

# Diabetes Management in the Kidney Patient

Rajesh Garg, MD<sup>a</sup>, Mark E. Williams, MD<sup>b,\*</sup>

## KEYWORDS

• Hyperglycemia • Chronic kidney disease • Diabetes

## KEY POINTS

- Multiple mechanisms including altered insulin clearance and changes in insulin resistance contribute to changes in glucose/insulin homeostasis in CKD.
- Hemoglobin A1c may not be an accurate measure of glycemic control in CKD. Glycated albumin may become an alternative to HbA1c in CKD/ESRD.
- Value of tight glycemic control in CKD is not proven. Therefore, goal of treatment should be moderate glycemic control and avoidance of hypoglycemia.
- Pharmacologic therapy for hyperglycemia should be aimed at achieving individualized glycemic goals using agents with lowest risk of hypoglycemia.

Contributing factors to the abnormalities in glucose homeostasis in people with kidney impairment are shown in **Fig. 1**. Multifactorial alterations in glucose homeostasis occur when kidney impairment progresses. Abnormal insulin metabolism involves reduced renal insulin clearance, which is typically present when chronic kidney disease (CKD) reaches stages 4 and 5.<sup>1</sup> Some evidence suggests that a reduction in pancreatic insulin secretion may also contribute.<sup>2,3</sup>

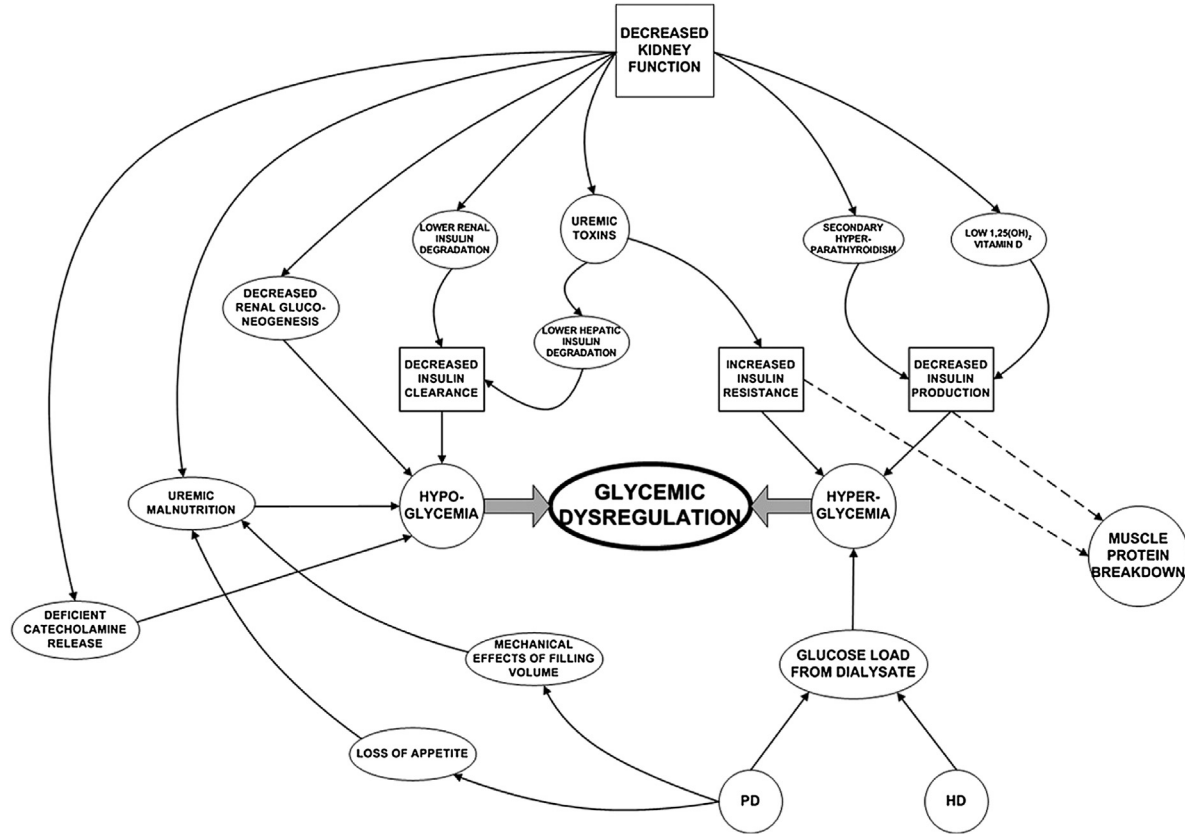
Recent research has explored the mechanisms and clinical significance of another abnormality, insulin resistance, in CKD. A cross-sectional study involving 128 individuals with diabetes showed that homeostasis model assessment–insulin resistance (HOMA-IR) increased significantly with worsening renal disease ( $P < .0001$ ), with no significant difference between the study groups with regard to age, body mass index, duration of diabetes, or glycemic control.<sup>4</sup> Glucose transport mediated by specific transporter proteins is 1 of the major actions of insulin and believed to be rate limiting for glucose uptake in peripheral tissues.<sup>5</sup> In muscle and adipose tissue, insulin stimulates translocation of an intracellular pool of glucose transporters to the plasma membrane and thus promotes glucose entry into the cells. Insulin action starts

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<sup>a</sup> Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, USA; <sup>b</sup> Renal Division, Joslin Diabetes Center, 1 Joslin Place, Boston, MA 02215, USA

\* Corresponding author.

