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NARRATIVE REVIEW

Glycemic Control in Diabetic CKD Patients: Where Do We Stand?

Csaba P. Kovesdy, MD,^{1,2} Kumar Sharma, MD,^{3,4} and Kamyar Kalantar-Zadeh, MD, MPH, PhD^{5,6,7}

Diabetes mellitus (DM) is a leading cause of chronic kidney disease (CKD) and a major source of morbidity and mortality in patients with established CKD. Loss of kidney function and dialytic therapies conspire to change glycemic regulation in ways that can both worsen and improve blood glucose control. Despite the unique nature of DM in patients with CKD, there currently are no specific guidelines to direct glycemic therapy in these patients. There is benefit of glycemic therapy in preventing such complications as diabetic kidney disease and mortality in patients with no kidney disease, but such benefits are largely unproven in patients with advanced CKD. By reviewing the relevant literature, we argue that glycemic control can still be beneficial in preventing complications, even in dialysis-dependent patients, but there is need for a much better understanding of the CKD-related characteristics of DM. More research is needed to determine whether uremia-related improvement in glycemic control can have a beneficial impact. Finally, we are at an important crossroads in the development of several novel therapeutic agents against diabetic kidney disease. We provide an overview of such agents and their stage of development.

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INDEX WORDS: Chronic kidney disease; diabetes mellitus; therapy; outcomes.

Diabetes mellitus (DM) represents the most common cause of chronic kidney disease (CKD) in the United States,¹ and patients with DM have a greater rate of morbidity and mortality.²⁻⁶ Glycemic therapy in patients with DM has been shown to improve outcomes, especially microvascular complications in patients without CKD.^{7,8} Although preventing diabetic kidney disease clearly is not a goal in patients with CKD stage 5, many of the other deleterious effects of hyperglycemia might still be averted, even at such an advanced stage. However, proving this concept is difficult; observational studies exam-

ining outcomes of glycemic control in dialysis patients gave conflicting results, and large clinical trials of glycemic therapy have not been conducted in this patient population. Complicating hypoglycemic therapy in patients with CKD are physiological changes in glucose and insulin metabolism and pharmacokinetic changes related to lower kidney function.

We reviewed the literature on outcomes associated with hyperglycemia in patients with CKD, with special emphasis on methodological difficulties posed by the characteristics of this disease state. We describe the challenges encountered in therapy for hyperglycemia in patients with CKD and provide suggestions for clinical practice and future research.

SIGNIFICANCE OF DM IN CKD

There are currently about 400,000 Americans on dialysis therapy.¹ According to some estimates, the number of patients with CKD stage 5 will reach one half million by 2010 and may exceed one million by 2018.⁹ These individuals experience low quality of life, high hospitalization rates, and increased mortality.¹

DM is the leading cause of CKD in the United States and most industrialized nations. The proportion of CKD patients with DM in the United States has increased from less than 30% in the late 1980s to almost 50% in 2004.^{1,10} Although the annual incidence of DM has shown less

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growth recently,¹¹ both glomerulonephritis and hypertensive renal disease rank below DM in the frequency of diagnosis in new dialysis patients,¹ and the cost of diabetic kidney disease is estimated to be greater than \$15 billion annually in the United States.¹² Despite the greater incidence of comorbidities and poorer outcomes in dialysis patients with DM,¹⁻⁴ it is not clear whether medical management of DM has a significant bearing on their clinical outcomes.¹³

IMPACT OF CKD PROGRESSION ON THE NATURAL HISTORY OF DM

Abnormal glycemic control is a known complication in patients with advanced CKD.¹⁴ Even individuals without DM with CKD can show mild fasting hyperglycemia and abnormal glucose tolerance, suggesting that the uremic state alters glucose homeostasis.¹⁵ However, decreasing insulin requirements and even spontaneous hypoglycemia also occur in patients with estab-

lished DM with advancing stages of CKD.^{15,16} The reason for the abnormal glucose homeostasis in patients with CKD is postulated to be multifactorial and inherent to this disease state (Fig 1).

