Glycemic Management in ESRD and Earlier Stages of CKD

Mark E. Williams, MD,1 and Rajesh Garg, MD2

The management of hyperglycemia in patients with kidney failure is complex, and the goals and methods regarding glycemic control in chronic kidney disease (CKD) are not clearly defined. Although aggressive glycemic control seems to be advantageous in early diabetic nephropathy, outcome data supporting tight glycemic control in patients with advanced CKD (including end-stage renal disease [ESRD]) are lacking. Challenges in the management of such patients include therapeutic inertia, monitoring difficulties, and the complexity of available treatments. In this article, we review the alterations in glucose homeostasis that occur in kidney failure, current views on the value of glycemic control and issues with its determination, and more recent approaches to monitor or measure glycemic control. Hypoglycemia and treatment options for patients with diabetes and ESRD or earlier stages of CKD also are addressed, discussing the insulin and noninsulin agents that currently are available, along with their indications and contraindications. The article provides information to help clinicians in decision making in order to provide individualized glycemic goals and appropriate therapy for patients with ESRD or earlier stages of CKD.


INDEX WORDS: Chronic kidney disease (CKD); hyperglycemia; diabetes mellitus; hemoglobin A1c (HbA1c); end-stage renal disease (ESRD).

EXECUTIVE SUMMARY

The management of hyperglycemia in patients with kidney failure has special challenges. The difficulty is due in part to the complexity of treatment and in part to lack of convincing data supporting the benefits of tight glycemic control. This article reviews metabolic changes in kidney failure, current views on glycemic goals, and treatment options for patients with diabetes and end-stage renal disease (ESRD) or earlier stages of chronic kidney disease (CKD).

Multifactorial alterations in glucose homeostasis occur when kidney function declines. Insulin resistance increases in CKD due to accumulation of uremic toxins, chronic inflammation, excess visceral fat, oxidative stress, metabolic acidosis, and vitamin D deficiency. It generally is acknowledged that insulin resistance is a feature of uremia, irrespective of kidney disease cause. Recent data suggest that alterations in body metabolism with CKD may alter adipose tissue patterns that are consistent with a more proinflammatory and insulin-resistant state. Decreased adiponectin concentrations also are seen in CKD and may contribute to the insulin resistance. Erythropoietin deficiency also may contribute to insulin resistance. Increased insulin resistance in turn may contribute to increased risk of cardiovascular disease in patients with CKD.

Glycemic management in patients with type 2 diabetes and CKD has become increasingly complex over the last 2 decades. Challenges in improving glycemic control in patients with advanced CKD (including ESRD) include therapeutic inertia, monitoring difficulties, and the complexity of available treatments.

According to the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines, HbA1c targets are no different in diabetic patients with and without CKD. However, it now is well understood that HbA1c level may overestimate glycemic control in kidney patients: HbA1c levels appear to be lower, leading to underestimation of hyperglycemia. A lack of correspondence in clinical studies between HbA1c level and other measures of glycemia has inspired concerns about the validity of the latter in predicting outcomes in patients with advanced CKD (including ESRD). Other measures of glycemic control, such as glycated albumin, may be more useful in CKD. Glycated albumin increasingly is proposed as a better measure of glycemic control in patients with diabetes and CKD, but in patients with nephrotic-range proteinuria, glycated albumin levels may be falsely reduced.

No randomized clinical trial has yet evaluated the effects of glycemic control in patients with ESRD. Observational data from the national ESRD database
have been contradictory, with one study showing no impact of HbA1c level on mortality and another showing that higher HbA1c levels are associated with increased risk of death. Overall, the relationship between glycemic control and survival outcomes seems weaker in the setting of ESRD. Moreover, the risk of hypoglycemia is greater in patients with reduced kidney function. The pathogenesis of hypoglycemia in patients with CKD is complex and includes derangements in glucose metabolism, decreased insulin degradation, and changes in drug metabolism. Severe hypoglycemia is known to increase the risk of poor clinical outcomes in patients with diabetes. Therefore, higher glycemic targets may be appropriate in patients with CKD with more comorbid conditions.

Regarding the treatment of hyperglycemia, insulin traditionally has been considered the safest antidiabetic agent in the presence of kidney failure. Although most patients need basal and nutritional insulin, it is important to individualize the insulin regimen. Some of the new noninsulin agents are considered safe and efficacious, and some may even be preferable over insulin.

Use of noninsulin agents may not only avoid the psychological stress of insulin injections for some patients, but also reduce the risk of hypoglycemia. Metformin does not cause hypoglycemia; however, it is contraindicated in patients with moderate to severe kidney failure due to the risk of lactic acidosis. Thiazolidinediones do not increase the risk of hypoglycemia and are relatively safe in CKD, but may cause fluid retention leading to heart failure. Dipeptidyl peptidase 4 (DPP-4) inhibitors are becoming more popular for the treatment of hyperglycemia in patients with CKD because of their better tolerability and low risk of hypoglycemia. Some agents (sitagliptin and saxagliptin) may need dose adjustment for reduced estimated glomerular filtration rate (eGFR). Long-term data for their safety and efficacy are still lacking. Glucagon-like peptide 1 (GLP-1) receptor agonists are associated with more severe side effects of nausea and vomiting in patients with ESRD and may not be well tolerated. Other drugs, such as alpha-glucosidase inhibitors, bile acid sequestrants, dopamine 2 agonists, and amylin mimetics, are of limited use in patients with CKD. There are few head-to-head clinical trials comparing various antidiabetic agents, and none has been conducted in patients with CKD.

Glycemic management is complex when diabetes is complicated by diabetic nephropathy. Although aggressive glycemic control has been shown to alter the clinical course of early diabetic kidney disease, data supporting the benefits of tight glycemic control on outcomes in patients with advanced CKD (including ESRD) are lacking. In the absence of better clinical trial data, glycemic management continues to be based on individualized decision making.

INTRODUCTION

The management of hyperglycemia in patients with kidney failure presents special challenges. The difficulty is due in part to the complexity of treatment in these patients and in part to the lack of data supporting the benefits of tight glycemic control. Therefore, goals of treatment and methods to achieve glycemic control in patients with chronic kidney disease (CKD) are not clearly defined. This article reviews metabolic changes in kidney failure, current views about glycemic goals, and treatment options for patients with diabetes and end-stage renal disease (ESRD) or earlier stages of CKD.