E-mail address: [mark.williams@joslin.harvard.edu](mailto:mark.williams@joslin.harvard.edu)



**Fig. 1.** Overview of glucose/insulin homeostasis in chronic kidney disease/ESRD. Disturbances of glucose metabolism include insulin resistance and glucose intolerance. Several factors contribute to hyperglycemia, which may coexist with hypoglycemia. *Abbreviations:* HD, hemodialysis; PD, peritoneal dialysis. (From Kovesdy, CP, Sharma K, Kalantar-Zadeh K. Glycemic Control in Diabetic CKD Patients: Where Do We Stand? American journal of kidney diseases: the official journal of the National Kidney Foundation 2008;52(4):766–77. Figure 1; with permission.)

when the hormone binds to its receptor, which then phosphorylates insulin receptor substrates such as IRS1.<sup>6</sup> Downstream events involve activation of multiple targets such as glycogen synthase, protein kinase C, and endothelial nitric oxide synthase (eNOS), culminating in wide-ranging effects such as enhancement of glucose uptake, glycogenesis, lipogenesis, and cellular proliferation.<sup>7</sup> In CKD, the specific mechanism of insulin resistance involves the insulin receptor-signaling pathway, at sites distal to the insulin receptor, from changes in the generation of intracellular messengers for insulin action,<sup>8</sup> to glucose transport, to effects of insulin on 1 of the intracellular enzymes involved in glucose metabolism itself.<sup>9</sup> Accumulation of uremic toxins, chronic inflammation, excess visceral fat, oxidative stress, metabolic acidosis, and vitamin D deficiency can all affect the insulin signaling mechanisms and induce insulin resistance in CKD. In reality, insulin resistance appears to be somewhat variable among individuals with kidney disease, as it is in other conditions such as type 2 diabetes, obesity, or even in normal subjects.<sup>10</sup>

The improvement in insulin sensitivity associated with dialysis treatment suggests a role for uremic toxins.<sup>11,12</sup> Other data suggest that alterations in body metabolism during CKD could alter adipose tissue secretion patterns. Altered adipokine secretion could then become an important source of proinflammatory molecules capable of creating insulin resistance.<sup>13</sup> Plasma adiponectin levels, for example, are inversely related to kidney function, and decreased adiponectin concentrations may contribute to inflammation and insulin resistance.<sup>14,15</sup> Production of proinflammatory molecules in adipose tissue may also be modulated by oxidative stress, a feature of uremia.<sup>16</sup> Finally, erythropoietin deficiency might contribute to insulin resistance. This possibility was suggested by a recent clinical study indicating that recombinant erythropoietin-treated hemodialysis patients had lower mean insulin levels and HOMA-IR levels than those not treated with erythropoietin.<sup>17</sup>

Clinically, insulin resistance could contribute to protein-energy wasting, atherosclerosis, and cardiovascular complications known to occur in CKD/end-stage renal disease (ESRD) patients. However, the clinical relevance of insulin resistance in the CKD patient is not yet fully understood. Insulin resistance in CKD is a result of known risk factors such as obesity, as well as metabolic abnormalities unique to uremia as already described. Insulin resistance is a common characteristic feature of uremia, regardless of the cause of CKD. The ability of insulin to stimulate peripheral glucose disposal by muscle and adipose tissue is markedly affected in CKD.<sup>18</sup> However, 2 other important actions of insulin, antiproteolytic action and the translocation of potassium ions into cells, may not be affected to the same extent.<sup>18,19</sup> Numerous studies suggest that insulin resistance in uremia appears to be restricted to defects in glucose uptake and muscle protein anabolism. Dialysis patients even without diabetes mellitus or obesity have significant insulin resistance and increased muscle protein breakdown. Protein breakdown in muscle during kidney failure is at least partly mediated through the ubiquitin-proteasome pathway, where it is related to suppression of phosphatidylinositol-3 kinase.<sup>20,21</sup> More attention has recently been focused on the role of insulin resistance in protein-energy wasting.<sup>22</sup> One metabolic report examined the relationship between HOMA-IR and fasting whole-body and skeletal muscle protein turnover, with a goal of determining mean skeletal muscle protein synthesis, breakdown, and net balance in chronic hemodialysis patients without diabetes.<sup>23</sup> HOMA-IR was found to correlate with negative net skeletal muscle protein balance.

Increased attention has been given recently to the contribution of the kidneys to glucose homeostasis through processes that include glucose filtration and reabsorption.<sup>24</sup> Normally, up to 180 g of glucose may be filtered each day by the glomerulus. Nearly all of this filtered glucose is actively reabsorbed in the proximal tubule,

mediated through 2 sodium-dependent glucose transporter (SGLT) proteins. The majority of this glucose reabsorption occurs through SGLT2, present in the S1 segment of the proximal tubule.<sup>25</sup> This process has achieved recent therapeutic significance because of the development of SGLT2 inhibitors.<sup>26</sup> Reports indicate that the administration of SGLT2 inhibitors can improve glycemic control through glucosuria in patients with type 2 diabetes, without the risk of inducing severe hypoglycemia.<sup>27</sup> Although SGLT2 mediates 90% of glucose reabsorption in the kidneys, SGLT inhibitors at best appear to inhibit only half that amount. Dapagliflozin is the most advanced SGLT2 inhibitor in clinical trials.<sup>28</sup>

Physiologic studies have also shown that kidney tissues respond to insulin, and activation of targets in the kidney elicits wide-ranging metabolic effects. Of note, insulin resistance in the glomerulus is similar to the insulin resistance found in other vascular tissues. Studies conducted by Mima and colleagues<sup>29</sup> showed dysfunctional insulin signaling in glomeruli and tubules of diabetic and insulin-resistant animals. Based on these data, it has been suggested that glomerular insulin resistance could contribute to the initiation and progression of glomerular lesions in diabetes.<sup>29</sup>

Dysglycemia in diabetes also includes challenges of hypoglycemia, which will be described in more detail. The pathogenesis of hypoglycemia in diabetic CKD patients coexists with other derangements in insulin/glucose metabolism in kidney failure. Altered glucose metabolism, related to insulin resistance and decreased insulin degradation, as well as to effects on metabolism of drugs used to treat hyperglycemia, combine to add further complexity to glycemic management. Reduced renal insulin clearance as the glomerular filtration rate (GFR) falls to 15 to 20 mL/min/1.73 m<sup>2</sup> results in a prolonged action of insulin. The kidneys are the most important extrahepatic organs for degradation of insulin, and renal insulin clearance decreases with declining kidney function. The decline in kidney mass and impaired kidney function simultaneously lead to decreased renal gluconeogenesis, a protective source of glucose production from precursor molecules during starvation.

