood pressure between the 2 treatment groups.

However, the benefit of dual RAS blockade has been in question. Data from ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) suggest that combined treatment with an ACE inhibitor and ARB was more effective than ACE inhibitor alone in reducing proteinuria, but the combination was associated with less desirable renal outcomes and faster decline in GFR. Available data suggest that individual components of RAS blockade help preserve kidney function better than other antihypertensives, at least in people with proteinuria.

**EFFECTS OF CKD ON GLUCOSE HOMEOSTASIS AND ASSESSMENT OF GLYCEMIC CONTROL**

Diabetes has been implicated in the development and progression of CKD, but progressive renal dysfunction also induces complex changes in insulin metabolism and clearance and affects glucose homeostasis in patients with diabetes. CKD is associated with increased insulin resistance on one hand and decreased insulin clearance on other. A decrease in GFR is associated with decrease in metabolic clearance of insulin, which becomes apparent as GFR decreases lower than 15 to 20 mL/min/1.73 m². Usually, as renal function declines, peritubular insulin uptake increases and maintains insulin clearance, but as GFR declines to levels lower than 15 to 20 mL/min/1.73 m², peritubular insulin uptake is unable to compensate for decreased renal function. With progression of CKD, the degradation of insulin in the liver and muscle is also impaired because of accumulation of the uremic by-products. This decreased insulin clearance can decrease the insulin requirements in diabetes and can lead to hypoglycemic episodes. The decreased insulin clearance in CKD is counterbalanced by increased insulin resistance and decreased insulin production in patients with CKD. Many other factors like loss of appetite, malnutrition and deficient renal gluconeogenesis and catecholamine release affect glucose homeostasis in renal disease. Complex interactions of multiple divergent pathways make the determination of insulin requirement challenging in patients with DKD.

Lack of a standardized clinical test for monitoring glycemic control in DKD complicates management of diabetes in this patient subgroup. Glycated hemoglobin (HbA1c), which is widely used to evaluate glycemic control in diabetes, provides a retrospective assessment of glycemic control. HbA1c has been found to reliably access glycemic control in patients with diabetes, but its accuracy in patients with DKD is questionable. HbA1c levels are affected by high urea levels, uremic acidosis, reduced red blood cell survival, and frequent blood transfusions, and hence there is a potential for erroneous glycemic control estimates in patients with DKD.

Other markers of glycemic control such as glycated albumin and serum fructosamine assess glycemic control over 2 weeks, but these are unreliable in conditions affecting albumin metabolism. These tests have not been standardized and are not used frequently in clinical practice. Further studies are required to assess their use for diagnosis of diabetes and evaluation of glycemic control.

**MARKERS OF DKD AND PROGNOSTIC VALUE OF EGFR AND MICROALBUMINURIA**

Traditionally, eGFR and UAE have been used to define and to follow progression of DKD. In clinical practice, eGFR is estimated using clearance of endogenous
creatinine. Release of creatinine into circulation is variable and depends on factors like age, gender, muscle mass, diet, volume status, medications, and so forth. Creatinine clearance further tends to overestimate GFR, because of tubular secretion of creatinine. Several equations like Cockcroft-Gault and Modification of Diet in Renal Disease 4-variable (MDRD) have been used to improve the accuracy of GFR estimation, but these equations are less than perfect.2 Recently, the Chronic Kidney Disease Epidemiologic Collaboration (CKD-EPI) equation was developed in an attempt to overcome the limitations of the MDRD equation. The CKD-EPI equation estimates GFR more accurately, especially at eGFR greater than 60 mL/min/1.73 m².54

Other markers of GFR such as cystatin C have been studied, but have not received widespread acceptance in clinical practice because of associated costs. Limitations of biomarkers for acute kidney injury and CKD have prompted active interest in study of biomarkers. Many biomarkers are under investigation, including urinary podocytes, neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, Smad-1, connective tissue growth factor, and transforming growth factor β.2

