Glycemic control and cardiovascular disease in a high-risk chronic kidney disease population

Diabetes is the leading cause of cardiovascular disease morbidity and mortality, and the presence of chronic kidney disease has been increasingly recognized as an independent cardiovascular disease risk factor. Sufficient evidence suggests that tighter glycemic control improves the macro- and micro-vascular complications in diabetic patients. However, the majority of the studies have not included individuals with advanced chronic kidney disease. Recent work has sought to determine the effectiveness of tighter glycemic control in diabetic kidney disease on cardiovascular mortality. Furthermore, recent evidence suggests that in addition to glycemic control in diabetic kidney disease, there are additional comorbid conditions such as obesity and hypertension that need to be considered. Lifestyle modifications in addition to glycemic control and reductions in systolic blood pressure are now recognized to be important in reducing cardiovascular disease mortality as compared with the tighter glycemic control alone.

KEYWORDS: cardiovascular disease ▪ chronic kidney disease ▪ CKD ▪ CVD ▪ diabetes ▪ glycemia

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There are an estimated 23.8 million people in the USA with diabetes, and 171 million worldwide [101,102]. The impact of diabetes on healthcare costs, mortality and comorbidity seems to be the highest amongst all chronic debilitating diseases. Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the USA, accounting for up to 40% of patients on dialysis. The number of patients receiving renal replacement therapy (RRT) was approximately 400,000 in the year 2000, and this number is projected to increase to approximately 2 million by the year 2030 [1], largely due to an increase in the worldwide diabetic population to 366 million, and patients with stage 1–4 CKD to approximately 24–28 million [2,101,102].

Diabetes is a leading cause of cardiovascular disease (CVD) morbidity and mortality along with other Framingham risk factors including hypertension, dyslipidemia, tobacco abuse and increasing age, and CKD itself has been recognized as an independent risk factor for CVD [3–6]. Most importantly, diabetes leads to several macrovascular and microvascular complications that contribute to the increased risk of CVD [7]. The complex interplay of the above factors and nontraditional risk factors, including increased oxidative stress, inflammation, altered mineral metabolism, acidosis and uremia, also raises the risk for CVD. Hence, both lifestyle modifications, including diet, exercise and smoking cessation, and pharmacological interventions are warranted to reduce the risk for cardiovascular disease.

There is a growing evidence for pharmacological interventions in diabetic kidney disease (DKD) for CVD risk reduction, especially in advanced kidney disease, aimed at several factors such as better blood pressure control, dyslipidemia management and the use of aspirin. However, in order to prevent CVD outcomes, our understanding of hyperglycemia management in addition to other CVD risk factors in early stages of DKD is limited. Hyperglycemia management guidelines exist for glycemic control in patients with diabetes, and CKD stage 1 and 2 have been derived with end points of development of either microalbuminuria and/or proteinuria, or worsening of renal function. However, there are very few studies that have shown the benefit of tighter glycemic control in patients with CKD (stages 3–5) and ESRD on hemodialysis [8]. Early diabetic education and care management in patients on hemodialysis have shown improvement in patient outcomes [9]. Otherwise, studies demonstrating lowering of CVD risk with tighter glycemic control, as indicated by lower hemoglobin A1c (HbA1c) levels, are lacking.

Diabetes & CVD risk

Diabetes has been shown to be a major risk factor for CVD; the age-adjusted risk for fatal CVD events could be as high as three times when compared with the nondiabetic population [6]. Morbidity and mortality due to CVD are also significantly higher in patients with diabetes

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and a prior history of coronary heart disease (CHD) compared with nondiabetic patients [5]. The presence of other traditional risk factors for CVD such as tobacco use, advanced age, hypercholesterolemia and hypertension, significantly increase the CVD events in the CKD population.