## DETERMINATION OF GLYCEMIC CONTROL IN CKD

Common tests for determining glycemic control in diabetes mellitus are shown in Fig. 2. Hemoglobin A1c (HgbA1c) is the standard clinical measure for glucose

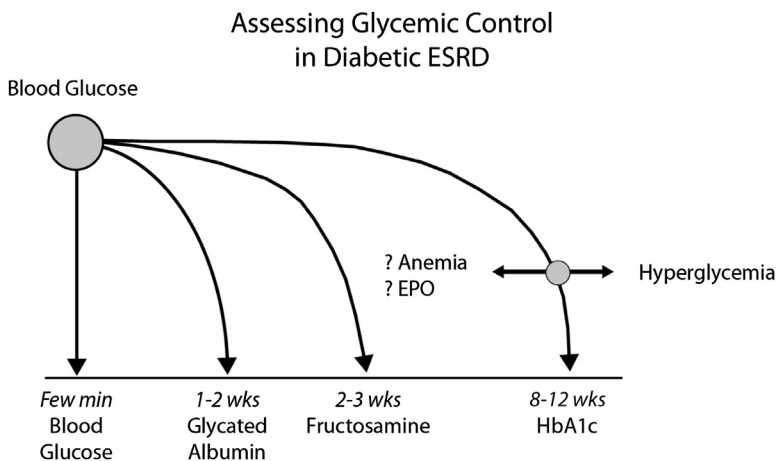


Fig. 2. Measures for assessing glycemic control in diabetic CKD.

monitoring in diabetic patients without kidney impairment. HgbA1c comprises about 4% of total hemoglobin in normal adult erythrocytes. The HgbA1c level reflects average blood glucose concentration over roughly the 3 preceding months.<sup>30</sup> Firm correlation between HgbA1c and blood glucose levels in those with preserved kidney function has been reported in the Diabetes Control and Complications Trial<sup>31</sup> and the A1c-Derived Average Glucose (ADAG) Study.<sup>32</sup> Because the major clinical trials that demonstrated a reduction in microvascular complications with good glycemic control, DCCT for type 1 diabetes<sup>31</sup> and UK Prospective Diabetes Study (UKPDS) for type 2 diabetes,<sup>33</sup> employed HgbA1c levels for predicting their outcomes, the glycohemoglobin level has become the primary basis of diabetes management. A lower HgbA1c in these clinical trials was found to reduce the risk of developing albuminuria, and in those with elevated baseline albumin creatinine ratio (ACR), progression of renal disease was reduced.

However, unreliability of HgbA1c attributed to the analytical, biologic, and clinical variability associated with HgbA1c has been recognized in several clinical conditions.<sup>34</sup> Analytical variability has resolved with introduction of newer assay methods, but the biologic and clinical variability of HgbA1c continue to limit its application to some patients.<sup>35</sup> Many of these factors become relevant when using HgbA1c as a measure of glycemic control in CKD. Analytical biases inherent in the HgbA1c assay that might affect HgbA1c levels in CKD compared with the general population do not appear to be clinically significant anymore with contemporary assays. Unlike the high-performance liquid chromatography assay previously used in routine clinical HgbA1c testing, the contemporary immunoturbidimetric assay is not influenced by high serum urea nitrogen levels. In fact, the most likely causes of HgbA1c discordance from other tests in kidney patients are anemia and the use of erythrocyte stimulating agents (ESAs). In patients with kidney disease, the red blood cell lifespan may be reduced by up to 30% to 70%.<sup>36</sup> Shortened erythrocyte survival in ESRD anemia would be expected to diminish HgbA1c levels by shortening the time for exposure to ambient glucose.<sup>37</sup> In addition, the widespread use of ESAs improves anemia in part by increasing the number of immature red blood cells in the circulation, each with less susceptibility to glycosylation. One case report described a lowering of HgbA1c values with both erythropoietin and darbopoietin analogs.<sup>38</sup>

In spite of that, in the setting of CKD, according to the frequently cited KDOQI (Kidney Dialysis Outcomes Quality Initiative) guidelines of the National Kidney Foundation, the currently recommended HgbA1c targets have not historically differed from those for the general diabetic population (ie, <7%).<sup>39</sup> It is worth noting that the previously referenced seminal glycemic control trials in type 1 and type 2 diabetes (DCCT and UKPDS) excluded patients with significantly impaired kidney function. Furthermore, the strength of the association between glycemic control and clinical outcomes, which hinges on the relationship between hyperglycemia and elevated HgbA1c levels, is now known to be weakened in CKD patients; HgbA1c may overestimate glycemic control in kidney patients. HgbA1c levels appear to be misleadingly lower, resulting in underestimation of hyperglycemia.

Discordance from other metrics of glycemia in clinical research studies<sup>40</sup> have raised concerns about the validity of HgbA1c in predicting outcomes in patients with late stages of CKD. The KDOQI guidelines for diabetic CKD acknowledge a deficiency in data, which would validate the HgbA1c test when kidney function is impaired.<sup>39</sup> This concern has been reinforced by a recent USRDS report indicating that the prevalence of HgbA1c levels over the 7% target was 63% for stages 1 to 2 CKD, but substantially lower (46%) in stages 3 to 4 CKD,<sup>41</sup> an effect unlikely to be attributed to better glycemic management. Similarly, in the authors' large national

ESRD database analysis, the mean HgbA1c value was only 6.77%, and only 35% of patient values were over 7.0%.<sup>42</sup> It is understood that HgbA1c levels tend to be lower in diabetic patients with advanced kidney impairment or in patients who are dialysis-dependent. Peacock and colleagues<sup>43</sup> measured levels of glycated hemoglobin and glycated albumin in 307 patients with diabetes, about 5/6 of whom were undergoing maintenance hemodialysis, and 1/6 were without overt kidney disease. In patients undergoing maintenance hemodialysis, the ratio of glycated albumin to HgbA1c was higher, suggesting that the HgbA1c was relatively reduced, serum glucose levels were significantly underestimated. More recently, Chen and colleagues<sup>44</sup> reported mean glucose levels that were about 10% higher in patients with stages 3 to 4 CKD than an estimated average glucose calculated from the same HgbA1c if applied to patients with normal kidney function, consistent with a reduction in HgbA1c levels in CKD. Poor correlation of HgbA1c and glucose levels were also reported in a recent small study that contrasted 4-day continuous glucose monitoring (CGMS) in type 2 patients undergoing maintenance hemodialysis (N = 19) with a larger group of type 2 diabetic patients without nephropathy (N = 39).<sup>45</sup> The CGMS results and glucose concentrations according to the glucose meter were comparable in patients in both groups. However, glycated hemoglobin and mean glucose concentrations were strongly correlated only in the nondialysis group ( $r = 0.71$ ); correlation was weaker in those undergoing hemodialysis ( $r = 0.47$ ). Hemodialysis patients were receiving erythropoiesis stimulating agents, and had lower hemoglobin levels than the comparator group (11.6 vs 13.6 g/dL,  $P < .0001$ ).