Uremia-Associated Changes in Insulin and Glucose Metabolism

Renal insulin clearance decreases as glomerular filtration rate (GFR) decreases to less than 15 to 20 mL/min/1.73 m² (to convert GFR to mL/s/1.73 m², multiply by 0.01667).¹⁵ Hepatic clearance of insulin is also decreased in patients with uremia, but may improve after the initiation of dialysis therapy.¹⁵ Opposing the effects of decreased insulin clearance are lower insulin production and increased insulin resistance. The reason for the decreased insulin secretion in patients with CKD is unclear, but it may be related to hyperparathyroidism and activated vitamin D deficiency, suggested by

Figure 1. Mechanisms of action responsible for the dysregulation of glycemic control observed with advancing stages of chronic kidney disease. Abbreviations: PD, peritoneal dialysis; HD, hemodialysis.

findings that insulin secretion improves after treatment of hyperparathyroidism and administration of activated vitamin D.¹⁷⁻²¹ The effect of the latter intervention is independent of its parathyroid hormone–lowering effect²¹ and could be one of the explanations for the improved outcomes associated with these medications.^{22,23}

The mechanism of increased insulin resistance in patients with CKD also is not fully understood. The role of a uremic toxin is supported by studies showing improved insulin sensitivity with dialysis.²⁴⁻²⁸ The exact site of insulin resistance in patients with CKD also is unclear, but it may be muscle tissue.^{29,30} Insulin resistance and deficiency are associated with muscle protein breakdown in dialysis patients, a process mediated through the ubiquitin-proteasome pathway^{31,32} through suppression of phosphatidylinositol-3 kinase.^{33,34} Insulin resistance and deficiency may conspire with other known acute and chronic conditions to engender a state of malnutrition and could contribute to the worsened outcomes seen in dialysis patients with DM beyond their effects related to known diabetic complications.

The complex changes caused by altered insulin metabolism are complicated further by the effect of diminished kidney function on renal gluconeogenesis.³⁵ Deficient gluconeogenesis, along with malnutrition, deficient catecholamine

release, and impaired renal insulin degradation and clearance, can contribute to a lower threshold for clinical hypoglycemia.¹⁶ It currently is unknown what the long-term impact of these changes is in patients with CKD and whether the better glycemic control that might result in some of these patients could be beneficial.

Dialysis Therapy and Non-Nutritional Glucose Absorption

Some of the alterations in insulin metabolism have been linked to uremic toxins, and initiation of dialysis therapy was shown to improve insulin sensitivity and glucose tolerance.²⁴⁻²⁷ A study comparing hemodialysis and peritoneal dialysis suggested that the latter is superior in achieving better insulin sensitivity.³⁶

Further complicating the effect of dialysis is the glucose load provided by both modalities. Peritoneal dialysis especially can result in significantly greater glucose intake from dialysate, particularly if greater concentrations are required to achieve ultrafiltration goals. The total amount of caloric intake from this source is estimated to be 10% to 30% of total energy intake,³⁷ yet the total nutritional intake of these patients is often less than ideal.³⁸ The reason for this discrepancy could be a loss of appetite related to continuous glucose absorption³⁹⁻⁴¹ and the mechanical effects of large filling volumes.⁴²

Table 1. Diagnostic Tests to Assess Integrated Glucose Control in Patients With Diabetes Mellitus

Diagnostic Test	Glycemic Control Period	Conditions Affecting Interpretation	Advantages	Disadvantages
Hemoglobin A _{1c}	2-3 mo	Hemoglobinopathies, diseases of shortened erythrocyte life span	Used in major trials that determined thresholds of glycemic control. Routine testing available in most clinical laboratories	No information about short-term glucose control
Fructosamine	2-3 wk	Proteinuria, dysproteinemias, malnutrition, thyroid abnormalities, liver disease, pregnancy, steroid therapy	Unaffected by disease states affecting hemoglobin	Reference levels lacking Testing not offered routinely by most clinical laboratories
Glycated albumin	2 wk	Proteinuria, dysproteinemias, malnutrition, thyroid abnormalities, liver disease, pregnancy, steroid therapy	Unaffected by disease states affecting hemoglobin	Reference levels lacking Testing not offered routinely by most clinical laboratories