GLUCOSE/INSULIN HOMEOSTASIS

Multifactorial alterations in glucose homeostasis occur when kidney function declines. Factors that contribute to the abnormalities in glucose homeostasis in people with reduced kidney function are shown in Fig 1. Abnormal insulin metabolism involves reduced renal insulin clearance, which usually occurs when CKD reaches stages 4 and 5. Reductions in pancreatic insulin secretion also may occur, perhaps related to hyperparathyroidism and vitamin D deficiency, and potentially could be ameliorated by correcting these disorders.2,3

Glucose transport across the cell membrane, mediated by specific transporter proteins, is one of the primary actions of insulin and is thought to be the rate-limiting step for glucose uptake in peripheral tissues.4 In muscle and adipose tissue, insulin triggers glucose uptake by prompting translocation of an intracellular pool of glucose transporters to the plasma membrane. The intracellular actions of insulin are complicated but increasingly understood. Upon binding of insulin to its receptor, the latter transduces the signal by phosphorylating insulin receptor substrate 1 (IRS1) and other such substrates.5 Activation of multiple downstream targets (glycogen synthase, protein kinase C, and endothelial nitric oxide synthase [eNOS] among them) leads to a broad variety of responses, including enhancement of glucose uptake, glycogenesis, lipogenesis, and cellular proliferation.6

Recent studies have examined the mechanisms and clinical significance of insulin resistance in CKD. Insulin resistance in CKD is an acquired defect (due to known risk factors such as obesity and to metabolic abnormalities unique to uremia). Proposed determinants in CKD include accumulation of uremic...
Toxins, chronic inflammation, excess visceral fat, oxidative stress, metabolic acidosis, and vitamin D deficiency. The specific mechanism involves steps in the insulin receptor signaling pathway downstream of the insulin receptor. These steps include the generation of intracellular messengers for insulin, glucose transport, and effects of insulin on an intracellular enzyme that itself functions in glucose metabolism. It generally is acknowledged that insulin resistance is a characteristic feature of uremia, irrespective of kidney disease cause. When there is insulin resistance, insulin-stimulated cellular glucose uptake is compromised. In uremia, insulin-mediated stimulation of peripheral glucose disposal by muscle and adipose tissue is dramatically affected, but hepatic glucose uptake continues normally and hepatic glucose production can be suppressed. Similarly, the antiproteolytic action of insulin and its role in the translocation of potassium into cells are not affected in advanced kidney failure. Because insulin sensitivity improves with initiation of dialysis therapy, uremic toxins may play a role in the derangements of insulin resistance. Some evidence has emerged suggesting that CKD-triggered changes in body metabolism may alter adipose tissue secretion patterns. Released adipokines subsequently become a key source of proinflammatory molecules, which in turn lead to insulin resistance. Plasma adiponectin levels are related inversely to kidney function, and decreased adiponectin concentrations may be involved in insulin resistance. Oxidative stress also may influence the production of proinflammatory molecules in adipose tissue. Moreover, erythropoietin deficiency also could be involved in insulin resistance, as suggested by a clinical report that found lower mean insulin levels and HOMA-IR (Homeostasis Model Assessment–Insulin Resistance) levels in hemodialysis patients treated with recombinant erythropoietin. In the setting of CKD, the clinical relevance of insulin resistance remains incompletely understood. However, existing evidence is consistent with insulin resistance in uremia contributing to muscle protein anabolism and perhaps other metabolic defects in uremia.

Clinically, insulin resistance might be involved in protein-energy wasting, atherosclerosis, and cardiovascular complications in patients with CKD. Recent attention has focused on the role of insulin resistance in protein-energy wasting. Even dialysis patients who are not obese and do not have diabetes mellitus have significant insulin resistance on account of elevated muscle protein catabolism. The ubiquitin-proteasome pathway, which is related to suppression of phosphatidylinositol 3 kinase, is involved in the catabolic process. Recently, the relationship between HOMA-IR and fasting whole-body and skeletal muscle protein turnover was studied with a goal of determining mean skeletal muscle protein synthesis, breakdown, and net balance in nondiabetic maintenance hemodialysis patients. This study found a correlation between higher HOMA-IR and negative net skeletal muscle protein. Another recent study, a cross-sectional examination of 128 patients with diabetes from India, looked at the extent of insulin resistance in individuals with micro-/macroalbuminuric diabetic kidney disease versus those with normoalbuminuria. Although there was no significant difference between study groups in terms of age, body mass index, diabetes vintage, or glycemic control, mean HOMA-IR (the measure of insulin resistance) increased with more severe kidney disease ($P < 0.0001$). In reality,
insulin resistance appears to be somewhat variable in kidney disease, similar to what is seen in other conditions, such as type 2 diabetes and obesity, or even what is observed in healthy individuals.22

Kidney tissues also respond to insulin, as shown by physiologic studies. Once this hormone binds to its receptor, a number of downstream targets (Akt [protein kinase B], glycogen synthase kinase 3, Ras, ERK [extracellular signal–regulated kinase], and protein kinase C) are recruited. Following their activation, a large variety of metabolic effects are triggered. Insulin resistance in the glomerulus is much like the insulin resistance observed in the endothelium of other vascular tissues, and it is recognized that the actions of insulin on the glomerulus may be blunted in the setting of diabetes.6 It has been suggested that this may be involved in the initiation and progression of glomerular lesions in diabetes.23 Progress in understanding the development of renal insulin resistance is ongoing. Mima et al24 performed analyses of insulin signaling and cellular actions involving the glomerulus and tubules, comparing diabetic, insulin-resistant, and control states. From this work emerged a detailed view of impaired insulin signaling in glomeruli and tubules of diabetic and insulin-resistant animals that suggested that a subset of these alterations may be involved in diabetic glomerulopathy.

Recently, the contribution of the kidneys to glucose homeostasis by processes such as gluconeogenesis and glucose filtration and reabsorption has been studied in both apparently healthy individuals and those with diabetes.24 Under normal conditions, up to 180 g/d of glucose may be filtered by the glomerulus. Essentially all this filtered glucose is reabsorbed in the proximal tubule because of secondary active transport through 2 sodium-dependent glucose transporter (SGLT) proteins. Most glucose reabsorption achieved occurs through sodium-glucose cotransporter 2 (SGLT2), which is found in the S1 segment of the proximal tubule.25 Of note, renal reabsorption of glucose may increase in type 2 diabetes, and this pathway is the target of recently developed oral “hypoglycemic” agents. In particular, SGLT2 inhibitors have been evaluated as new treatments for diabetes.26 Reports indicate that SGLT2 inhibitors, by inducing glucosuria, can improve glycemic control in patients with type 2 diabetes while avoiding the danger of triggering severe hypoglycemia.27 Although SGLT2 mediates 90% of glucose reabsorption in the kidneys, SGLT inhibitors at best appear to inhibit half that amount. In 2013, canagliflozin became the first SGLT2 inhibitor to be approved in the United States.28 A second SGLT2 inhibitor, dapagliflozin, is approved in Europe and many others are at advanced stages of development.29