Variance in the HgbA1c levels cited previously have raised particular concern with regard to relying on this test as the sole measure of glycemia in the diabetic CKD population. Fructosamine is comprised of those glycated serum proteins that have stable ketoamines (carbonyl group of glucose reacting with the protein's amino group) in their structure. Fructosamine, while increasingly available for the monitoring of diabetes treatment, may not correlate as strongly with fasting serum glucose levels,<sup>34</sup> and the need to correct values for total protein or albumin concentrations remains a potential problem.<sup>46</sup> In a recent report, elevated fructosamine levels were associated with infection and all-cause hospitalization in 100 diabetic CKD patients on hemodialysis.<sup>47</sup> Similar to the HgbA1c findings discussed previously, the study by Chen and colleagues<sup>44</sup> reported that fructosamine levels were also lower than expected for the same glucose concentration in CKD patients, as compared with patients with normal kidney function. Of note, false elevations of fructosamine levels may result from nitroblue tetrazolium assay interference by serum uric acid.

Relative to the limited use of fructosamine, glycated albumin (GA) is increasingly proposed as a better measure of glycemic control in diabetic patients with CKD/ESRD. Unlike HgbA1c, it has also been suggested that glycated albumin *in vivo* has biologic properties that could contribute to the pathogenesis of diabetic complications,<sup>48</sup> as an Amadori-modified reaction product capable of inducing oxidative stress and enhancing proinflammatory responses. Albumin undergoes a process of nonenzymatic glycation during glucose exposure, similar to hemoglobin, and accounts for most of the serum glycated proteins. Because the residence time of serum albumin is shorter (a half-life of approximately 20 days),<sup>49</sup> it reflects a shorter glucose exposure, so that the testing interval for monitoring should be monthly. Glycated albumin reflects glycemic control for only the 1 to 2 weeks before obtaining the sample.<sup>50</sup> Glycated albumin can be measured using a bromocresol purple method, and calculated as the percentage relative to total albumin. Using this method, a reference range of about 12% has been determined for nondiabetic individuals with normal renal function.<sup>43</sup> There appears to be a somewhat wider reference interval compared with the

more compressed range of measured values for HgbA1c. It has not been validated in dialysis patients. Its precision may be limited in states 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, glycosylated albumin levels may be falsely reduced. However, the case for glycosylated albumin has been strengthened by an improved assay that is unaffected by changes in serum albumin.

Comparison of glycosylated albumin to HgbA1c was evaluated in 2 recent studies of kidney patients.<sup>48,50</sup> In a large Japanese study of 538 maintenance hemodialysis patients with type 2 diabetes, 828 patients without diabetes, and 365 diabetic patients without significant kidney impairment, Inaba and colleagues<sup>48</sup> demonstrated significantly lower HgbA1c levels relative to blood glucose or to glycosylated albumin levels with dialysis, as compared with those without kidney impairment. The ratio of glycosylated albumin to HgbA1c (with a previously reported ratio of approximately 3.0 in the absence of ESRD) was 2.93 in patients without CKD, and 3.81 in those on dialysis. In a subsequent study from the United States, the glycosylated albumin/HgbA1c ratio was again significantly higher in patients who were on dialysis (2.72 vs 2.07).<sup>43</sup> Thus, as an alternative to HgbA1c, evidence linking glycemic control as determined by serum glycosylated albumin levels to diabetic ESRD outcomes is now emerging. In a recent report, Freedman and colleagues<sup>51</sup> analyzed the association between 3 measures (glycosylated albumin, HgbA1c, and serum glucose levels) and hospitalization/survival outcomes in diabetic dialysis patients (90% were on hemodialysis). Time-dependent analyses allowed comparisons with available HgbA1c and monthly random serum glucose levels. In the report, mean (standard deviation) serum glycosylated albumin was 21.5 SDs plus or minus 6%, and HbA1c was 6.9 SDs plus or minus 1.6%. The primary finding was that increased glycosylated albumin, but not HbA1c or random serum glucose concentrations, was predictive of hospitalization and survival.

## VALUE OF GLYCEMIC CONTROL IN CKD PATIENTS

Glycemic management in patients with diabetes and CKD has become increasingly complex, in part reflecting controversies raised in recent studies about safety and efficacy as applied to type 2 diabetes.<sup>52</sup> Challenges cited in improving glycemic control in patients with advanced CKD include therapeutic inertia, monitoring difficulties, and complexity regarding use of a growing list of available treatments in CKD.<sup>53</sup> While HgbA1c combined with home glucose monitoring remains the mainstay for monitoring glycemic control (despite information presented previously), until recently the available evidence regarding the benefit and safety of tight glycemic control in patients with advanced CKD has been limited. There have been no randomized clinical trials to evaluate the effects of glycemic control in patients with late stages of CKD/ESRD. Recent observational studies have added significantly to available evidence, while providing somewhat contrasting results and significant methodological differences.<sup>42,54,55</sup> Williams and colleagues<sup>42</sup> reported observational findings from a large national ESRD database that mortality risks in diabetic patients did not differ when grouped by Hgb1c levels. There was no overall correlation between glycohemoglobin levels and subsequent 12-month mortality risk, even when adjusted for case-mix and laboratory values. Results in a second study, by Kalantar-Zadeh and colleagues,<sup>54</sup> from a similar-sized retrospective database analysis, differed somewhat, in indicating that higher HgbA1c levels were statistically associated with increased death risk. HgbA1c greater than 10% was associated with a 41% greater risk for all-cause and