Glucose absorbed during dialysis could at the same time decrease patients' energy expenditures,⁴³ limit amino acid losses, and stimulate insulin secretion.⁴⁴

MEASURES OF GLUCOSE CONTROL: DIFFICULTIES AND CAVEATS IN CKD

Glucose homeostasis is altered significantly in patients with CKD, making glucose control a difficult task. Glycated hemoglobin (expressed as percentage of total hemoglobin) is used as an indicator of integrated glucose control because it is a reliable marker of fasting, postprandial, and random blood glucose levels in patients with normal kidney function (Table 1).⁴⁵ Glycated hemoglobin is formed by the nonenzymatic reaction between glucose and the N-terminal amino group on the beta chain of hemoglobin.⁴⁶ Four different fractions of glycated hemoglobin can be detected by means of cation exchange chromatography (hemoglobin A_{1a1} [HbA_{1a1}], HbA_{1a2}, HbA_{1b}, and HbA_{1c}).⁴⁵ The current standard therapeutic targets for glycemic control are set based on outcomes associated with certain HbA_{1c} levels in populations with normal kidney function.^{8,47}

Glycated hemoglobin levels can be affected by several factors that are CKD specific. Increased blood urea nitrogen levels can cause the formation of carbamylated hemoglobin, which cannot be distinguished from glycated hemoglobin by using electrical charge-based assays.⁴⁸ It has been estimated that an increase in time-averaged blood urea nitrogen concentration from 10 to 70 mg/dL (to convert blood urea nitrogen to mmol/L, multiply by 0.357) will result in an increase in glycated hemoglobin of 1.26%. This effect is much smaller compared with the impact of an increase in blood glucose concentration of similar proportion.⁴⁹ Overestimation of glycated hemoglobin can be overcome by using assays that do not depend on electrical charge⁵⁰⁻⁵³ or assays specific for HbA_{1c}, which are less prone to interference from carbamylated hemoglobin.⁴⁸ Other factors implicated in causing a falsely increased level of glycated hemoglobin in patients with uremia include metabolic acidosis⁵⁴ and uremia-related increased glycosylation rate,⁵⁵ but none of these was subsequently

proved to be significant.^{56,57} Factors associated with a potential decrease in glycated hemoglobin levels in patients with uremia include a shortened life span of red blood cells and blood transfusions. However, the life span of red blood cells is close to normal in well-dialyzed patients, and routine blood transfusions are rarely needed nowadays.

Based on these considerations, glycated hemoglobin appears to be a reasonable measure of integrated glucose control in patients with CKD, although its overestimation is possible when using charge-dependent chromatography assays.⁴⁵ Other potential measures of long-term glucose control in patients with uremia are glycated fructosamine and albumin.^{58,59} Glycated albumin better correlated with plasma glucose levels compared with HbA_{1c} in 538 dialysis patients in Japan.⁵⁹ HbA_{1c} was associated with the weekly administered dose of erythropoietin in this study, suggesting that the greater proportion of young erythrocytes found in the circulation of patients treated with erythropoietin could lead to underestimation of glycemic control by using HbA_{1c} level.⁵⁹ Use of these latter markers is hampered by their lack of availability in routine practice and the lack of established reference levels. Furthermore, both are affected by conditions that alter protein metabolism, which are frequently present in patients with CKD (Table 1).^{58,60,61}