**Glycemic Management in CKD and ESRD**

Glycemic management in patients with diabetes (predominantly type 2) and CKD has become increasingly complex, in part reflecting controversies about safety/efficacy as applied to type 2 diabetes.30 Challenges cited in improving glycemic control in patients with advanced CKD include therapeutic inertia, monitoring difficulties, and complexity regarding the use of available treatments.31

Hemoglobin A1c (HbA1c) is the standard measure for glucose monitoring in patients without kidney impairment. According to NKF-KDOQI guidelines, currently recommended HbA1c targets in the setting of CKD are no different from those for the general diabetic population; that is, <7.0%, although the seminal glycemic control trials in type 1 and type 2 diabetes have excluded patients with significantly decreased kidney function.33 Although HbA1c combined with home glucose monitoring is the mainstay for assessing glycemic control, until recently, available evidence regarding the role of tight glycemic control on morbidity and mortality in patients with advanced CKD was sparse.

HbA1c remains the most widely used index of glycemic control in the diabetic population. Superior glycemic control helps prevent diabetic CKD and other diabetic microvascular complications in individuals without CKD. Since the DCCT (Diabetes Control and Complications Trial)34 and UKPDS (UK Prospective Diabetes Study)35 showed that HbA1c levels are strong predictors of the risk of microvascular complications in type 1 and type 2 diabetes, respectively, glycohemoglobin level has been the main focus of diabetes management. Strict glycemic control was found to reduce the risk of developing albuminuria, and in those with elevated baseline albumin-creatinine ratios, progression was found to be reduced with strict glycemic control. In a recent observational report from the Alberta Kidney Disease Network,36 in patients with diabetes and non–dialysis-dependent CKD stages 3-5, higher HbA1c levels were associated with markedly worse outcomes, including progression of kidney disease regardless of baseline estimated glomerular filtration rate (eGFR). The renoprotective effect associated with intensive control of glycemia in type 2 diabetes also was suggested by the recent ADOPT (A Diabetes Outcomes Prevention Trial) Study.37 Greater durability of glycemic control in those treated with rosiglitazone (compared with metformin and glyburide) was associated with a smaller increase in albuminuria and with preservation of eGFR. The firm association between glycemic control and clinical outcomes hinges on the connection between hyperglycemia and elevated HbA1c.
levels. HbA1c makes up ~4% of total hemoglobin in normal adult erythrocytes. HbA1c level mirrors average blood glucose concentration over the preceding 3 months or so. Firm correlation between HbA1c and blood glucose levels in those with intact kidney function has been reported in DCCT and the ADAG (A1c-Derived Average Glucose) Study.

**HbA1c and Reduced Kidney Function**

It now is understood that HbA1c level may overestimate glycemic control in kidney patients: HbA1c levels appear to be lower, leading to underestimation of hyperglycemia. The unreliability of HbA1c now is appreciated to occur in several clinical conditions, especially hematologic diseases involving anemia or hemolysis, and has been blamed on the analytical, biological, and clinical variability associated with HbA1c levels. Analytical variability is no longer an issue because of newer assay methods. However, biological and clinical variability of HbA1c levels persist and limit the utility of this marker in some patients, even in the general diabetic population, in which variability arises in part from differential glycation rates. The relationship between HbA1c and time-averaged serum glucose levels also may vary across different racial backgrounds.

More importantly, discrepancies between levels of HbA1c and other measures of glycemia in clinical studies have inspired questions about the validity of HbA1c level in predicting outcomes in patients with advanced CKD. The NKF-KDOQI guidelines for diabetic CKD accept that there is a deficiency in data for validating methods for monitoring glycemia in patients with reduced kidney function. The US Renal Data System (USRDS) reported that the prevalence of HbA1c levels greater than the 7.0% target is higher for stages 1-2 CKD, but decreases to lower levels in stages 3-4 CKD. In our large national ESRD database analysis, mean HbA1c value is only 6.77%, and only 35% of patient values are >7.0%.

Inherent biases in the previous HbA1c assays that might lead to a higher or lower HbA1c level for a given level of glycemia in patients with CKD compared with the general population do not appear to be clinically significant with contemporary assays. As opposed to the high-performance liquid chromatography assay that was the previous method for routine laboratory measurement of HbA1c, the current immunoturbidimetric assay methodology is unaffected by high serum urea nitrogen levels. Instead, the most commonly mentioned influences on HbA1c level variability in patients with kidney disease include anemia and erythropoiesis-stimulating agent treatment. In patients with kidney disease, the red blood cell life span may be reduced by 30%-70%. Shortened erythrocyte survival in ESRD anemia would be consistent with decreased HbA1c levels on account of reduced duration of exposure to ambient glucose and resulting glycation. Moreover, use of erythropoiesis-stimulating agents increases the number of immature red blood cells in circulation, each with less likelihood for glycosylation. One publication reported lowering of HbA1c values in a patient, both when he was treated with an erythropoietin analogue and also when receiving a darbepoetin analogue.

It now is understood that HbA1c levels tend to be lower in patients with diabetes who have reduced kidney function or who are dependent on dialysis. Peacock et al looked at HbA1c and glycated albumin levels in 307 patients with diabetes, about five-sixths of whom were hemodialysis dependent, with the rest without evident kidney disease. In patients treated by dialysis, the ratio of glycated albumin to HbA1c level was higher, implying that HbA1c level substantially underestimated serum glucose levels. More recently, Chen et al reported mean glucose levels that were 5%-10% higher in patients with stages 3-4 CKD than an estimated average glucose value calculated from the same HbA1c level applied to patients without reduced kidney function. Recently, a study examined 4-day continuous glucose monitoring in patients with type 2 diabetes treated by maintenance hemodialysis (n = 19) with a larger group of patients with type 2 diabetes but without nephropathy (n = 39). Although continuous glucose monitoring results were comparable with glucose concentrations according to the glucose meter in all patients, HbA1c and mean glucose concentrations showed strong correlation in only the nondialysis group (r = 0.71); by contrast, they were correlated weakly in those receiving hemodialysis (r = 0.47). In this study, hemodialysis patients were treated with erythropoiesis-stimulating agents and had lower hemoglobin levels than the nondialysis group (11.6 vs 13.6 g/dL; P < 0.0001).