cardiovascular death. The study used a longer follow-up period, time-dependent survival models, and adjustments for surrogates of malnutrition and inflammation. A subsequent study by Williams and colleagues<sup>55</sup> (Fig. 3) modified its analysis to more directly match that of Kalantar-Zadeh, and found that only extremes of glycemia were associated with worsened survival. These studies indicate that the overall relationship between glycemic control and survival outcomes in the presence of ESRD is somewhat weak. A logical conclusion in terms of benefit/risk is to allow somewhat higher HbA1c targets in CKD. The concept that higher HgA1c targets (ie, 7%–8%) may be preferable in those patients with higher levels of comorbidity<sup>56</sup> was also supported by a recent regression analysis involving A1c levels and mortality from the Dialysis Outcomes and Practice Patterns Study (DOPPS).<sup>57</sup> In another observational study, a post-hoc analysis of the 4-D study, a graded relationship between poor glycemic control and mortality caused by sudden cardiac death was reported.<sup>58</sup> Over a median follow-up of 4 years, using patients with an HgbA1c less than 6.0% as the comparator, patients with sudden cardiac death were identified. Patients with an HgbA1c greater than 8% had a greater than 2-fold higher risk of sudden death compared with those with an HgbA1c less than or equal to 6% (hazard ratio [HR] 2.14), with each 1% increase in HgbA1c associated with an 18% increase in the risk of sudden death after statistical adjustments. Sudden death was the single largest cause of mortality (26%). The specific mechanism by which poor glycemic control increases risk of sudden death was not clear. A recent report of 23,296 patients with diabetes and an eGFR between 15 and 60 mL/min/1.73 m<sup>2</sup> evaluated outcomes according to baseline HgbA1c levels (<7, 7–9, >9) over a median follow-up of 3.8 years.<sup>59</sup> For both stage 3 and 4 CKD, higher levels of HgbA1c were associated with an increased risk of death. More recently, an observational report from the

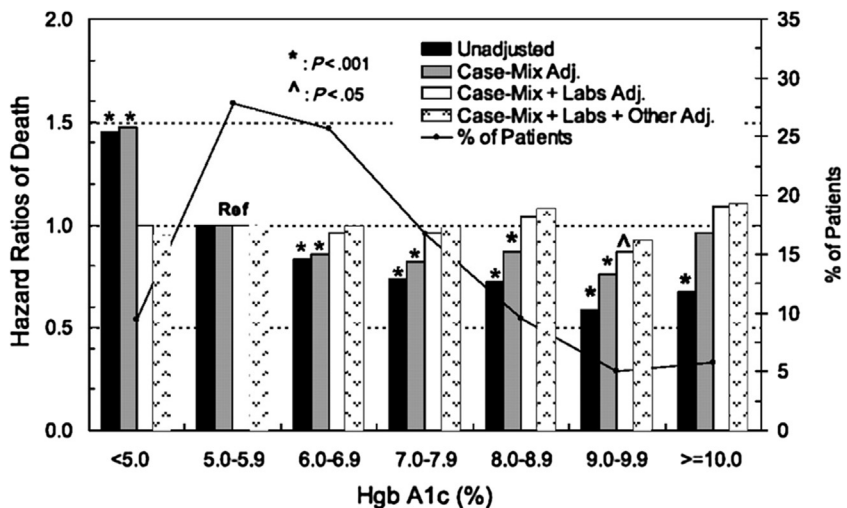


Fig. 3. Relation between glycemic control and hemodialysis survival, among 24,875 hemodialysis patients with follow-up of 3 years, using time-dependent survival models with repeated measures and multiple case-mix adjustments. Data were collected at baseline and every quarter to a maximum of 3 years' follow-up. Extremes of glycemia were weakly associated with survival in the study population. (Reprinted from Williams ME, Lacson E Jr, Wang W, et al. Glycemic control and extended hemodialysis survival in patients with diabetes mellitus: comparative results of traditional and time-dependent Cox model analyses. *Clin J Am Soc Nephrol* 2010;5(9):1595–601; with permission.)



Alberta Kidney Disease Network,<sup>59</sup> in patients with diabetes and more advanced stages of CKD (nondialysis CKD stages 3–5), confirmed that higher HgbA1c levels were associated with markedly worse outcomes, including progression of kidney disease regardless of the baseline eGFR. Confirmation of the renoprotective effect associated with intensive control of hyperglycemia in type 2 diabetes was also suggested by the ADOPT study.<sup>60</sup> Greater durability of glycemic control in those treated with rosiglitazone (compared with metformin and glyburide) was associated with a smaller rise in albuminuria and with preservation of eGFR.

## HYPOGLYCEMIA

Patients with diabetes and CKD are at increased risk for hypoglycemia. Diabetes treatment options for patients with advanced CKD are somewhat limited due to safety and tolerability concerns. Increasing attention is being given to the risks of hypoglycemia (<70 mg/dL) in the diabetic CKD population. This is reflected in recent diabetes guidelines, which not express greater concern than in the past about the dangers of hypoglycemia.<sup>52</sup> The American Diabetes Association (ADA) continues to recommend a goal hemoglobin A1c of less than 7.0% or as close to normal and as safely as possible, but without unacceptable hypoglycemia.<sup>61</sup> Increasing pressure to achieve tight glycemic control targets may result in episodes of hypoglycemia, in many cases iatrogenic. Specific factors that might increase the risk of hypoglycemia include use of insulin secretagogues, missed meals, advanced age, duration of diabetes, and unawareness of hypoglycemia.<sup>62</sup> However, published reviews on glycemic control in diabetic CKD patients give little emphasis to risks of hypoglycemia. The greatest risk of harm is in patients with both CKD and diabetes, particularly in the elderly.<sup>63</sup> Partly as a result of mounting concerns about hypoglycemia, the ADA's current Standards of Medical Care in Diabetes recommend less stringent HgbA1c goals, (ie, 7.5–8.0%), as appropriate for those patients with advanced complications, extensive comorbid conditions, or a history of severe hypoglycemia.<sup>52</sup> Adverse consequences of hypoglycemia could partially explain the outcomes from 3 recent clinical trials, ACCORD,<sup>64</sup> ADVANCE,<sup>65</sup> and VADT.<sup>66</sup> The purpose of these landmark studies was to determine whether glycemic management more aggressive than previously recommended (with a goal of achieving HgbA1c levels near 6.0%) would reduce cardiovascular risk in patients with longstanding diabetes. Hypoglycemia occurred more frequently in the intensive therapy arms of all 3 studies. In the ACCORD trial, the rate of hypoglycemic episodes requiring medical assistance was 3 times higher in the intensive group. Likewise, in ADVANCE, severe hypoglycemia was nearly twice as common in the intensive control group, with half of patients in the low HgbA1c group having at least a minor hypoglycemic event during the trial. Notably, these studies failed to demonstrate cardiovascular benefit with the intensive therapy strategy. With regard to the additional risk of CKD, in the ADVANCE trial analysis, higher creatinine levels were an independent risk factor for severe hypoglycemia. Reports on hypoglycemia and advanced kidney disease have generally occurred as case reports, small series, and reviews.<sup>67</sup> However, as many as half of chronic hemodialysis patients with diabetes may suffer hypoglycemia over a 3-month period.<sup>68</sup> Preliminary findings suggest that the risk of hypoglycemia is especially high in diabetic ESRD patients who have greater glycemic variability.<sup>69</sup>