OUTCOMES ASSOCIATED WITH HYPERGLYCEMIA IN CKD

Development and Progression of Diabetic Kidney Disease

The impact of glycemic control on the development and progression of diabetic kidney disease has received substantial attention in the general population and in patients with early stages of diabetic kidney disease. Blood glucose control was found to decrease the incidence of new-onset microalbuminuria in retrospective^{62,63} and prospective studies^{7,8} of patients with DM. Progression of established diabetic kidney disease (defined both as worsening of albuminuria^{7,8,64,65} and progressive decrease in GFR⁶⁶⁻⁶⁹) can also be retarded through strict glycemic control, although results of studies assessing this outcome were not uniform.^{70,71} The reason for the discrep-

ancy could be the multifactorial nature of DM or the long time needed for better glucose control to persist before its beneficial impact materializes. Results of the Diabetes Control and Complications Trial (DCCT) suggest that at least 3 years of strict glycemic control are needed for the renal benefits to become significant.⁷ Interestingly, benefits that become apparent after this seem to be persistent even if glycemic control worsens subsequently.⁴⁷ In a study of patients with established diabetic kidney disease (presence of albuminuria, but normal GFR) who underwent pancreas transplantation, gradual resolution in histological changes of diabetic kidney disease was detected on kidney biopsy, but only after 5 years of normoglycemia.⁷² The benefit of glucose control on progression in patients with diabetic kidney disease who have advanced (stage ≥ 3) CKD is unclear.

Mortality and Morbidity

Studies performed in patients with early diabetic kidney disease in the 1970s and 1980s indicated that death occurred about 5 to 7 years after the development of proteinuria.⁷³⁻⁷⁵ Because these studies were conducted in an era when many of the current therapeutic interventions were not yet prevalent, subsequent improvements in the described outcomes were attributed to overall better medical care,⁷⁶ but without clearly indicating which aspect of this care was responsible for the better outcomes. The impact of glucose control on mortality in patients with type 1 DM, normal serum creatinine level, and variable degrees of albuminuria was examined in 939 patients followed up for 10 years. This study found that greater HbA_{1c} concentration was associated with greater mortality.⁷⁷ The incidence of cardiovascular disease in patients with type 1 DM and early diabetic kidney disease was studied in the DCCT/Epidemiology of Diabetes Interventions and Complications Study, in which intensive insulin therapy proved to decrease the progression of carotid intima-media thickness⁷⁸ and coronary artery calcification⁷⁹ and improve cardiovascular survival.⁸⁰ In the United Kingdom Prospective Diabetes Study (UKPDS), strict glycemic control resulted in a trend toward lower cardiovascular events in patients with type 2 DM.⁸ The Steno-2 Study examined multiple risk factor modification in patients with type 2 DM (including intensive treatment of hyperglycemia)

and showed a 50% decrease in cardiovascular events,⁸¹ lower mortality, and progression of CKD.⁸²

The effect of glucose control on outcomes in patients with advanced CKD is less well studied. Greater mortality was associated with greater HbA_{1c} levels in the Modification of Diet in Renal Disease (MDRD) Study.⁸³ Although conceptually interesting, results of this study are difficult to extrapolate to the general CKD population because MDRD Study participants were mostly nondiabetic and the mortality rate seen in that study was much less than that reported in nonselect CKD populations.^{84,85} The association of HbA_{1c} level with all-cause mortality was examined in 519 male US veterans with CKD stages 3 and 4.⁸⁶ This study found an inverse association between HbA_{1c} level and mortality, but significant interactions with blood Hb and serum albumin concentrations indicate that this association may not be causal and invites further studies. The benefit of glycemic therapy in patients with CKD was corroborated in a post hoc analysis of a large clinical trial in which treatment with pioglitazone in patients with an estimated GFR less than 60 mL/min/1.73 m² resulted in a lower incidence of cardiovascular events.⁸⁷ It is unclear whether the benefit of therapy was related to glucose-lowering effects of pioglitazone or a mechanism independent of insulin-sensitization, such as an anti-inflammatory effect.⁸⁸ However, the role of peroxisome proliferator activated receptor agonists in patients with DM with CKD remains controversial because fluid retention is a significant complication.