Along with eGFR, UAE is used to monitor progression and for staging of DKD. Although debatable, microalbuminuria is considered a risk predictor for progression to overt DKD and for CVD. Screening for microalbuminuria is widely recommended for risk stratification. Numerous population-based and intervention studies support microalbuminuria as a risk factor for CVD and as a strong predictor of cardiovascular morbidity and mortality in patients with diabetes.55,56 Data from a study of 3431 diabetic patients in the United Kingdom57 show that eGFR declined rapidly in people with macroalbuminuria and microalbuminuria, at rates of 5.7% and 1.5% per annum, respectively. The progression of DKD was slower in patients with normalalbuminuria: an eGFR decline of only 0.3% per year. Recently, a post hoc analysis of the HUNT-2 (Nord-Trøndelag Health) study58 showed that CKD progression risk increases substantially, in presence of microalbuminuria or macroalbuminuria. Data from this analysis suggest a strong synergistic interaction between albuminuria and reduced eGFR, which together confer higher risk of progression to ESRD than is attributable to either risk factor individually.58 This study highlights the importance of using UAE in combination with eGFR for better classification and risk stratification of patients with CKD.58

The risk for all-cause and cardiovascular mortality increases with increase in UAE and decrease in eGFR. Data from a large retrospective study involving 1,120,295 adult patients showed that low eGFR (≤60 mL/min/1.73 m²) was independently associated with increased risk of death, cardiovascular events, and hospitalization. The risks were substantially increased when eGFR decreased further to levels lower than 45 mL/min/1.73 m². The adjusted hazard ratios for death were 1.2 (95% confidence interval [CI], 1.1–1.2), 1.8 (95% CI, 1.7–1.9), 3.2 (95% CI, 3.1–3.4), and 5.9 (95% CI, 5.4–6.5) for eGFR 45 to 59, 30 to 44, 15 to 29, and less than 15, respectively.17 Data from RIACE (Renal Insufficiency And Cardiovascular Events), a cross-sectional study involving 15,773 patients with T2DM,59 led to similar conclusions. The data further showed that low eGFR and albuminuria ≥10.5 mg/24 h are associated with coronary artery disease in patients with T2DM. A meta-analysis of albumin-to-creatinine ratio (ACR) data from more than 1 million participants and urine protein dipstick data from 112,310 participants showed a significant increase in mortality risk at low eGFR (≤60 mL/min/1.73 m²) compared with optimum eGFR (90–104 mL/min/1.73 m²).6 Albuminuria was measured by ACR or urine dipstick in the included studies. The analyses showed that even trace protein on urine dipstick is associated with increased mortality in the general population, independent of eGFR and traditional cardiovascular risk factors.6 The hazard ratios for all-cause mortality were 1.20 (95% CI, 1.15–1.26), 1.63 (95% CI, 1.50–1.77) and 2.22 (95% CI, 1.97–2.51) for ACR 1.1 mg/mmol, 3.4 mg/mmol, and
33.9 mg/mmol, respectively, compared with ACR of 0.6 mg/mmol. These findings highlight the importance of urine dipstick, an imprecise but inexpensive measure of albuminuria, in detection of DKD.

Although some data suggest that CKD is not an independent risk factor for cardiovascular mortality, many believe that CKD is independently associated with cardiovascular mortality and all-cause mortality. Confounding by previous CVD and by traditional and nontraditional CVD risk in patients with established CKD makes data interpretation challenging. It is unclear if the increased cardiovascular mortality in CKD is an independent effect or if it can be attributed to confounding factors. The role of other pathologic changes like hypercoagulability, endothelial dysfunction, arterial stiffness, and increased inflammatory response as cardiovascular outcome modulators in people with CKD is an area of active interest.

The literature supports the simultaneous use of eGFR and UAE for better risk stratification of patients with DKD. When used simultaneously, these markers help predict CKD progression and cardiovascular risk in patients with DKD.