**Glycemic Control and Outcomes in ESRD**

Effects of glycemic control in patients with ESRD have not yet been studied in a randomized clinical trial. Recent observational studies have added significantly to the available evidence, albeit with relatively contrasting results and substantial methodological differences. Using a large national ESRD database, Williams et al found that mortality curves in patients with diabetes did not differ when grouped by HbA1c levels, with no correlation between glycohemoglobin levels and 12-month mortality risk singly or adjusted for case-mix and laboratory values. Results from Kalantar-Zadeh et al in a similar-sized retrospective database analysis differed, showing that greater HbA1c levels were associated with increased risk of death. HbA1c levels >10% were found to be associated with a 41% greater risk for
all-cause and cardiovascular death. The study used longer follow-up, time-dependent survival models, and adjustments for surrogates of malnutrition and inflammation. A subsequent report by Williams et al modified its analysis to more directly match that of Kalantar-Zadeh et al and found that glycemia is associated with poorer survival only at concentration extremes.

As a result of these studies, it is evident that the connection between glycemic control and survival outcomes is weaker in the setting of ESRD (Fig 2). In particular, higher HbA1c targets may be preferable in patients with more comorbid conditions, an approach supported by a recent regression analysis involving HbA1c levels and mortality from the DOPPS (Dialysis Outcomes and Practice Patterns Study). In another observational study, a post hoc analysis of 4D (Die Deutsche Diabetes Dialyse Studie), a graded relationship between inferior glycemic control and mortality due to sudden cardiac death was reported. During a median follow-up of 4 years, using patients with HbA1c levels < 6.0% as the comparator, patients with sudden cardiac death were identified. Patients with HbA1c levels > 8.0% had a more than 2-fold higher risk of sudden death compared with those with HbA1c levels ≤ 6.0% (HR, 2.14). Furthermore, with each 1% increase in HbA1c level, the risk of sudden death, after statistical adjustments, increased by 18%. The impact of HbA1c level on sudden death led to increased risks of both cardiovascular events and mortality, although the prevalence of myocardial infarction was not affected. Sudden death was the single largest cause of mortality (26%). The specific mechanism by which poor glycemic control might lead to sudden death is not clear.

Relative to the limited reliance on fructosamine level, glycated albumin level increasingly is proposed as a better measure of glycemic control in patients with diabetes who have CKD. Glycated albumin represents glycated serum proteins that have stable ketoamines (carbonyl group of glucose reacting with the protein’s amino group) in their structure. Fructosamine level is becoming more available for the monitoring of diabetes treatment, but its correlation with fasting serum glucose levels may not be as strong, and the issue of correcting values for total protein or albumin concentrations is unresolved. Also, Chen et al reported that compared with patients with normal kidney function and for the same glucose concentration, patients with CKD have fructosamine levels that also are lower than expected. Of note, false elevations in fructosamine levels may result from nitroblue tetrazolium assay interference by serum uric acid. In a recent report, elevated fructosamine levels were associated with infection and all-cause hospitalization in 100 patients with diabetes who were on hemodialysis therapy.

Alternative Measures of Glycemic Control

Given the variability in HbA1c levels, there are serious questions about the wisdom of relying on this test as the only measure of glycemia in patients with diabetes and CKD. Fructosamine represents glycated serum proteins that have stable ketoamines (carbonyl group of glucose reacting with the protein’s amino group) in their structure. Fructosamine level is becoming more available for the monitoring of diabetes treatment, but its correlation with fasting serum glucose levels may not be as strong, and the issue of correcting values for total protein or albumin concentrations is unresolved. Also, Chen et al reported that compared with patients with normal kidney function and for the same glucose concentration, patients with CKD have fructosamine levels that also are lower than expected. Of note, false elevations in fructosamine levels may result from nitroblue tetrazolium assay interference by serum uric acid. In a recent report, elevated fructosamine levels were associated with infection and all-cause hospitalization in 100 patients with diabetes who were on hemodialysis therapy.

Relative to the limited reliance on fructosamine level, glycated albumin level increasingly is proposed as a better measure of glycemic control in patients with diabetes who have CKD, with a reference range of 0.6%-3.0% using column chromatography. Albumin undergoes nonenzymatic glycation in a manner similar to hemoglobin and represents the bulk of the serum glycated proteins. Because the residence time of serum albumin is shorter (half-life ~ 20 days), it...
represents shorter glucose exposure and should be checked monthly. Glycated albumin is a readout of glycemic control for just the 1-2 weeks preceding sampling. It can be assayed with a bromocresol purple method and expressed as percentage relative to total albumin. Using this method, a reference value of \( \approx 12\% \) for nondiabetic American individuals with normal kidney function has been reported, with a modestly wider reference interval versus the more compressed range of measured values for HbA1c. Although not influenced by age or erythrocyte lifespan, anemia, or erythropoietin, glycated albumin has not been validated in dialysis patients. The test’s precision may suffer in periods of abnormal protein turnover, such as from inflammation, hypercatabolic states, peritoneal dialysis, proteinuria, albumin infusions, or gastrointestinal protein losses. In patients with nephrotic-range proteinuria, glycated albumin levels may be falsely reduced. However, there now is an improved assay that is not affected by changes in serum albumin level. Another factor in favor of measuring glycated albumin is that unlike HbA1c, it may have in vivo effects involved in the pathogenesis of diabetic complications, such as being an Amadori-modified reaction product capable of inducing oxidative stress and enhancing pro-inflammatory responses.

The superiority of glycated albumin to HbA1c level was concluded in 2 recent studies of kidney patients. The first, a study from Japan of 538 maintenance hemodialysis patients with type 2 diabetes, 828 hemodialysis patients without diabetes, and 365 patients with diabetes but without significantly reduced kidney function, found significantly lower HbA1c levels relative to blood glucose or glycated albumin levels with dialysis patients compared with those without reduced kidney function. The ratio of glycated albumin to HbA1c level (with a previously reported ratio of \( \approx 3.0 \) in the absence of ESRD) was 2.93 in patients without CKD and 3.81 in those on dialysis therapy. In a subsequent study from the United States, the ratio again was significantly higher in patients with ESRD (2.72 vs 2.07).

Evidence linking glycemic control, as determined by serum glycated albumin level, to diabetic ESRD outcomes is now emerging. Freedman et al analyzed the association between 3 measures—glycated albumin, HbA1c, and serum glucose—and outcomes (hospitalization and survival) in patients with diabetes who were undergoing dialysis (90% hemodialysis; Fig 3). Quarterly serum glycated albumin levels were measured for up to 2.3 years in 444 prevalent patients with ESRD. Time-dependent analyses were used to compare these measurements with available HbA1c and monthly random serum glucose levels. Mean serum glycated albumin level was 21.5% ± 6.0% (SD) and HbA1c level was 6.9% ± 1.6%. Increasing concentrations of glycated albumin, but not of HbA1c or random serum glucose, predicted hospitalization and survival. However, it is unclear what the therapeutic target range should be in CKD. A fourth potential marker of glycemia in patients with reduced kidney function, serum 1,5-anhydroglucitol (1,5-AG) level, recently was reported. The study suggested that 1,5-AG levels were not influenced by moderately reduced kidney function.