Outcomes associated with glycemic control are better studied in dialysis patients (Table 2).^{86,89-95} Except for 1 nonrandomized trial,⁹¹ these studies are also observational. All except 1 study⁹³ had small sample sizes and 3 studies^{89,90,92} examined exclusively Asian patients. A recent large study of 24,875 dialysis patients⁹³ found no association between HbA_{1c} level and survival at 12 months. The lack of survival association in this study could have been caused by the short duration of follow-up and other method limitations, including inadequate controlling for malnutrition, inflammation, and anemia. This was suggested by a recent study that examined 23,618 dialysis patients with DM that also found a paradoxically lower unadjusted mortality associated with greater HbA_{1c} levels. However,

Table 2. Studies of the Association of Glycemic Control With Survival in Patients With DM With CKD

Reference	Type of Study	Patients and Background	Duration of Follow-Up	Results
Rossing et al, ⁷⁷ 1996	Observational	939 patients with type 1 DM, albuminuria, and normal creatinine	10 y	Death HR with 1% higher HbA _{1c} , 1.11 (95% CI, 1.03-1.20)
Menon et al, ⁸³ 2005	Observational	768 patients without DM with moderate and advanced CKD	125 mo	All-cause death HR with 1% higher HbA _{1c} , 1.73 (95% CI, 1.24-2.41) CV death HR with 1% higher HbA _{1c} , 1.53 (95% CI, 0.96-2.43)
Kovesdy et al, ⁸⁶ 2007	Observational	519 men with DM with moderate and advanced CKD	2.7 y	All-cause death HR with HbA _{1c} < 6.5, 1.45 (95% CI, 1.01-2.08)
Tzamaloukas et al, ⁹⁵ 1993	Observational	226 patients with DM on long-term dialysis	Unknown	Better survival in patients with good diabetic control
Tzamaloukas et al, ⁹⁴ 1993	Observational	110 diabetic patients on CAPD	Unknown	Better survival in patients with good diabetic control
Wu et al, ⁸⁹ 1997	Observational	137 Taiwanese long-term HD patients with type2 DM	1- to 5-y survival	Death HR, 0.37 with HbA _{1c} < 10 compared with poor glycemic group
Morioka et al, ⁹⁰ 2001	Observational	150 Japanese incident long-term HD patients	2.7 y	Death HR, 1.13% with HbA _{1c} ≥ 7.5
McMurray et al, ⁹¹ 2002	Non-randomized trial	83 US dialysis patients	1 y	HbA _{1c} ↓ & QoL ↑ after intervention, but no survival benefit
Oomichi et al, ⁹² 2006	Observational	114 Japanese long-term HD patients	45.5 mo	Death HR, 2.89 with HbA _{1c} ≥ 8 compared with < 6.5
Williams et al, ⁹³ 2006	Observational	24,875 US long-term HD patients (Fresenius)	1 y	No difference in survival across HbA _{1c} increments
Kalantar-Zadeh et al, ⁹⁶ 2007	Observational	26,187 US long-term HD patients (DaVita)	3 y	Incremental increase in death risk across HbA _{1c} increments
Schneider et al, ⁸⁷ 2008	Post hoc analysis of randomized controlled trial	597 patients with eGFR < 60 mL/min/1.73 m ²	34.5 mo	Lower incidence of composite outcome of CV events in patients treated with pioglitazone

Note: To convert GFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.

Abbreviations: DM, diabetes mellitus; CKD, chronic kidney disease; HD, hemodialysis; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; QoL, quality of life; CAPD, continuous ambulatory peritoneal dialysis; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}.

Figure 2. All-cause mortality associated with various hemoglobin A_{1c} (HbA_{1c}) levels in 23,618 patients with diabetes receiving maintenance hemodialysis. Associations were examined in unadjusted Cox models and after adjustment for case-mix characteristics (age, sex, race/ethnicity, preexisting comorbid states, tobacco smoking, dialysis vintage, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function) and 11 laboratory variables of nutrition and inflammation. Abbreviation: MICS, malnutrition, inflammation, cachexia syndrome. Based on data from Kalantar-Zadeh et al.⁹⁶

after adjusting for markers of malnutrition and inflammation, greater HbA_{1c} levels became associated with greater mortality (Fig 2).⁹⁶ The results of this study indicate that in dialysis patients with DM, competing risk factors related to malnutrition, wasting, and anemia may confound the association between glycemic control and survival.