**DKD WITHOUT ALBUMINURIA**

Proteinuria has traditionally been considered a diagnostic and prognostic marker of DKD, and its presence prompts interventions such as initiation of ACE inhibitors or ARBs. Absence of proteinuria can render a false sense of reassurance for clinicians and often delays diagnosis and treatment of DKD. Development and progression of microalbuminuria in patients with DKD are not rules, and there is a distinct population who do not develop any level of proteinuria until late in disease. There is a possibility of stabilization and even regression of microalbuminuria in patients with diabetes. DKD is believed to arise from microvascular damage, which leads to increased UAE. Over time, data have accumulated to suggest a high prevalence of kidney disease in patients with diabetes and normal UAE, suggesting the presence of renal lesions other than classic diabetic glomerulosclerosis in this population subgroup. This finding has prompted investigators to consider other explanations like interstitial fibrosis, ischemic vascular disease, cholesterol microemboli, atherosclerotic involvement of the renal vasculature, and so forth.

Recently, researchers studied the development of nephropathy in the Cohen diabetic rat (an experimental model of human T2DM). The Cohen diabetic sensitive rats develop CKD with reduced eGFR and histologic changes consistent with DKD, as shown by light and electron microscopy, in absence of proteinuria, when fed a diabetogenic diet. These rats develop changes suggestive of nonproliferative retinopathy as well, although these changes appeared later than development of DKD.

The characteristic histologic lesions seen in classic diabetic glomerulosclerosis are often seen with other systemic manifestations of microvascular disease. These lesions include increased basement membrane thickness, diffuse mesangial sclerosis with nodular formation, hyalinosis, microaneurysm, and hyaline arteriosclerosis.

Data from DEMAND (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes), a global cross-sectional study, showed that kidney dysfunction is not uncommon in T2DM with normal UAE. Kramer and colleagues performed a cross-sectional analysis of a nationally representative sample of adults with T2DM and found that about 30% individuals with eGFR less than 60 did not have retinopathy or microalbuminuria. Data from other cross-sectional studies like RIACE, and longitudinal studies like ARIC (Atherosclerosis Risk in Communities) and UKPDS suggest that normoalbuminuric renal impairment occurs frequently in patients with T2DM. Macroangiopathy could be the underlying renal disease as
opposed to microangiopathy, in diabetic patients with normoalbuminuric CKD.\textsuperscript{73} This change in phenotype of DKD could be related to better control of risk factors like hyperglycemia, hyperlipidemia, hypertension, and early use of ACE inhibitors and ARBs.\textsuperscript{73}

Recent findings have encouraged investigators to think of microalbuminuria and reduced eGFR as markers of different pathologic processes. Microalbuminuria could be a phenotypic expression of endothelial dysfunction, whereas reduced eGFR could be a renal manifestation of systemic atherosclerosis.\textsuperscript{67}

**DOES BETTER GLYCEMIC CONTROL REDUCE DKD?**

Data from DCCT and UKPDS have shaped the understanding and management of diabetes over the years for risk reduction of cardiovascular and kidney disease. In UKPDS, patients with T2DM were randomly assigned to intensive or conventional glycemic control using insulin or oral hypoglycemic agents. Over 10 years, HbA1c levels of 7% and 7.9% were achieved in the intensive and conventional groups, respectively. The patients assigned to intensive treatment protocols had decreased risk of microvascular complications, but the intensive treatment was associated with more hypoglycemic episodes and weight gain. The data also suggested that intensive control was associated with decreased progression of albuminuria.\textsuperscript{76} Posttrial monitoring of patients enrolled in UKPDS, without any attempt to maintain previous diabetes therapies, showed an early loss (at 1 year) of glycemic differences between the 2 cohorts. Over a 10-year follow-up, sustained benefit and continued risk reduction for microvascular complications were observed in the cohort previously subject to intensive diabetes therapy.\textsuperscript{77}

ADVANCE is a multicenter randomized controlled trial designed to study the effects of intensive glucose control (target HbA1c <6.5%) on vascular outcomes in T2DM. Mean HbA1c levels of 6.5% and 7.3% were achieved in the intensive and standard therapy groups, respectively. Data from this trial showed significant reduction in the incidence of nephropathy with intensive glycemic control. Intensive treatment was also associated with decreased need for renal replacement therapy and death from complications related to kidney disease.\textsuperscript{78}