The health consequences of hypoglycemia can be severe, while fear of iatrogenic hypoglycemia may result in poor glycemic control and further risk of diabetic complications. Episodes of cold sweats, agitation, dizziness, disorientation, slurred speech, fatigue, and decreased level of consciousness are typical. However, hypoglycemia

unawareness worsens with duration of diabetes. The occurrence of hypoglycemia complicated by central pontine myelinolysis and quadriplegia was recently described.<sup>70</sup> Severe hypoglycemia is known to increase the risk of poor outcomes in patients with diabetes.<sup>71</sup> A powerful stimulant to the sympathetic nervous system, severe hypoglycemia may cause acute secondary adverse cardiovascular outcomes, including chest pain due to coronary vasoconstriction and ischemia, myocardial infarction, serious cardiac arrhythmias, and sudden death.<sup>72</sup> Therefore, 1 of the goals of antihyperglycemic treatment in CKD should be avoidance of hypoglycemia.

### **STRATEGIES FOR MANAGEMENT OF HYPERGLYCEMIA IN CKD**

The management strategy for hyperglycemia in CKD involves a multifaceted approach including dietary changes, an exercise regimen, and drug therapy. Diet and exercise are central components of any therapeutic regimen for all patients with diabetes. Dietary changes and physical activity often improve insulin sensitivity. Meal plans should be individualized to accommodate not only the considerations about renal impairment but also lifestyle and personal preferences of the patient. Most patients with diabetes are overweight, and a dietary plan to promote weight reduction may be appropriate. Protein restriction may be appropriate in some patients, but data on the effect of protein restriction on progression of CKD are controversial. A diet that includes complex carbohydrates from fruits, vegetables, whole grains, legumes, and low-fat milk is encouraged. Similar to diet, the exercise regimen also needs to be individualized. Exercise in diabetic patients with CKD is associated with potential risks as well as benefits. A pre-exercise evaluation should be conducted to determine whether the patient has any contraindications to exercise. Because of the high prevalence of cardiovascular disease in these patients, all patients with typical or atypical cardiac symptoms or an abnormal resting electrocardiogram (ECG) should undergo a cardiac stress test. Patients with severe diabetic retinopathy should avoid exercises that involve valsalva (eg, lifting heavy weights). Patients with severe peripheral neuropathy should avoid repetitive stepping exercise (eg, jogging), which may increase the risk of a foot ulcer. In the absence of contraindications, the exercise program should include both aerobic and resistance exercises. Patients also should be counseled about how to coordinate timing of exercise, meals, medications, and glucose monitoring. Low- to moderate-intensity exercise, such as walking, may have the most significant benefits with minimal risks for most patients. Patients should be encouraged to start with short periods of low-intensity exercise and increase the intensity and duration slowly.

Pharmacologic therapy for hyperglycemia in patients with CKD also needs individualization, because it is affected not only by altered insulin resistance and glucose metabolism and higher risk of hypoglycemia as described previously, but also by altered drug metabolism and concerns about the renal effects of antihyperglycemic drugs. Goals for glycemic control need to be revised and readjusted frequently once renal function starts deteriorating, and pharmacologic management needs frequent changes and/or dose adjustments. Many new noninsulin agents offer a safe and effective option for diabetic patients with CKD.

### **USE OF NONINSULIN ANTIDIABETIC DRUGS IN THE PRESENCE OF CKD**

Many noninsulin agents are currently available for the treatment of type 2 diabetes. Most of these agents have become available within the last 2 decades. While some physicians are skeptical about their use because of a lack of long-term data, the new antidiabetic agents do offer an alternative to insulin therapy and may reduce

the risk of hypoglycemia in patients with CKD. There are very few head-to-head comparisons between various noninsulin agents, and data in patients with CKD are scanty. Professional society guidelines on the use of noninsulin agents also leave out patients with CKD.<sup>52,73–76</sup> However, patients with CKD are often eligible for 1 or more of the noninsulin agents and may benefit from them. A brief summary of the available noninsulin agents is given in **Table 1**.

### SULFONYLUREAS

Sulfonylureas (SUs) are the oldest and most commonly used noninsulin agents for treatment of type 2 diabetes. They lower blood glucose levels by releasing insulin from the pancreatic  $\beta$  cells via their action on SU receptors that close the adenosine triphosphate (ATP)-sensitive potassium channels. Patients with longer duration of diabetes often have poor  $\beta$  cell reserves and may not respond to SUs. When used in newly diagnosed patients with type 2 diabetes, SUs tend to lose their effectiveness earlier than metformin or thiazolidinediones (TZDs).<sup>77</sup> However, when effective, SUs can cause unregulated insulin release and lead to severe hypoglycemia that can be particularly serious in the presence of CKD.<sup>78</sup> Long-acting SUs like glyburide and chlorpropamide are more notorious for causing hypoglycemia.<sup>79</sup> Shorter-acting drugs, especially those metabolized in the liver like glipizide and glimepiride, are relatively safe and preferred in patients with CKD.<sup>80</sup>

### BIGUANIDES

Biguanides are insulin sensitizers, with their main site of action being the liver. They do not cause hypoglycemia when used alone. Metformin is the only biguanide available in the United States. It became available in the United States in 1995, but it has been used in Europe and other parts of the world for the last 3 decades. Therefore, extensive experience is available with this drug. Metformin use was associated with a reduction in incidence of cardiovascular events in the UKPDS trial.<sup>81,82</sup> Metformin use is also associated with a small weight loss. As a result, it is the first-line agent recommended by the ADA and European Association for the Study of Diabetes (EASD) for treatment of type 2 diabetes.<sup>61</sup> However, metformin use in certain patients is associated with a risk of lactic acidosis, a rare but life-threatening condition. Metformin is contraindicated in women with serum creatinine greater than 1.4 mg/dL and in men with serum creatinine greater than 1.5 mg/dL.<sup>83</sup> Other risk factors for lactic acidosis include hypoxemia, sepsis, alcohol abuse, liver failure, myocardial infarction, and shock. It is important to know these contraindications and stop metformin promptly when any of these conditions is present. Studies have shown frequent irrational use of metformin in patients with diabetes and renal failure.<sup>84</sup> Diarrhea and gastrointestinal adverse effects are other common adverse effects of metformin and should lead to a decrease in dose or discontinuation of this drug.