**PERITONEAL DIALYSIS**

Although no randomized comparison trials are available, several analyses of observational data over the years have indicated that patients with ESRD who begin treatment with hemodialysis or peritoneal dialysis have similar outcomes. Subgroup analyses now suggest that hemodialysis may be associated with improved survival in some patients with diabetes, with a survival disadvantage emerging after...
24 months among diabetic patients with at least one comorbid condition and/or who were older than 65 years. Modality-survival effect modification by diabetes has been shown in other studies, including one incorporating a propensity-matched mortality comparison. In addition, diabetic patients undergoing peritoneal dialysis more rapidly develop peritoneal fibrosis and loss of ultrafiltration.

Exposure to glucose from peritoneal dialysis fluid, which is absorbed systemically in significant amounts, accentuates the metabolic abnormalities of diabetes and metabolic syndrome. The addition of intraperitoneal insulin, while uncommon, is the most physiologic approach to the management of major fluctuations in blood glucose levels in diabetic patients. However, it requires higher doses than the conventional subcutaneous approach due to dilution and adsorption to the plastic surface of the dialysis solution delivery system. Glycemic control also may be achieved by reduced reliance on hypertonic dextrose solutions through substitution of icodextrin solution, a glucose polymer minimally absorbed across the peritoneal membrane. Icodextrin is the only alternative to dextrose approved in the United States for use in the long dwell of the peritoneal dialysis cycle. An important patient safety issue with its use is the development of spurious hyperglycemia: oligosaccharide metabolites such as maltose lead to erroneous blood glucose measurements specific to glucose dehydrogenase/pyrroloquinolinequinone cofactor-based glucometers, with large overestimation of glucometer glucose levels compared with finger-stick or laboratory values.

**HYPOGLYCEMIA**

Patients with diabetes and progressively declining kidney function are at increased risk for hypoglycemia. Diabetes treatment options for patients with advanced CKD therefore may be limited due to safety and tolerability concerns. Because the risk of adverse events related to hypoglycemia may be greater in patients with reduced kidney function, attention increasingly is being given to the risks of hypoglycemia (glucose < 70 mg/dL) in patients with diabetes and CKD. In recent diabetes guidelines, there is greater concern than in the past about the dangers of hypoglycemia. The American Diabetes Association (ADA) has recommended a target HbA1c level < 7.0% or as close to normal and as safely as possible without unacceptable hypoglycemia. However, with increasing emphasis on tight glycemic control targets, hypoglycemia, often iatrogenic, is a growing concern with use of insulin secretagogues, missed meals, advanced age, duration of diabetes, and unawareness of hypoglycemia, factors that might increase the risk of hypoglycemia. However, published reviews of glycemic control in patients with diabetic CKD typically mention hypoglycemia only in passing. The greatest risk of harm is in patients with both CKD and diabetes, especially the elderly, in whom hypoglycemic episodes may be difficult to diagnose. Partly as a result of mounting concerns about hypoglycemia, the ADA’s *Standards of Medical Care in Diabetes* recommends less stringent HbA1c targets (ie, 7.5%-8.0%) as appropriate for patients with advanced complications, extensive comorbid conditions, or severe hypoglycemia.

Adverse sequelae of hypoglycemia could be part of the reason behind the outcomes from 3 recent studies, ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Cardiovascular Disease: Preterax and Dia-micron Modified Release Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial), which tried to determine whether more aggressive diabetes management than previously recommended (with a goal of achieving HbA1c levels near 6.0%) would reduce cardiovascular risk in patients with long-standing diabetes. Hypoglycemic episodes were more frequent in the intensive therapy arms of all 3 studies, and in the ACCORD trial, the rate of such episodes requiring medical assistance was 3 times higher in the intensive group. In ADVANCE, severe hypoglycemia was nearly twice as common in the intensive control group, and half the patients in the low-HbA1c group experienced at least a minor hypoglycemic event. All 3 trials failed to demonstrate that intensive therapy had a cardiovascular benefit. Information for hypoglycemia and kidney disease generally has emerged through case reports, small series, and reviews. In the ADVANCE trial analysis, higher creatinine levels were an independent risk factor for severe hypoglycemia. ESRD unrelated to diabetes is the second most frequent cause of hyperglycemia in hospitalized patients and carries a high mortality rate. As many as half the maintenance hemodialysis patients with diabetes may experience hypoglycemia over a 3-month period. The pathogenesis of hypoglycemia in patients with diabetic CKD is complex, particularly because there are other derangements in glucose metabolism in kidney failure. Consistent glycemic control is difficult to achieve in patients with ESRD due to altered glucose metabolism related to insulin resistance, impaired insulin secretion, and decreased insulin degradation, as well as effects on drug metabolism, adding further complexity to glycemic management. Diminished renal insulin clearance, as GFR decreases to 15-20 mL/min/1.73 m², prolongs the action of insulin. Aside from the liver, the kidneys represent the main site for insulin degradation, and as kidney function declines, so does the ability to remove...
insulin. Reductions in kidney mass and diminished kidney function lead to decreased renal gluconeogenesis, a major source of glucose production from precursor molecules during starvation. Preliminary findings hint that the risk of hypoglycemia is particularly high in patients with diabetic ESRD who have more glycemic variability.80

The health effects of hypoglycemia can be severe. There may be hypoglycemic unawareness. Episodes of cold sweats, agitation, dizziness, disorientation, slurred speech, fatigue, and decreased level of consciousness are typical. A case of hypoglycemia complicated by central pontine myelinolysis and quadriplegia has been described.81 Severe hypoglycemia can powerfully stimulate the sympathetic nervous system and may bring about acute secondary adverse cardiovascular outcomes, such as chest pain due to coronary vasoconstriction and ischemia, myocardial infarction, serious cardiac arrhythmias including QT prolongation and ventricular arrhythmias, and sudden death.82 Severe hypoglycemia is known to increase the risk of poor outcomes in patients with diabetes.83 Fear of iatrogenic hypoglycemia may result in poor glycemic control and further risk of diabetic complications.