These pitfalls can be overcome by using more sophisticated analytical methods in observational studies or by randomized controlled trials. Unfortunately, only a single interventional study examined clinical outcomes in 83 dialysis patients undergoing intensive diabetes-related intervention compared with standard care.⁹¹ Patients in the intensive intervention arm experienced improved quality of life and a decrease in need for amputations and hospitalizations.⁹¹ Larger clinical trials are needed to conclusively prove the concept that better glycemic control is beneficial in patients with advanced CKD and establish what an ideal blood glucose level should be in these patients.

THERAPY FOR DM IN PATIENTS WITH CKD

The complex changes in glucose and insulin homeostasis in patients with CKD make glycemic therapy in these patients more complicated.

Glycemic control could worsen as a result of decreased insulin production and insulin sensitivity and the glucose load of dialysis, but could also improve as a result of longer insulin half-life, dialytic clearance of uremic toxins, or complex interactions with morbid conditions (such as sepsis, malnutrition, liver disease, and congestive heart failure) that could even lead to hypoglycemia.¹⁶ Therapeutic interventions are made even more complicated by pharmacokinetic alterations caused by lower kidney function. The medications used to treat patients with DM can be affected to various extents in patients with CKD. A recent review discussed in detail CKD-specific considerations for the various currently available glycemic therapies.⁹⁷

Therapeutic Targets of Glycemic Control

The currently applied therapeutic targets of glycemic control are based on trials performed in patients with DM with normal kidney function.^{8,47} It was suggested that the risk of microalbuminuria increased only at a threshold HbA_{1c} level greater than 8.1%⁹⁸; however, this finding was at odds with findings from the DCCT, in which the risk of microvascular complications decreased continuously, even with HbA_{1c} levels less than this threshold.⁹⁹ However, lower achieved HbA_{1c} levels in the DCCT came at the expense of significantly higher hypoglycemic episodes.⁴⁷ Realizing the tradeoff between tighter glucose control and the greater incidence of treatment-related complications and the long time required for the better glycemic control to exert its benefits, the current American Diabetes Association clinical practice recommendations allow for less strict glycemic control (without a specific level mentioned) in patients with shorter life expectancy (a description that would fit the average patient with CKD).¹⁰⁰ To complicate matters further, a major trial designed to test the hypothesis that control of blood glucose to near-normal levels decreases cardiovascular events in high-risk patients with DM¹⁰¹ stopped its intensive treatment arm after finding an increased risk of death compared with the conventional treatment strategy. The lack of CKD-specific data makes it difficult to recommend glycemic targets for this patient population, but the aforementioned considerations should prompt a cautious and individualized treatment plan, rather than a 1-size-fits-all approach.

Table 3. Potential Future Medications for the Treatment of Diabetic Kidney Disease

Agent	Mechanism of Action	Stage of Development
Sulodexide	Restores glycoproteins in the glomerular basement membrane	Phase I and II clinical trials completed, phase III and IV trials under way
Ruboxistaurin	Protein kinase C inhibitor	Completed phase I and II clinical trials
Pyridoxamine	Blocks advanced glycation	Completed phase I and II clinical trials
Fenofibrate	Suppression of plasminogen activator inhibitor 1 and tumor growth factor β 1	No human studies yet
SPP301 (avosentan)	Endothelin receptor antagonist	Completed phase I and II clinical trials; phase III trial terminated
Pirfenidone	Antifibrotic agent	Open label trial for focal segmental glomerulosclerosis and exploratory trial for diabetic nephropathy in progress
XL784	Metalloproteinase inhibitor	Phase II clinical trial in progress

Novel Treatments of Diabetic Kidney Disease

Despite the importance of diabetic kidney disease in driving the worldwide epidemic of CKD,¹ current therapeutic interventions directed against this entity are limited to control of blood glucose levels and blood pressure and use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Specific pharmacological agents for the treatment of patients with established diabetic kidney disease are not available for clinical use, but several new agents are studied in clinical trials (Table 3).¹⁰² Glycosaminoglycans can restore glycoproteins in the glomerular basement membrane through a complex mechanism of action.¹⁰³ Treatment with the oral glycosaminoglycan sulodexide has resulted in consistent decreases in albuminuria in phase I and II clinical trials,¹⁰⁴ and phase III and IV clinical trials with this agent have begun (ClinicalTrials.gov identifiers: NCT00130312, NCT00130208, NCT00342238, and NCT00462202).