As many as 11% of adults in the USA have CKD [102]; the prevalence of CKD is even higher among patients with CVD [5]. In turn, CKD is a major risk amplifier for CVD [5,10]. The presence of CKD in diabetic patients augments the risk of CVD by mechanisms discussed earlier. The presence of proteinuria and decreased glomerular filtration rate (GFR) results in the increase of low-density lipoprotein (LDL) cholesterol levels, increased lipoprotein(a) (Lp[a]) levels, accumulation of advanced glycation end products (AGEs), elevations in systolic blood pressure, increases in insulin resistance and vascular calcification. The risk of CVD could be as much as 20–30-times higher in dialysis patients when compared with the general population. Due to the complex interplay of a multitude of CVD risk factors in patients with diabetes and CKD, early risk stratification and intervention directed at tight glycemic control, weight loss and reductions in systolic blood pressure as well as LDL are needed [11].

Guidelines on glycemic control

There are several studies that support the tighter glycemic control (HbA1c < 6.5–7.0%) for prevention of microvascular complications, especially diabetic retinopathy and the development of microalbuminuria (30–299 mg/dl) and overt proteinuria (>300 mg/dl) [7,12,13]. This conclusion is based on numerous large, randomized, controlled trials, such as the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study [12,14], and the United Kingdom Prospective Diabetes Study (UKPDS), among others. Collectively, this work suggests there is a reduction in macro- and microvascular complications of diabetes with tighter glucose control (HbA1c < 7.0%).

Importantly, recent data from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [15] demonstrate that tighter glycemic control, as defined by HbA1c of less than 6.5%, results in 10% relative reduction in the combined outcome of microvascular and macrovascular events, as compared with the conventional glycemic control as defined by HbA1c of 7.0%. Interestingly, the authors conclude the relative risk reduction due to a reduction in incident nephropathy is 21% with tighter glycemic control. Alternatively, data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [16] suggests that intensive glycemic control (HbA1c < 6.0%) to prevent CVD contributes to an excess mortality. Additionally, the data from the Veterans Affairs Diabetes Trial (VADT) [17] also suggest that there are no benefits with tighter glycemic control (HbA1c of 6.9 vs 8.4%) on the rates of major cardiovascular events, death or microvascular complications. Recent evidence does suggest that intensive glucose control during the initial phases of diabetes can lead to reductions in cardiovascular events in the long term, independent of glycemic control, as shown by the 10-year follow-up of intensive glucose control in Type 2 diabetes patients in the UKPDS [18]. Other studies have not consistently shown a protective effect for tight glycemic control with regard to macrovascular complications, and may be associated with higher incidence of hypoglycemia [19]. Presently, consensus guidelines recommend a target HbA1c of 6.5–7.0% for prevention of CVD in those with diabetes [11].

Factors influencing glycemic control in CKD

It is of note that individuals with CKD stages 1 and 2 with GFR greater than 60 ml/min/1.73 m^2 and a relatively preserved clearance require no special glucose monitoring when compared with the general diabetic population. However, patients who have advanced CKD stages 3 through 5 with GFR less than 60 ml/min/1.73 m^2 pose certain challenges for glucose monitoring. In advanced kidney disease, a paradoxical situation exists whereby elevated blood glucose levels from insulin resistance and impaired glucose tolerance due to CKD can impair the level of insulin sensitivity further. Alternatively, the decreased clearance of insulin and oral hypoglycemic agents predispose these patients with CKD to an increased risk of hypoglycemia. Collectively at this level of GFR, there is a complex relationship of other factors, including altered mineral metabolism, acidemia, accumulation of uremic toxins and, importantly, anemia, which can make glycemic control and monitoring more difficult.

Further challenges are encountered in monitoring long-term glycemic control with HbA1c in patients with CKD stages 3 through 5. The factors that may lead to lower HbA1c readings include decreased lifespan of red blood cells (RBCs), iron deficiency and a minor amount of blood loss in the patients on hemodialysis. The factors that could artificially raise the HbA1c are increased carbamylation of hemoglobin and acidosis. Therefore, it

is essential to compare the HbA1c with the blood glucose monitoring at home. Some authors have suggested monitoring the average of preprandial and bedtime glucose rather than HbA1c alone, which may provide a better index of glycemic control in patients with advanced CKD and may help in avoiding the wide variation of glycemic levels in patients. Another alternative is measuring glycated albumin, which may be used to estimate glycemic control in patients with DKD, as serum hemoglobin levels and anemia do not significantly impact the glycated albumin level [20]. Indeed, the levels of mean serum glucose and glycated albumin concentrations may be higher than indicated by HbA1c in those with DKD [20].

Glycemia management in DKD

As discussed, there is a complex interaction of factors influencing glycemic control in patients with advanced DKD. A major factor interfering with tighter glycemic control to HbA1c of 6.5 or less is hypoglycemia [19]. Sulfonylureas have been shown to mildly increase the risk of hypoglycemia in the UKPDS [7]. Furthermore, it has been recognized that patients treated with insulin tend to have more episodes of hypoglycemia in DKD. Hypoglycemia is more prevalent in patients with Type 1 diabetes [19] as compared with patients with Type 2 diabetes; nevertheless, the chances of hypoglycemia increase with insulin treatment in Type 2 diabetes [7,12,19]. Therefore, close monitoring and dose adjustment of either oral hypoglycemic agents and/or insulin are warranted with advancing kidney disease [21].

Oral hypoglycemic agents for glycemic control in patients with CKD

Consensus statements from the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) for management of hyperglycemia in patients with CKD [11] suggest clinicians should have a good working knowledge of the pharmacokinetics of drugs (oral hypoglycemic agents or any other drugs for that matter) in patients with impaired renal function, as there could be accumulation of the drugs and/or its metabolites, resulting in adverse outcomes. Some of the oral hypoglycemic agents that are useful in patients without CKD should be altogether avoided, and the dosages of other agents need to be adjusted to account for impaired renal clearance.

The first-generation sulfonylureas (e.g., chlorpropamide, tolazamide and tolbutamide) should be avoided, as both the parent drug and their metabolites have significant renal clearance, and there is a greater incidence of hypoglycemia with these agents. Amongst the second- and third-generation sulfonylureas, glyburide and glimepride are associated with hypoglycemia, and a dose adjustment of these agents based on fasting blood glucose is recommended, if they have to be used at all. Glyburide should be altogether avoided in advanced renal disease due to its longer half life. Another second-generation drug, glipizide, and the first generation drug, gliclazide, are relatively safe oral hypoglycemic agents for diabetic patients with CKD.

Meglitinides are short-acting inhibitors of ATP-dependent K^+ channels on pancreatic β-cells, amongst which mitiglinide and repaglinide appear to be safe in early CKD. Mitiglinide is not yet US FDA approved. No clinical trials to study the use of these medications in advanced renal disease have been carried out and caution is advised. Mitiglinide and nateglinide are said to have an increase in active metabolites in CKD patients, and hypoglycemia has been reported more often. However, no dose adjustment is recommended, only cautious use with careful titration of these agents is recommended in advanced kidney disease.

Metformin (biguanides) should not be used in patients with impaired renal function with creatinine concentrations of greater than or equal to 1.5 mg/dl in men and greater than or equal to 1.4 mg/dl in women, as it is cleared by the kidney and can result in lactic acidosis [22]. Also, patients with a previous history of heart disease, congestive heart disease, chronic obstructive pulmonary disease and patients older than 80 years are more prone to the development of lactic acidosis. Importantly, metformin monotherapy is not associated with hypoglycemia.

There is no dose reduction of thiazolidinediones (TZDs) required in CKD. However, it should be noted that rosiglitazone could be associated with increased fluid retention, and may also increase the risk of death, myocardial infarction and congestive heart failure [23,24]. Pioglitazone, on the other hand, may improve the risk of cardiovascular events in patients, but there is increased risk of fluid retention as compared with the placebo [25]. TZDs are associated with improvements in cardiovascular outcomes in patients with non-insulin-dependent diabetes [26].

The dipeptidyl peptidase IV inhibitors sitagliptin and vidagliptin are relatively newer agents, and cautious use and dose adjustment is currently advised in advanced kidney disease by the manufacturers. Currently, we are unaware of any published reports in regards to the beneficial cardiovascular effects in CKD

patients. As per the manufacturer, exenatide is not recommended in advanced CKD with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m^2, and no dose reduction is recommended with an eGFR greater than 30 ml/min/1.73 m^2. There are no data in advanced CKD and hemodialysis patients available on amylin analogues such as pramlinitide, and no dose adjustments are recommended by the manufacturer in patients with CKD.

Insulin therapy in CKD

There are no dose and type of insulin recommendations in patients with diabetes and CKD, but similar to first-generation sulfonylureas and advancing kidney disease, there are decreases in clearance of insulin and a risk for hypoglycemia. Therefore, closer monitoring of blood glucose levels is warranted and more frequent dose adjustments of insulin may be required with diminishing GFR; otherwise, there could be a significant risk of hypoglycemia in the patients with advanced CKD. The dose reduction could be to the tune of 40–60% in the patients with advanced CKD (with eGFR of <10 ml/min/1.73 m^2) as compared with the patients with eGFR of more that 80 ml/min/1.73 m^2 [16,21].

Lifestyle interventions & dietary modifications

The increased incidence of diabetes over the past several years has correlated with the increased incidence of obesity, which has now reached epidemic proportions. In addition, obesity is associated with derangements in the lipid and protein metabolism, and elevations in systolic blood pressure. It is no surprise that there is an increased incidence in CKD and ESRD secondary to obesity and diabetes. Several large observational studies have demonstrated a close association between increase in body mass index (BMI) with increased incidence of albuminuria/proteinuria, CKD and ESRD, independent of the effects of diabetes and hypertension [27,28]. The mechanism for CKD in obesity has been postulated to be the complex interplay of factors leading to increased oxidative stress and inflammation [29] – the release of hormones and cytokines causing direct and indirect renal injury along with increased GFR and albuminuria due to volume expansion, increased renal plasma flow (RPF) and altered glomerular hemodynamics [30–32].

Various interventions that have shown beneficial effects in modifying the natural history of DKD include changes in lifestyle from a sedentary to an active one, routine daily exercise and decrease in calorie intake reducing obesity, incidence of metabolic syndrome and subsequent DKD. Reducing weight has shown to reduce proteinuria [33], decrease blood pressure [34], prevent progression of CKD [35] and may prevent development of DKD. If the traditional measures of weight loss – that is, exercise and decreased calorie intake – fail, bariatric surgery has been presented as a potential option as it may improve various metabolic and renal measures [36,37] and result in better glycemic control, and thereby potentially improve future risk of CVD events [38].

Dietary modifications

Dietary modifications aimed at better glycemic control, reduced salt intake for blood pressure control and dietary protein restriction have been shown to have beneficial effects on DKD. It is of note, due to the complexity of dietary recommendations and risk for malnutrition with advancing CKD, that clinicians should recommend a healthy lifestyle.

Nutritional surveys have shown that Americans eat more than the recommended dietary allowance (RDA) of proteins, which is 0.8 g/kg body weight/day [103]. High protein intake may increase albuminura and may accelerate the loss of kidney function in DKD. Increased albuminuria/proteinuria can lead to hyperfilteration and worsening of renal function, in both human and animal studies [39–45]. In addition to DKD, it has been shown that more than 20% increase in protein intake over RDA may be associated with progression of kidney disease in early CKD [46,47].

On the other hand, data suggests that lowering the protein intake from 1.02 g/kg body weight/day to 0.89 g/kg body weight/day slows down the progression of CKD stage 2 to CKD stage 5 and death in Type 1 diabetes [48]. Data further support the increased benefits of decreased protein intake in patients with Type 1 as compared with Type 2 diabetes. In a meta-analysis [49,50] it was found that a low-protein diet reduces the risk of progression of albuminuria/proteinuria and loss of GFR. Alternatively, a recent meta-analysis of available randomized, controlled trials does not support any beneficial effects of a low-protein diet for DKD [51]. The collective weight of the evidence questions the utility of a low-protein diet in management of DKD. However, the NKF-KDOQI guidelines currently recommend a dietary protein intake of 0.8 g/kg body weight/day in light of the available evidence to prevent the progression of proteinuria and CKD [11].

Future perspective

Diabetes is a leading cause of CVD morbidity and mortality, and CKD itself has been recognized as an independent risk factor for CVD. Importantly, diabetes and elevated blood glucose levels contribute to macro- and micro-vascular complications that contribute to the increased risk of CVD. There is a growing body of evidence for pharmacological interventions in DKD for CVD risk reduction, especially in advanced kidney disease, aimed at several factors such as glycemic control. However, in order to prevent CVD outcomes our understanding of hyperglycemia management in early stages of DKD is limited. Hyperglycemia management guidelines for glycemic control in patients with diabetes and CKD stage 1 and 2 have been derived with end points of development of either microalbuminuria and/or proteinuria, or worsening of renal function. However, there are very few studies that have shown the benefit of tighter glycemic control on progression of CKD (stages 3–5) and incident ESRD, as well as CVD events. There is still need for future work to determine optimal management strategies and monitoring of DKD. In addition, the risk for anemia with advanced DKD further complicates our understanding of monitoring and management, and HbA1c should be closely correlated with routine home monitoring of glycemia. Lifestyle modifications including weight loss, low sodium diet, exercise program, inclusion of more plant protein in diet and smoking cessation are important areas of intervention to prevent progression of CKD in the diabetic population.

Executive summary

Diabetes & cardiovascular disease risk

- Diabetes confers a threefold higher risk for a fatal cardiovascular event.
- The co-existence of traditional risk factors, including tobacco use, advanced age, hypercholesterolemia and hypertension, augments cardiovascular disease (CVD) risk.
- Diabetes and chronic kidney disease (CKD) together augment CVD risk further via accumulation of advanced glycation end products, oxidative stress, increased insulin resistance and vascular calcification.
- Excess death in diabetic patients over nondiabetic patients is strongly associated with proteinuria.

Guidelines on glycemic control

- Strong recommendations exist for tighter glycemic control (HbA1c $\leq$ 7.0%) for prevention and reduction in risk of microvascular complications.
- Weaker evidence exists for tight glycemic control for prevention of macrovascular complications.

Factors influencing glycemic control in CKD

- Glycemic control in CKD stages 1 and 2 (GFR > 60 ml/min/1.73 m^2) can be uniformly achieved and monitored per guidelines for non-CKD patients.
- CKD stages 3–5 (<60 ml/min/1.73 m^2) pose special challenges to monitoring of glucose, primarily due to decreased excretion of insulin and oral hypoglycemic agents.
- Factors that contribute to hyperglycemia include insulin resistance and medications such as β-blockers and thiazides.
- Altered mineral metabolism, acidemia, accumulation of uremic toxins and hypertension can interfere with tight glycemic control.
- HbA1c is not the best marker for long-term glycemic control in CKD patients, and values should always be compared with home blood glucose values.

Glycemia management in diabetic kidney disease

- Choice of drug therapy depends on previous glycemic control, with most patients eventually requiring insulin.
- Maintaining HbA1c of less than 7.0% or as close to normal as possible is recommended for all CKD stages/diabetic kidney disease (DKD), despite most trials excluding patients with CKD stages 3–5.
- First-generation sulfonylureas should be avoided except for gliclazide. Glipizide is the preferred drug, as it is mostly excreted by the liver.
- Metformin should be avoided in patients with creatinine greater than1.5 g/dl in men and 1.4 g/dl in women.
- TZDs should be used with caution and patients monitored for fluid overload.
- Meglitinides are useful alternative insulin secretagogues; however, the problems with hypoglycemia are bothersome, especially with nateglinide.
- Insulin remains the mainstay of therapy for glycemia control.

Lifestyle interventions & dietary modifications

- Body mass index remains an excellent predictor of diabetes.
- Mild weight loss (7%) and moderate exercise (~150 min/week) results in risk reduction of approximately 60% for development of new diabetes.
- Dietary protein intake should be restricted to 0.8 g/kg body weight per day, and intake should be cut down further to 0.6 g/kg body weight per day, with decreasing glomerular filtration rate.

Future perspective

- There is a need for clinical trials that test the effects of tight glycemic control on different stages of CKD/DKD, whether this is achieved singly with insulin or with a multifaceted approach including behavior, nutrition and several drugs.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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