MANAGEMENT OF HYPERGLYCEMIA

Pharmacologic management of diabetes mellitus in patients with decreased kidney function is complicated by several factors, including (1) altered insulin resistance and glucose metabolism, (2) altered pharmacokinetics and safety profile of antihyperglycemic agents, (3) concerns about the effect of drugs on kidney function, (4) altered nutritional status, and (5) higher risk of hypoglycemia. Therefore, when kidney function starts deteriorating in a patient with diabetes, pharmacologic management needs frequent changes and/or dose adjustments. Moreover, the benefits of tight glycemic control in patients with kidney failure may not be the same as for patients in the early stages of diabetes without decreased kidney function, and the risk of hypoglycemia may outweigh the benefits of tight glycemic control. Therefore, goals for glycemic control need to be revised and readjusted.

Insulin traditionally has been considered the safest antidiabetic agent in the presence of kidney failure. However, many new noninsulin agents are safe and effective, and some may be even better than insulin, as explained next.

INSULIN THERAPY IN PATIENTS WITH DECREASED KIDNEY FUNCTION

Insulin is metabolized partly in the kidneys, and in the presence of CKD, insulin action is prolonged.84 Therefore, the risk of hypoglycemia is increased in CKD and one study suggested an insulin dose reduction of ~50% in these patients.85 Some patients on dialysis therapy may require different doses on different days due to the effect of dialysis on insulin sensitivity.86 Basic tenets of insulin therapy in CKD are the same as in any other patient with diabetes. The patient needs basal insulin coverage and nutritional insulin coverage. In a typical insulin regimen, basal insulin coverage is provided by intermediate- or long-acting insulin and nutritional coverage is provided by short- or rapid-acting insulin (Table 1). Insulin glargine is the longest acting insulin analogue currently available for clinical use. In kidney failure, its duration of action may be even longer and careful monitoring is needed. Insulin detemir and NPH insulin may be used once or twice daily for basal coverage. Regular insulin and rapid-acting insulin analogues are used commonly for nutritional coverage. The risk of hypoglycemia theoretically is higher with regular insulin due to its longer duration of action than rapid-acting insulin analogues, which may have the additional advantage of more flexibility in CKD. Due to their quick onset and shorter duration of action, they sometimes can be used after meals in patients with unreliable oral intake. Studies of hemodialysis patients have shown the pharmacokinetics of rapid-acting insulin analogues to be more favorable for nutritional coverage.87-89

Although most patients need basal insulin and nutritional insulin, it is important to individualize the insulin regimen. Some patients can achieve their glycemic goals using 1 or 2 injections of basal insulin alone, whereas others may need complex

Table 1. Profiles of Available Insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Insulin Name</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration</th>
<th>Typical Use</th>
<th>Other Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td>Lispro, aspart, glulisine</td>
<td>5-15 min</td>
<td>1-2 h</td>
<td>4-6 h</td>
<td>Nutritional</td>
<td>Can be taken after meals if food intake is unreliable</td>
</tr>
<tr>
<td>Short acting</td>
<td>Regular</td>
<td>30 min</td>
<td>2-4 h</td>
<td>6-8 h</td>
<td>Nutritional</td>
<td>Used in IV insulin infusion</td>
</tr>
<tr>
<td>Intermediate or long</td>
<td>NPH</td>
<td>1-2 h</td>
<td>4-8 h</td>
<td>12-18 h</td>
<td>Basal</td>
<td>1-2×/d</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>2 h</td>
<td>No peak</td>
<td>20-24 h</td>
<td>Basal</td>
<td>1×/d</td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td>2 h</td>
<td>3-9 h</td>
<td>16-24 h</td>
<td>Basal</td>
<td>1×/d</td>
</tr>
</tbody>
</table>

Table 1. Profiles of Available Insulins

Williams and Garg

Table 2. Noninsulin Antidiabetic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Primary Physiologic Action</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Role in Kidney Failure</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Activates AMP-kinase; ↓ hepatic glucose production</td>
<td>Extensive experience; no hypoglycemia; weight neutral; likely ↓ CVD</td>
<td>GI side effects; lactic acidosis; B12 deficiency; multiple contraindications including kidney failure, acidosis, hypoxia, infection, dehydration, older age</td>
<td>Cannot be used with SCr &gt; 1.5 mg/dL in men and &gt; 1.4 mg/dL in women</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfonlyureas</td>
<td>Glyburide, glipizide, glimepiride, gliclazide</td>
<td>Closes K&lt;sub&gt;ATP&lt;/sub&gt; channels on β-cell membrane; ↑ insulin secretion</td>
<td>Extensive experience; ↓ microvascular complications; ↓ postprandial glucose excursions; dosing flexibility</td>
<td>Hypoglycemia; weight gain; frequent dosing</td>
<td>Use with caution</td>
<td>Low</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide, nateglinide</td>
<td>K&lt;sub&gt;ATP&lt;/sub&gt; channels on β-cell membrane; ↑ insulin secretion</td>
<td>Hypoglycemia; weight gain; frequent dosing</td>
<td>Safer than sulfonyureas</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>PPAR-γ activator; ↑ insulin sensitivity</td>
<td>No hypoglycemia; ↑ triglycerides, ↑ HDL-C; ↓ CVD (pioglitazone)</td>
<td>Weight gain; edema/heart failure; bone fractures; ↑ MI? (rosiglitazone); bladder cancer? (pioglitazone)</td>
<td>Safe, but concerns about fluid retention</td>
<td>High</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose, miglitol</td>
<td>Slows carbohydrate digestion/absorption</td>
<td>No hypoglycemia; nonsystemic; ↓ postprandial glucose excursions; ↓ CVD events?</td>
<td>GI side effects; ↑ HbA&lt;sub&gt;1c&lt;/sub&gt;</td>
<td>Contraindicated in kidney failure with SCr &gt; 2 mg/dL</td>
<td>Moderate</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin, saxagliptin, linagliptin, alogliptin</td>
<td>↑ GLP-1 and GIP; ↑ insulin, ↓ glucagon</td>
<td>No hypoglycemia; well tolerated</td>
<td>Modest ↓ HbA&lt;sub&gt;1c&lt;/sub&gt;; pancreatitis?; urticaria</td>
<td>Safe and effective</td>
<td>High</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Exenatide, exenatide extended release, liraglutide</td>
<td>↑ Insulin; ↓ glucagon; ↓ gastric emptying; ↑ satiety</td>
<td>Weight loss; no hypoglycemia; ↑ β-cell mass; CV protection</td>
<td>GI side effects; pancreatitis?; kidney failure?; medullary cancer?; injectable</td>
<td>Should not be used due to severe side effects and concerns about AKI</td>
<td>High</td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>Pramlintide</td>
<td>↓ Glucagon; ↓ gastric emptying; ↑ satiety</td>
<td>Weight loss; ↓ postprandial glucose</td>
<td>GI side effects; modest ↓ HbA&lt;sub&gt;1c&lt;/sub&gt;; injectable; hypoglycemia w/ insulin; dosing</td>
<td>No data in kidney failure, should not be used</td>
<td>High</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam</td>
<td>Unknown; ↓ hepatic glucose production</td>
<td>No hypoglycemia; ↓ LDL</td>
<td>Constipation; ↑ triglycerides; modest ↓ HbA&lt;sub&gt;1c&lt;/sub&gt; may ↓ absorption of other medications</td>
<td>No data</td>
<td>High</td>
</tr>
<tr>
<td>Dopamine 2 agonists</td>
<td>Bromocriptine</td>
<td>Modulates hypothalamic control of metabolism; ↑ insulin sensitivity</td>
<td>No hypoglycemia; ↓ CVD events?</td>
<td>Modest ↓ HbA&lt;sub&gt;1c&lt;/sub&gt;; dizziness/syncope; nausea; fatigue</td>
<td>No data</td>
<td>High</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Canagliflozin, dapagliflozin</td>
<td>↑ Glucosuria</td>
<td>No hypoglycemia; weight loss</td>
<td>Genitourinary infections</td>
<td>Cannot be used in kidney failure</td>
<td>High</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; AMP, adenosine monophosphate; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL-C, high-density lipoprotein cholesterol; K<sub>ATP</sub>, potassium adenosine triphosphatase pump; LDL, low-density lipoprotein; MI, myocardial infarction; PPAR-γ, peroxisome proliferator-activated receptor γ; SCr, serum creatinine; SGLT2, sodium-dependent glucose transporter 2.