A second alternative therapy for patients with diabetic kidney disease involves blockade of protein kinase C,¹⁰⁵ high expression of which has been implicated in tissue damage in this condition.¹⁰⁶ Early trials of the protein kinase C inhibitor ruboxistaurin in the treatment of patients with diabetic kidney disease,¹⁰⁷ diabetic retinopathy,¹⁰⁸ and diabetic neuropathy¹⁰⁹ have shown mixed efficacy results. Phase III clinical trials of this agent are awaited. A third potential avenue in the treatment of patients with diabetic complications involves blocking the nonenzymatic formation of advanced glycation end products.¹¹⁰⁻¹¹² Pyridoxamine is an advanced glyca-

tion end product inhibitor with a complex mechanism of action.¹¹³ Early clinical trials of pyridoxamine in patients with diabetic kidney disease have shown promising results in retarding the decrease in kidney function, but without an effect on albuminuria.¹¹⁴ Further evaluation of this agent in phase III clinical trials is needed.

Other agents have also been studied in patients with diabetic kidney disease, albeit to a lesser extent. The cholesterol-lowering drug fenofibrate has shown renoprotective effects through suppression of plasminogen activator inhibitor 1 and transforming growth factor β 1 in rats.¹¹⁵ Human trials have not yet been performed. Neutralizing transforming growth factor β 1 antibodies has been shown by Sharma et al¹¹⁶ to prevent early¹¹⁶ and late changes¹¹⁷ of DM and the prospects for human trials in the future appear promising.¹¹⁸ The oral endothelin antagonist SPP301 (avosentan) effectively decreased urinary albumin excretion in a phase II clinical trial,¹¹⁹ but a large phase III clinical trial examining its safety and efficacy (ClinicalTrials.gov identifier: NCT00120328) was terminated early because of safety concerns. Pirfenidone is a promising oral antifibrotic agent¹²⁰ that effectively decreases glomerulosclerosis and interstitial fibrosis in animal models¹²¹ and currently is being studied in an open label trial for focal segmental glomerulosclerosis and an exploratory trial for diabetic nephropathy (ClinicalTrials.gov identifiers: NCT00063583 and NCT00105391). Finally, the oral metalloproteinase inhibitor XL784 is undergoing evaluation for efficacy in reducing albuminuria in patients with type 1 or 2

DM and GFR greater than 40 mL/min/1.73 m² in a phase II clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00312780) identifier: NCT00312780).

CONCLUSIONS

DM represents an important comorbidity in patients with CKD. Although in some hemodialysis patients with DM, glycemic control may improve spontaneously with the loss of residual renal function or weight loss, treatment of hyperglycemia could be beneficial in improving outcomes in the entire CKD patient population. Glycemic control retards progression of diabetic kidney disease in its early stages. It is possible that mortality could be decreased by glycemic control in patients with CKD; there is still uncertainty about this because of the lack of randomized controlled trials and the sometimes contradictory results of observational studies. Insulin resistance and deficiency could represent a distinct therapeutic target in patients with CKD given their effects not only on hyperglycemia, but also on uremic malnutrition. Finally, there is hope that therapeutic agents directed against the specific pathophysiological process of diabetic kidney disease will become available in the near future.

Glycated hemoglobin still represents the best available monitoring tool. Treatment of hyperglycemia in patients with CKD has to take into account the complex changes in glucose and insulin metabolism and the pharmacokinetic changes of many hypoglycemic medications and the specific aspects of the type of renal replacement therapy administered in patients with CKD stage 5. Careful monitoring and individualized therapy are recommended to achieve good glycemic control and minimize the occurrence of hypoglycemic episodes.

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