### THIAZOLIDINEDIONES

Thiazolidinedione (TZD) drugs are insulin sensitizers and therefore do not cause hypoglycemia if used alone. They act on the PPAR $\gamma$  receptors and improve insulin sensitivity of peripheral tissues like muscle and adipose tissue. Pioglitazone and rosiglitazone are the 2 TZDs currently available in the United States, and both agents are safe in CKD and seem to be effective for glycemic control in patients on hemodialysis.<sup>85–87</sup> However, rosiglitazone is not available in the United States in the open market, because a meta-analysis showed its association with myocardial infarction.<sup>88</sup> Rosiglitazone

**Table 1**  
**Noninsulin antidiabetic agents**

Drug	Mechanism of Action	Advantages	Disadvantages	Role in Renal Failure
Biguanides: • Metformin	Insulin sensitizer ↓ Hepatic glucose production	Extensive experience No hypoglycemia Weight neutral Likely ↓ CVD Low cost	Gastrointestinal adverse effects Lactic acidosis B-12 deficiency Multiple contraindications, including renal failure, acidosis, hypoxia, infection, dehydration, older age	Cannot be used with serum creatinine >1.5 in men and >1.4 in women
Sulfonylureas: • Glyburide • Glipizide • Glimepiride • Gliclazide	Insulin secretagogue	Extensive experience ↓ Microvascular risk Low cost	Hypoglycemia Weight gain Low durability of effect	Use with caution Glipizide preferred
Meglitinides: • Repaglinide • Nateglinide	Insulin secretagogue	↓ Postprandial glucose excursions Dosing flexibility	Hypoglycemia Weight gain Frequent dosing High cost	Safer than sulfonylureas
Thiazolidinediones: • Pioglitazone • Rosiglitazone	Insulin sensitizer ↑ Insulin sensitivity in muscle and adipose tissue	No hypoglycemia Durability of effect ↓ TGs, ↑ HDL-C ? ↓ CVD (pioglitazone)	Weight gain Edema/heart failure Bone fractures ? ↑ MI (rosiglitazone) ? Bladder ca (pioglitazone) High cost	Safe but concerns about fluid retention
α-glucosidase inhibitors: • Acarbose • Miglitol	Slows carbohydrate digestion/absorption	No hypoglycemia ↓ Postprandial glucose excursions ? ↓ CVD events	Nonsystemic Gastrointestinal adverse effects Dosing frequency Modest ↓ A1c	Contraindicated in renal failure with serum creatinine >2 mg/dL

DPP-4 Inhibitors: • Sitagliptin • Saxagliptin • Linagliptin	Increased GLP-1, GIP leading to ↑ insulin, ↓ glucagon	No hypoglycemia Well tolerated	Modest ↓ A1c reduction ? Pancreatitis Urticaria High cost	Safe and effective
GLP-1 receptor agonists: • Exenatide • Exenatide- extended release • Liraglutide	Activates GLP-1 receptor leading to ↑ insulin, ↓ glucagon ↓ Gastric emptying ↑ Satiety	Weight loss No hypoglycemia ? Beta cell mass ? CVD protection	Gastrointestinal adverse effects ? Pancreatitis ? Renal failure ? Medullary thyroid ca Injectable High cost	Contraindicated in renal failure due to severe adverse effects and concerns about acute renal failure
Amylin mimetics: • Pramlintide	↓ Glucagon ↓ Gastric emptying ↑ Satiety	Weight loss ↓ Postprandial glucose	Gastrointestinal adverse effects Modest ↓ A1c Injectable Hypoglycemia with insulin Dosing frequency Injection	No data in CKD, should not be used
Bile acid sequestrant: • Colesevelam	Unknown	No hypoglycemia ↓ Low-density lipoprotein	Constipation ↑ Triglycerides Modest ↓ A1c may ↓ absorption of other medications	No data
Dopamine-2 agonists: • Bromocriptine	Modulates hypothalamic control mechanisms ↑ Insulin sensitivity	No hypoglycemia ? ↓ CVD events	Modest ↓ A1c Dizziness/syncope Nausea Fatigue	No data

Abbreviations: ca, carcinoma; CVD, cardiovascular disease.

has also been shown to be associated with increased cardiovascular mortality in hemodialysis patients.<sup>89</sup> Pioglitazone, on the other hand, may have some cardiovascular-protective benefits.<sup>90,91</sup> Pioglitazone also has a favorable effect on lipids. Both TZDs cause fluid retention and increase the risk of heart failure, a problem that may be worse in patients with CKD/ESRD. Their use is also associated with increased risk of fractures.<sup>92</sup> Recently, concerns have been raised about the increased risk of bladder cancer with pioglitazone.<sup>93</sup> Because of these reasons, TZDs are not a preferred class of drugs for treatment of type 2 diabetes, especially in patients with CKD.

#### DIPEPTIDYL PEPTIDASE 4 INHIBITORS

Dipeptidyl peptidase 4 (DPP-4) inhibitors are becoming more popular for the treatment of hyperglycemia in CKD patients because of their better tolerability and low risk of hypoglycemia. By blocking the DPP-4 enzyme, these drugs increase the concentrations of endogenous incretins GLP-1 and GIP. Incretins are hormones secreted by the gastrointestinal tract in response to ingestion of food. Incretins stimulate pancreatic  $\beta$  cells to increase insulin secretion and suppress  $\alpha$  cells to decrease glucagon secretion. These effects are dependent on ambient glucose levels, being more potent when glucose levels are high and less potent when glucose levels are low. Thus, incretinomimetic drugs are more effective in the postprandial period, when glucose levels are high. However, in a fasting state, their effect is mitigated by low glucose levels, removing the risk of hypoglycemia. Both, GLP-1 and GIP are rapidly broken down by the DPP-4 enzyme, leading to a very short half-life (approximately 2 minutes). Therefore, DPP-4 inhibitors increase the bioavailability of GLP-1 and GIP. They lower glucose levels and do not cause hypoglycemia when used by themselves. Sitagliptin, saxagliptin, and linagliptin are the 3 drugs currently available in this class in the United States. Sitagliptin and saxagliptin need dose adjustment for reduced eGFR because of their renal excretion. Linagliptin is metabolized in the liver and can be used at a fixed dose irrespective of the renal function. Randomized controlled trials have demonstrated safety and efficacy of DPP-4 inhibitors in patients with CKD.<sup>94-98</sup> DPP-4 inhibitors were also found to be weight neutral in their clinical trials. However, long-term data on their safety and efficacy are still lacking.