Reproduced with permission of American Diabetes Association from Inzucchi et al.31
multiple daily insulin regimens. Some patients on multiple daily insulin injections may benefit further from an insulin pump. Insulin pumps infuse rapid-acting insulin on a continuous basis and therefore insulin doses can be fine-tuned more precisely. However, an insulin pump is more expensive, requires intense patient involvement, and may not be appropriate for all patients. No studies are available to show a lower risk of hypoglycemia with an insulin pump in CKD.

**NONINSULIN HYPOGLYCEMIC AGENTS**

Before 1995, sulfonylureas were the only non-insulin agents available in the United States for the treatment of diabetes. The last 2 decades have seen many new drug classes coming to market. Although these new drugs have made the treatment of type 2 diabetes more exciting, they also have added complexity to the field. There are very few head-to-head comparisons between these agents, and the benefits of one agent over the other are not always clear. As a result, passionate debates favoring one drug over the other have taken place. Several professional organizations have written and revised their guidelines for drug use in type 2 diabetes. However, these guidelines often do not cover patients with CKD. Patients with CKD often are eligible for one or more of the noninsulin glucose-lowering agents. Use of these agents may not only avoid the psychological stress of insulin injections for some patients, but also reduce the risk of hypoglycemia. A summary of currently available noninsulin agents is given in Table 2.

**Sulfonylureas**

Sulfonylureas lower blood glucose levels by releasing insulin from the pancreatic \(\beta\) cells. Acting through sulfonylurea receptors, they close the adenosine triphosphate (ATP)-sensitive potassium channels and depolarize the plasma membrane. Depolarization of \(\beta\)-cell membrane leads to degranulation of cells and insulin secretion. Thus, the effectiveness of sulfonylureas is dependent on insulin release that in turn depends on \(\beta\)-cell reserves. Patients with longer durations of diabetes often have poor \(\beta\)-cell reserves and may respond poorly to sulfonylureas. However, if effective, the glucose-lowering effect of these drugs is not dependent on ambient glucose levels. Therefore, sulfonylureas can cause unregulated insulin release and the risk of severe hypoglycemia is high. Long-acting sulfonylureas (eg, glyburide and chlorpropamide) are more notorious for hypoglycemia. Sulfonylurea-induced hypoglycemia often is severe and can even be life-threatening in patients with CKD. Shorter acting drugs, especially those metabolized in the liver (eg, glipizide and glimepiride) are relatively safe and preferred in patients with CKD.

**Biguanides**

Metformin is the only biguanide available in the United States and is the most commonly used drug for treatment of type 2 diabetes. Metformin is an insulin sensitizer, with its main site of action in the liver. Therefore, it does not cause hypoglycemia. Metformin use also is associated with a small loss of weight. Moreover, this is the only drug for which available data are convincing for a decrease in macrovascular complications of diabetes. However, metformin is contraindicated in women with serum creatinine levels > 1.4 mg/dL and men with serum creatinine levels > 1.5 mg/dL due to the risk of lactic acidosis. Other risk factors for lactic acidosis include hypoxemia, sepsis, alcohol abuse, liver failure, myocardial infarction, and shock. It is important to be aware of this risk and stop metformin treatment promptly when kidney function deteriorates in patients with diabetes. Some physicians tend to use metformin until eGFR is <40 mL/min/1.73 m\(^2\) (or sometimes even <30 mL/min/1.73 m\(^2\)) due to its cardiovascular benefits. However, it seems prudent to stop this drug treatment and switch to another safer agent in a patient with deteriorating kidney function. Studies have shown frequent irrational use of metformin in patients with kidney failure. Diarrhea and gastrointestinal events are other common side effects of metformin and may create further problems in the presence of CKD.

**Thiazolidinediones**

Currently, pioglitazone and rosiglitazone are the 2 thiazolidinediones available for clinical use. They improve insulin sensitivity by acting on the peroxisome proliferator-activated receptor \(\gamma\) (PPAR-\(\gamma\)) receptors, mainly in skeletal muscle and adipose tissue. These agents do not increase the risk of hypoglycemia and are relatively safe in CKD. Both agents seem to be effective for glycemic control in patients on hemodialysis therapy. Pioglitazone is the most widely used thiazolidinedione because it has been shown to have some cardiovascular benefits, whereas rosiglitazone has been shown to be associated with increased risk of myocardial infarction in a meta-analysis. Additionally, rosiglitazone recently was shown to be associated with increased risk of cardiovascular mortality in hemodialysis patients. All thiazolidinediones cause fluid retention that may lead to heart failure, a problem especially pertinent to patients with CKD. Their use also is associated with increased risk of fractures, and more recently, concerns have been
raised about increased risk of bladder cancer with pioglitazone.106

DPP-4 Inhibitors

Sitagliptin, saxagliptin, alogliptin, and linagliptin are the drugs in this class that are approved by the FDA. Dipeptidyl peptidase 4 (DPP-4) inhibitors are becoming more popular for the treatment of hyperglycemia in patients with CKD because of their better tolerability and low risk of hypoglycemia. These drugs increase concentrations of the endogenous incretins GLP-1 and GIP. Some agents (sitagliptin and saxagliptin) may need dose adjustment for reduced eGFR. Randomized controlled trials have demonstrated their short-term safety and efficacy in patients with CKD.107-111 However, long-term data for their safety and efficacy are still lacking.