Previously, data from DCCT showed beneficial effects of intensive versus conventional glycemic control on kidney function in patients with type 1 diabetes. Conventional therapy aimed at prevention of symptoms attributable to glycosuria or hyperglycemia and maintenance of normal growth and development, whereas intensive therapy aimed at achieving preprandial blood glucose levels of 70 to 120 mg/dL and postprandial blood glucose concentration less than 180 mg/dL. Over a mean follow-up period of 6.5 years, microalbuminuria and albuminuria developed in fewer patients on intensive treatment, compared with patients on conventional treatment, leading to conclusions that intensive management of blood glucose in patients with insulin-dependent diabetes can delay the onset and slow the progression of diabetic nephropathy.\textsuperscript{79} The DCCT participants were followed in the EDIC (Epidemiology of Diabetes Interventions and Complications) study, an observational study after the DCCT closeout. The DCCT intensive treatment cohort were encouraged to continue the intensive treatment, and the conventional treatment cohort were encouraged to switch to intensive treatment. Over 8 years of further follow-up, the HbA1c difference between the 2 groups narrowed, with mean values of 8.0% and 8.2% in the 2 cohorts, respectively. The incidence of microalbuminuria and clinical albuminuria was significantly lower in the group subject to intensive treatment during the DCCT trial.\textsuperscript{80} Further follow-up data have shown the extension of benefits of early intensive diabetes
treatment in patients with insulin-dependent diabetes for up to 22 years. The patients in the intensive treatment arm of DCCT had a 50% lower risk of impaired GFR at 22 years of follow-up, compared with patients in the conventional treatment arm, suggesting a metabolic memory effect. These data further suggest that intensive therapy for insulin-dependent diabetes in 29 patients for 6.5 years can prevent impaired GFR in 1 patient over 20 years.

Data from these well-designed prospective trials indicate that better glycemic control has an important role in delaying the onset and slowing the progression of nephropathy in patients with diabetes.

Although good glycemic and blood pressure control remain the cornerstones of treatment strategy, to prevent or to slow progression of DKD, other treatment approaches are being explored. Recently, effects of treatment with linagliptin, either alone or in combination with telmisartan, were studied in a mouse model of diabetic nephropathy. The combination seemed to have beneficial effects on albuminuria in mice, but its role in treatment or prevention of DKD in humans needs to be explored.

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN DKD/USE OF OLD AND NEW DRUGS OTHER THAN INSULIN

CKD affects metabolism of oral hypoglycemic agents and leads to accumulation of their metabolites, thus limiting the therapeutic options for patients with DKD. As discussed previously, renal dysfunction alters glucose homeostasis in unpredictable ways via multiple mechanisms in patients with DKD. This finding makes management of diabetes, especially glycemic control, challenging in DKD. The alterations in glucose and insulin handling by kidneys and other body tissues in DKD lead to a state of glycemic dysregulation, which is associated with increased risk of hypoglycemia as well as hyperglycemia.

Selection of an appropriate therapeutic modality is complicated by pharmacokinetic alterations caused by reduced kidney function (Table 1).

Sulfonylureas

Sulfonylureas are insulin secretagogues and they increase endogenous insulin secretion. There is a high risk of hypoglycemia, especially with the use of longer-acting sulfonylureas like glyburide.

Second-generation sulfonylureas like glipizide and glimepiride can be used in patients with diabetes and CKD. Glyburide should be avoided because of its long half-life. Glimepiride should be initiated at a low dose in patients with CKD and should be avoided in patients on dialysis.

Glipizide is the preferred second-generation sulfonylurea for patients with diabetes and CKD, and no dosage adjustment is required for patients with CKD or for those on dialysis.

Meglitinides

These are insulin secretagogues with rapid onset of action and short half-life. Repaglinide and nateglinide are the 2 meglitinides available in the United States.