#### GLP-1 RECEPTOR AGONISTS

These drugs have a molecular structure similar to endogenous GLP-1, but they are resistant to metabolism by the DPP4 enzyme. They increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner, thus eliminating the risk of hypoglycemia. These drugs slow gastric emptying and suppress appetite through their central effect, and these effects are responsible for weight loss. However, these effects also lead to nausea and vomiting, which can be more severe in patients with ESRD.<sup>99</sup> Exenatide and liraglutide are the 2 drugs currently available in this class. Both are injectable agents. There are also concerns of acute pancreatitis and acute renal failure with both these agents.<sup>100,101</sup> Moreover, there are concerns of medullary thyroid carcinoma with liraglutide due to C-cell hyperplasia seen in mice injected with liraglutide. Due to their potential adverse effects and poor tolerance, GLP-1 agonists are often not a good choice in patients with CKD.

#### MEGLITINIDES

Meglitinides are insulin secretagogues acting by mechanisms similar to SUs. However, they are shorter acting, and their effects are dependent on ambient glucose

levels. Therefore, their risk of hypoglycemia is lower, and they are more effective for postprandial glycemic control. Repaglinide and nateglinide are the 2 agents available in the United States. Nateglinide may be preferred in CKD because of lower risk of hypoglycemia, and it has been studied in CKD.<sup>102,103</sup> These drugs require frequent dosing, because they need to be taken before each meal.

### **$\alpha$ -GLUCOSIDASE INHIBITORS**

$\alpha$ -glucosidase inhibitors block the enzyme responsible for digestion of carbohydrates. Acarbose and miglitol are the 2 agents in this class, and both have been shown to reduce HgbA1c in patients with type 2 diabetes. A major adverse effect of these drugs is flatulence. They are also contraindicated in patients with serum creatinine greater than 2 mg/dL because of a risk of accumulation that may lead to liver failure.

### **BILE ACID SEQUESTRANTS**

Colesevelam is a bile acid sequestrant that was originally used for hypercholesterolemia. It can also lower glucose levels in patients with type 2 diabetes and is approved by the US Food and Drug Administration (FDA) for this purpose. The mechanism of the glucose-lowering effect of colesevelam is poorly understood. A major adverse effect is constipation. The drug is used infrequently for patients with or without CKD.

### **DOPAMINE-2 AGONISTS**

Bromocriptine, a dopaminergic agent available for several decades, was recently approved for treatment of hyperglycemia in type 2 diabetes. Its mechanism of action is considered to involve resetting of circadian rhythm in the hypothalamus. Studies have suggested disturbed circadian rhythm in patients with type 2 diabetes that is associated with insulin resistance. Specific benefits or harms of the use of dopamine-2 agonists in CKD are unknown.

### **AMYLIN MIMETICS**

Amylin is a hormone synthesized in pancreatic  $\beta$ -cells and cosecreted with insulin. It slows gastric emptying, increases satiety, and also suppresses secretion of glucagon after a meal. Pramlintide is an amylin agonist that can be used along with insulin to lower the postprandial glycemic excursions. The drug has limited use in patients with type 1 or type 2 diabetes and has not been studied in CKD.

## **INSULIN THERAPY IN PATIENTS WITH RENAL DYSFUNCTION**

Insulin therapy in CKD patient is no different from patients without CKD, other than the fact that insulin requirements may be lower, and insulin action may be prolonged.<sup>104</sup> Therefore, the risk of hypoglycemia with insulin therapy is increased in CKD. A study in hospitalized patients suggested that insulin dose may be reduced by approximately 50% in CKD.<sup>105</sup> Effects of dialysis on insulin sensitivity can further complicate insulin therapy in patients with ESRD.<sup>106</sup> Moreover, presence of glucose in dialysis fluid can affect glycemic control, especially in those on peritoneal dialysis. Insulin therapy is often divided into basal insulin coverage and nutritional insulin coverage. Basal insulin coverage is typically provided by using an intermediate- or long-acting insulin, and nutritional insulin coverage is provided by a short- or rapid-acting insulin (**Table 2**). In CKD, insulin detemir or neutral protamine Hagedorn (NPH) insulin used once or twice daily may be appropriate for basal coverage. Rapid-acting insulin analogs are



	<b>Insulin Name</b>	<b>Onset of Action</b>	<b>Peak Effect</b>	<b>Duration</b>	<b>Other Remarks</b>
Basal	NPH	1–2 h	4–8 h	12–18 h	1–2 times daily
	Glargine	2 h	No peak	20–24 h	Once daily
	Detemir	2 h	3–9 h	16–24 h	Once daily
Nutritional	Lispro, Aspart, Glulisine	5–15 min	1–2 h	4–6 h	Can be taken after meals if food intake is unreliable
	Regular	30 min	2–4 h	6–8 h	Less commonly used

appropriate for nutritional coverage in CKD.<sup>107–109</sup> These insulins may even be prescribed after meals in patients with unreliable food intake. It is important to individualize the insulin regimen according to patient's lifestyle, food intake, and dialysis regimen. A regimen consisting of noninsulin agents and basal insulin may be appropriate in many patients with type 2 diabetes. Continuous insulin infusion via an insulin pump may improve quality of life in patients requiring multiple insulin injections, but no studies are available to show a lower risk of hypoglycemia or better glycemic control in patients with CKD.

### EFFECT OF TREATMENT CHOICES ON RENAL FUNCTION

A renoprotective effect of glycemic control was demonstrated in early clinical trials of diabetes and confirmed in recent clinical trials. However, an effect of 1 antidiabetic agent over another has not been demonstrated. As mentioned previously, there are few head-to-head clinical trials comparing various antidiabetic agents, and none of these trials was conducted in patients with CKD. A retrospective study suggested that metformin may be associated with lower decline in renal function over time as compared with the use of SUs.<sup>110</sup> However, a possibility of selection bias cannot be ruled out in this study. Some noninsulin agents need to be avoided in patients with CKD, and the doses of others need to be adjusted to avoid their adverse effects. However, at this point of time, no 1 agent can be preferred over another for renoprotective effect.

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