GLP-1 Receptor Agonists

GLP-1 receptor agonists have a molecular structure similar to native GLP-1 but are resistant to metabolism by DPP-4. Exenatide and liraglutide are the 2 drugs available in this class. Both are injectable agents that increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner and thus are associated with reduced risk of hypoglycemia. They also slow gastric emptying and suppress appetite, both of which are responsible for weight loss but can lead to nausea and vomiting. Liraglutide can be more convenient for patients than exenatide because it is taken once rather than twice a day, and a superior glucose-lowering effect of exenatide because it is taken once rather than twice a day. Moreover, exenatide undergoes renal excretion and is not approved for patients with eGFRs < 30 mL/min/1.73 m². Conversely, liraglutide is not renally excreted and thus decreased kidney function has been found to have little effect on its pharmacokinetics, suggesting its likely safety for use in patients with kidney disease.112

However, side effects associated with GLP-1 agonists seem to be particularly severe in patients with ESRD.115 There have been concerns of acute kidney injury with these agents.116,117 However, a recent retrospective analysis of an insurance-based database found no association between exenatide and acute kidney injury.118 Concerns of acute pancreatitis with GLP-1 agonists and DPP-4 inhibitors received wide publicity after a case-control study showed an association between exenatide or sitagliptin and pancreatitis.119 However, 2 larger long-term observational studies found no association between exenatide and pancreatitis.120,121 In vitro studies show pancreatic duct metaplasia in rats that may raise the possibility of pancreatic cancer on long-term use.122 However, no clinical data are available to show such an association. Similarly in rats, there is C-cell hyperplasia on exposure to liraglutide, raising concerns about medullary thyroid carcinoma.123 Again, no clinical data are available to show such an association and the findings in rodents seem not to apply in humans.124 Because GLP-1 agonists can lead to nausea and vomiting, they are an unfavorable treatment option in CKD.

Meglitinides

These drugs cause insulin release from pancreatic \( \beta \) cells by mechanisms similar to those of sulfonylureas, but they are much shorter acting and their effects are more glucose-level dependent. Therefore, the risk of hypoglycemia is lower with meglitinides than with sulfonylureas. Also, they are more effective for postprandial hyperglycemia. Of the 2 agents, repaglinide and nateglinide, currently available in the United States, nateglinide may have a lower risk of hypoglycemia and has been studied in CKD.125,126 These drugs require frequent dosing because they need to be taken prior to each meal.

\( \alpha \)-Glucosidase Inhibitors

Acarbose and miglitol are the 2 agents available in this class. \( \alpha \)-Glucosidase inhibitors reduce the rate of digestion and absorption of carbohydrates, resulting in modest reductions in HbA\(_1c\) levels. Their main limitation is frequent dosing and gastrointestinal side effects, mainly flatulence.127 These drugs are contraindicated in patients with serum creatinine levels \( > 2 \) mg/dL due to the risk of accumulation that may cause liver failure.128

Bile Acid Sequestrants

Colestervelam is a bile acid sequestrant that originally was used for cholesterol level reduction but now is approved as an antihyperglycemic agent for type 2 diabetes. Its mechanism of action is poorly understood and it has the main side effect of constipation. This drug may be a particularly good choice for patients with type 2 diabetes and elevated low-density lipoprotein cholesterol levels.129 No studies are available in patients with CKD.

Dopamine-2 Agonists

Bromocriptine is a dopaminergic agent approved for the treatment of hyperglycemia in type 2 diabetes. Its mechanism of action is not clear, but it is considered to involve resetting of the circadian rhythm in the hypothalamus, which leads to lower insulin resistance.130 The main advantage of bromocriptine is its proven cardiovascular safety profile.131 Specific benefits or harms of its use in CKD are unknown.
Amylin Mimetics

Amylin is a hormone synthesized in pancreatic β cells and cosecreted with insulin. Although its exact role in glucose control is unknown, it slows gastric emptying, increases satiety, and also suppresses glucagon secretion after a meal, actions similar to GLP-1. Pramlintide is an amylin agonist and can be used alongside insulin to lower postprandial glycemic excursions. The drug is not useful in CKD and has limited use even in patients without CKD.

SGLT2 Inhibitors

Canagliflozin is the first SGLT2 inhibitor approved recently by the US FDA for management of type 2 diabetes. Dapagliflozin already was available in Europe. As mentioned previously, SGLT2 inhibitors lower glucose levels by increasing glucosuria. They do not cause hypoglycemia by themselves and are associated with a modest weight loss. However, their antidiabetic effect is limited by osmotic diuresis and they are associated with increased risk of genitourinary infections. They are contraindicated in patients with eGFRs < 45 mL/min/1.73 m² and must be used at lower doses at eGFRs of 45-60 mL/min/1.73 m².

EFFECT OF TREATMENT CHOICES ON KIDNEY FUNCTION

There are few head-to-head clinical trials comparing various antidiabetic agents, and none of these trials was conducted in patients with CKD. One recent retrospective study that used regional Veterans Administration data has suggested that metformin use may be associated with a lower decline in kidney function over time compared to the use of sulfonylureas. However, these data should be interpreted with caution because metformin use may have been avoided in patients at higher risk of kidney failure and the patients using sulfonylureas may have had poor glycemic control over years.

SUMMARY

Glycemic management is unavoidable but becomes complex when diabetes is complicated by diabetic nephropathy. Although aggressive glycemic control has been shown to alter the clinical course of early diabetic kidney disease, data supporting the benefits of tight glycemic control on clinical outcomes in patients with advanced CKD, including ESRD, are lacking. Conversely, growing evidence indicates that glycemic regulation in patients with diabetes and CKD is difficult. Monitoring is imperfect because HbA1c levels tend to be lower and may underestimate the degree of hyperglycemia. The risk of hypoglycemia appears to be increased. Pharmacologic management with antidiabetic drugs in patients with decreased kidney function is complicated in many cases by altered pharmacokinetics. In the absence of better clinical trial supportive data, the practice of glycemic management will continue to be based on individualized decision making. Information on which to base determinations of glycemic goals and selection of therapy has been reviewed.

ACKNOWLEDGEMENTS

Support: The development of this journal supplement was funded by Novo Nordisk. Technical editing was provided by Watermeadow Medical, funded by Novo Nordisk. Costs associated with publication were funded by Novo Nordisk. The authors received no financial support or remuneration for this work.

Financial Disclosure: The authors declare that they have no relevant financial interests.

REFERENCES