No dose adjustment is required while using repaglinide in patients with CKD or for those on dialysis, but it is recommended that repaglinide be initiated at a lower dose (0.5 mg before each meal) in patients with GFR less than 40. Use in people with GFR less than 20 or those on dialysis has not been studied. Nateglinide should be initiated at a lower dose (60 mg before each meal) in patients with CKD and should be avoided in patients on dialysis.
Table 1  
Dosage of drugs used to manage hyperglycemia in patients with diabetes and CKD/DKD

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Major Action</th>
<th>Dosing Recommendation in CKD</th>
<th>Dosing Recommendation in Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide</td>
<td>Insulin secretagogue</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td>Insulin secretagogue</td>
<td>Initiate at 1 mg/d and titrate slowly</td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Insulin secretagogue</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Slow carbohydrate absorption</td>
<td>Not recommended in sCr &gt;2 mg/dL</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td>Slow carbohydrate absorption</td>
<td>Not recommended if sCr &gt;2 mg/dL</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>Insulin secretagogue</td>
<td>Initiate at a lower dose 0.5 mg before each meal if GFR &lt;40</td>
<td>Use not studied</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td>Insulin secretagogue</td>
<td>Initiate at a low dose 60 mg before each meal</td>
<td>Avoid</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Liver insulin sensitizer</td>
<td>Contraindicated if sCr &gt;1.5 mg/dL in men, and ≥1.4 mg/dL in women</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone</td>
<td>Peripheral insulin sensitizer</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>Peripheral insulin sensitizer</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td>Exenatide</td>
<td>Improved insulin secretion</td>
<td>GFR &gt;50 no dose adjustment</td>
<td>Use not recommended</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>Improved insulin secretion</td>
<td>GFR &gt;50 no dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Dipeptidylpeptidase-4 inhibitors</td>
<td>Sitagliptin</td>
<td>Improved insulin secretion</td>
<td>GFR &gt;50 no dose adjustment, use 100 mg/d</td>
<td>Use 25 mg/d</td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td>Improved insulin secretion</td>
<td>GFR &gt;50 no dose adjustment</td>
<td>Use 6.25 mg/d</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Improved insulin secretion</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>Improved insulin secretion</td>
<td>GFR &gt;50 no dose adjustment</td>
<td>Use 2.5 mg/d</td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>Pramlintide</td>
<td>Increased satiety and decreased glucagon</td>
<td>GFR &gt;20 no dose adjustment</td>
<td>Lacks clinical data</td>
</tr>
<tr>
<td>Sodium glucose cotransporter 2 inhibitors</td>
<td>Canagliflozin</td>
<td>Glucuresis</td>
<td>GFR ≥60 no dose adjustment (use 100–300 mg daily)</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Abbreviation: sCr, serum creatinine level.
Adapted from Refs. 84,86–90
\textbf{α-Glucosidase Inhibitors}

α-Glucosidase inhibitors prevent or decrease postprandial hyperglycemia. They work by decreasing the rate of breakdown of complex carbohydrates in the intestine, and thus decrease the amount of glucose available for absorption.\textsuperscript{86} Acarbose has minimal systemic absorption, but the drug and its metabolite tend to accumulate in patients with severe renal dysfunction. Similarly, higher plasma levels of miglitol are present in patients with severe renal failure compared with patients with normal renal function, when on equal doses of miglitol. Acarbose and miglitol are available in the United States, but are not recommended for patients with serum creatinine greater than 2 mg/dL or on dialysis, because long-term safety of these drugs in patients with CKD has not been studied.\textsuperscript{84}

\textbf{Biguanides}

Metformin suppresses gluconeogenesis by decreasing hepatic insulin resistance. It effectively decreases glucose concentration in fasting as well as postprandial states.\textsuperscript{85} Metformin should be avoided in patients with moderate and severe renal failure, because renal clearance of metformin is decreased in patients with renal impairment, leading to accumulation of the drug and increased risk of lactic acidosis. Its use is contraindicated in men with serum creatinine level 1.5 mg/dL or greater and women with serum creatinine level 1.4 mg/dL or greater.\textsuperscript{84}

\textbf{Thiazolidinedione}

Thiazolidinediones are agonists of peroxisome proliferator-activated receptor $\gamma$. The stimulation of this receptor increases insulin-stimulated glucose uptake in muscles and adipose tissue and decreases hepatic glucose production and insulin resistance.\textsuperscript{85} Rosiglitazone and pioglitazone are available in the United States, and these can be used in patients with CKD without dose adjustment. However, these drugs should be used with caution in those with advanced CKD, because of concerns of volume retention. Careful attention should be given to volume status of patients, because thiazolidinediones can cause fluid retention, hemodilution, and exacerbation of heart failure.\textsuperscript{84}

\textbf{Incretin Mimetics}

Glucagonlike peptide 1 (GLP-1) is an incretin that increases glucose-dependent insulin secretion. It also slows gastric emptying and increases satiety, and thus decreases food intake.\textsuperscript{85} Exenatide and liraglutide are the GLP-1 analogues available in the United States. Use of an exenatide is not recommended in patients with creatinine clearance less than 30 mL/min, or in those on dialysis.\textsuperscript{84} Close monitoring is required while initiating or up-titrating the dose of exenatide, especially in patients with mild to moderate renal dysfunction, because use of exenatide is associated with nausea and vomiting, and potential for volume depletion and worsening of renal function. No renal dose adjustment is required for liraglutide, and it can be used safely in patients with CKD or ESRD, although attention to volume status is warranted because of associated nausea and vomiting.\textsuperscript{84}

\textbf{Dipeptidylpeptidase-4 Inhibitors}

Dipeptidylpeptidase-4 (DPP-4) inhibitors inhibit DPP-4 and thus prevent degradation of GLP-1. Sitagliptin, linagliptin, saxagliptin, and alogliptin are the DPP-4 inhibitors available in the United States. The dose of sitagliptin and alogliptin needs to be
decreased by 50% and 75% for GFR 50 to 30 mL/min/1.73 m² and less than 30 mL/min/1.73 m², respectively. Saxagliptin can be dosed at 2.5 to 5 mg daily if the GFR is greater than 50, but for patients with lower GFR or ESRD, a dose of 2.5 mg/d should be used. No dosage adjustment is required in patients with CKD for linagliptin.

**Amylin Analogue**

Amylin is secreted along with insulin by pancreatic β cells. Pramlintide is a synthetic analogue of amylin, and preprandial administration of pramlintide is associated with decreased plasma glucagon, slower gastric emptying, and increased satiety. This medication is metabolized primarily in the kidney, but no change in dose is required if the creatinine clearance is more than 20 mL/min/1.73 m². Data are lacking to recommend use of pramlintide in patients on dialysis.

**Sodium Glucose Cotransporter 2 Inhibitors**

Sodium glucose cotransporter 2 (SGLT2) inhibitors decrease renal threshold for glucose and induce glucuresis independent of insulin action. These agents induce renal excretion of glucose and have the potential to cause weight loss, by disposing excess calories/glucose. Canagliflozin is an SGLT2 inhibitor that has been recently approved in the United States. Its efficacy in patients with diabetes and stage 3 CKD (eGFR ≥30 and <50 mL/min/1.73 m²) has been shown in a placebo-controlled randomized, controlled trial. Efficacy of canagliflozin depends on renal function and this drug is not expected to be effective in patients with eGFR less than 30 mL/min/1.73 m² or in those on dialysis. SGLT2 inhibitors have an osmotic diuretic effect and can lead to plasma volume depletion, so kidney function should be monitored while initiating this drug in patients with DKD.

Many new therapeutic agents have been introduced for treatment of diabetes in patients with or without CKD, but special attention to renal function is warranted when choosing the appropriate agent, and dose adjustments should be made to prevent any deleterious effects.

**SUMMARY**

Diabetes is increasingly prevalent and is an important cause of CKD and ESRD. Recently, attention has been focused on DKD without albuminuria, and its pathogenesis is being studied. There are some indications that pathogenesis of diabetic nephropathy, in the absence of albuminuria, might differ from that of traditional diabetic nephropathy with microalbuminuria. Review of recent trial data indicates that better glycemic and blood pressure control can delay the onset and slow the progression of kidney disease in patients with diabetes. Use of several older oral hypoglycemic agents is either contraindicated or requires dosage adjustment in CKD. New medications for diabetes have been approved recently and many can be used safely in patients with CKD, thus providing treatment alternatives for better glycemic control in patients who are reluctant to use insulin. We further suggest that DKD should be considered in a broader context of cardiorenal metabolic syndrome rather than just diabetes, and close attention should be paid to other modifiable cardiorenal risk factors.

**REFERENCES**


76. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes


