Diabetes Management Issues for Patients With Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common condition that is estimated to affect 11% of the U.S. population, or 19 million people, and > 50 million people worldwide.[1,2] Similarly, diabetes is of an epidemic scale, with prevalence estimates of 20 million people in the United States and 171 million people worldwide.[3] Diabetes is often associated with CKD, and for 45% of patients who receive dialysis therapy, diabetes is the primary cause of their kidney failure.[4] Additionally, moderate to severe CKD is estimated to be found in 15–23% of patients with diabetes.[5,6] It is important to recognize the impact of this combination of diagnoses because the risk of events and death from cardiovascular disease is significantly increased compared to patients without the combination,[7,8] and for patients with microalbuminuria, the risk of cardiovascular disease is twice that compared to patients with no albuminuria.[9] Identification and diagnosis of CKD is important to optimize clinical management recommendations for this complex patient population.

Management of diabetes includes many areas that may be influenced by the severity of a patient's kidney dysfunction. This includes the methods that are used to determine the adequacy of diabetes control, such as hemoglobin A_{1c} (A1C), the potential complications and cautions regarding oral hyperglycemic therapies, and the variable response to insulin therapy as kidney dysfunction progresses. Additionally, management of comorbid conditions, such as hypertension and hyperlipidemia, and evaluation

Table 1. KDOQI Classification of CKD		
Stage	**Description**	**GFR (ml/min per 1.73 m²)**
1	Kidney damage with normal GFR	> 90
2	Kidney damage with mild decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–20
5	Kidney failure	< 15 (or dialysis)

for the development of conditions associated with CKD, such as anemia, hyperphosphatemia, and hyperparathyroidism, must also be considered in the care of patients with diabetes and CKD. Finally, special considerations regarding additional dietary restrictions may also be required in patients with diabetes and CKD. This article explores

IN BRIEF

Chronic kidney disease (CKD) is common and can be found in up to 23% of patients with diabetes. The recommended hemoglobin A_{1c} goal for these patients is also < 7.0%. Medication therapy for diabetes may require dose adjustments or may be contraindicated in patients with CKD. Assessment and management of comorbid diseases, including hypertension, hyperlipidemia, anemia, hyperphosphatemia, and hyperparathyroidism, is important in the care of patients with diabetes and CKD. Multidisciplinary care may provide the optimal system for maximizing care of these complex patients.

current evidence to guide the pursuit of comprehensive care for patients with diabetes and CKD.

Diagnosis of CKD

Traditionally, CKD believed to result from diabetes has been termed "diabetic nephropathy." Recently, the Diabetes and Chronic Kidney Disease work group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) suggested that a diagnosis of CKD presumed to be caused by diabetes should be referred to as "diabetic kidney disease (DKD)" and the term "diabetic nephropathy" should be reserved for kidney disease attributed to diabetes with histopathological injury demonstrated by renal biopsy.[10] These definitions will be applied throughout this article, as appropriate.

CKD, regardless of its underlying etiology, is defined as either kidney damage or decreased kidney function for ≥ 3 months.[11] Evidence of kidney damage may be demonstrated by abnormal imaging studies, urine sediment, urine chemistries, or, more commonly, proteinuria.[12] Staging of CKD is classified into five levels grouped by kidney function as described by the estimated

glomerular filtration rate (eGFR). The KDOQI CKD Stages 1–5 are described in Table 1.[11] Kidney function is now often reported by laboratories as an eGFR using estimating equations, such as the Modification of Diet in Renal Disease (MDRD) study equation. Commonly used is the abbreviated MDRD study equation, which includes the patient's age, sex, race, and serum creatinine to estimate GFR.[13] Although this equation is the most widely used to determine eGFR, the development of the equation did not include patients with diabetes, and it has not been validated in large populations of patients with CKD and diabetes.[14]

The clinical diagnosis of DKD is primarily identified by detection of proteinuria. Microalbuminuria is defined as an albumin-creatinine ratio (ACR) of 30–300 mg/g from a spot urine collection, 30–300 mg/24 hours in a 24-hour urine collection, or 20–200 mg/min in a timed urine collection. Macroalbuminuria is defined as > 300 mg/g, > 300 mg/24 hours, and > 200 mg/min in the same tests, respectively.[10] For initial screening of DKD, measurement of a spot urine collection for proteinuria rather than a 24-hour urine collection is recommended because the ACR by spot urine sample has demonstrated excellent correlation with the 24-hour urine protein measurements.[15] If protein is detected, then conditions such as infection, congestive heart failure, pregnancy, severe hypertension, or hematuria must be excluded as a possible cause, and because of the wide intra-individual variation of urinary albumin measurement, three tests should be performed and found to be positive over a 3- to 6-month period before making a definitive diagnosis of persistent proteinuria.[10,16]

Patients with diabetes who are found to have macroalbuminuria are very likely to have CKD caused by diabetes because this has been demonstrated by strong correlations with kidney biopsy pathology in patients with type 1 diabetes.[17] Microalbuminuria in patients with type 1 diabetes appears to be associated with less severe pathological lesions but still confers risk of progression of CKD, especially in the setting of hypertension.[18] The association between DKD and microalbuminuria is not as strong for patients with type 2 diabetes; only 30% of those with microalbuminuria demonstrated typical findings by kidney biopsy of diabetic nephropathy.[19] However, if retinopathy is present in patients with type 2 diabetes and microalbuminuria, this is strongly suggestive of DKD, with a sensitivity of 100% and specificities of 46–62%.[10] Despite these general findings, nearly 30% of patients with type 2 diabetes and significant DKD do not demonstrate either retinopathy or proteinuria.[20]

In summary, in patients with diabetes who have macroalbuminuria or microalbuminuria in combination with diabetic retinopathy, kidney disease may be attributed to diabetes, and the severity of kidney impairment should be classified depending on the eGFR. Patients who have evidence of severely impaired renal function, albuminuria > 500 mg per day, rapid increase in the degree of proteinuria, or declining eGFR should be referred to a specialist for further evaluation.

Measurement of Glycemic Control
A1C is the most common measure to determine glycemic control for patients with diabetes. There is concern that the measurement of A1C may be affected by the severity of kidney dysfunction or the hematological complications of kidney disease, such as iron deficiency, hemolysis, shorter red blood cell lifespan, or acidosis. A small study compared correlations between A1C measures and blood glucose in patients with moderate to severe kidney disease who did not require dialysis to those of patients without kidney disease and found no difference in the magnitude of the correlations between A1C and blood glucose between these patient groups.[21] This suggests that, in patients not requiring dialysis but with kidney disease, the measure of A1C is likely reflective of glucose control similar to that in a population of patients without kidney disease. Therefore, a target goal of < 7.0% may be applied to this patient group.[10,22]

A special consideration should be given to patients who are receiving dialysis. The correlation between A1C and blood glucose in hemodialysis patients is unclear. Two small studies found conflicting results, with one study concluding that A1C was an underestimate of glycemic control,[21] and the other concluding that A1C measures > 7.5% were likely to be an overestimate of glycemic control.[23] There is no evidence that the hemodialysis treatment acutely changes the A1C measure.[24] Additional studies are needed to clarify the interpretation of A1C in patients receiving dialysis. Lower A1C has been associated with lower mortality risk in patients receiving hemodialysis[25]; therefore, current recommendations are also to aim for an A1C < 7.0% in this patient population.[10,22]

Patients who receive peritoneal dialysis may be exposed to dialysis solutions composed of extreme glucose concentrations as high as 1,500 mg/dl of glucose. Few studies describe associations between blood glucose measures and A1C in peritoneal dialysis patients, and, again, the evidence is conflicting.[26,27]

Serum fructosamine measures failed to show a significant correlation with blood glucose measures in patients receiving dialysis or in those with severe CKD.[21,23] Fructosamine does not appear to most accurately reflect glycemic control in patients with CKD.

A1C is the most widely used estimate measure of long-term glycemic control, and it is also the best measure of its type available for patients with CKD. Despite the significant limitations noted for patients receiving dialysis, it is still the measure most commonly used. However, the "gold standard" of measures remains serum blood glucose, and, ultimately, therapy recommendations may be best made by using the daily glucose meter

readings of patients with CKD, keeping in mind the known errors and limitations of this method.[28]

Considerations for Pharmacological Treatment of Hyperglycemia

Insulin

When the goal is to achieve a lower A1C and tighter glycemic control, the risk of greater frequency and severity of hypoglycemic episodes also increases. In the 1,441 patients with type 1 diabetes studied in the Diabetes Control and Complications Trial, those who received intensive diabetes therapy had greater than three times the risk of having a severe hypoglycemic episode than those receiving conventional therapy.[29] Although the rates of hypoglycemia are much lower for patients with type 2 diabetes, there is also increased risk seen with insulin therapy.[30,31] Exogenous insulin is normally metabolized by the kidney. However, when there is impairment of kidney function, the half-life of insulin is prolonged because of lower levels of degradation.[32] Therefore, in patients with type 1 diabetes and moderate to severe kidney dysfunction, the frequency of hypoglycemic episodes may be as much as five times that of patients without kidney disease.[33]

There are no evidence-based guidelines or recommendations about which types of insulin to use or avoid depending on severity of CKD. Some studies suggest avoiding long-acting insulin, whereas others support its use.[34] One small study comparing type 1 diabetic patients with and without DKD demonstrated that clearance is reduced for both regular insulin and insulin lispro; however, the effect of regular insulin was also impaired in patients with DKD.[35] Thus, a higher dose of regular insulin may be required, despite lower clearance in patients with kidney disease. Insulin lispro did not demonstrate any differences in metabolic effects on glucose in patients with or without DKD.[35] Regardless of the form of insulin chosen to

treat diabetes, caution must be exercised when administering therapy to patients with kidney disease, and frequent blood glucose monitoring may be used to adjust dosing and prevent hypoglycemia.

Oral agents

As with insulin, clearance of many drugs is decreased by kidney disease, and this results in prolonged exposure to higher levels of the drug or its metabolites and potentially leads to adverse side effects. The greatest risk for this to occur is with patients with moderate to severe CKD (Stages 3–5). A diagnosis of kidney disease or progression of kidney disease warrants a reevaluation of drug therapies chosen for treatment of diabetes and possible adjustments to their dosing to achieve glycemic control while minimizing adverse effects.

In 2001, more than 91 million prescriptions were written for oral hyperglycemic agents, and ~ 33% were for sulfonylureas.[36] The clearance of both sulfonylureas and its metabolites is highly dependent on kidney function, and severe prolonged episodes of hypoglycemia as a result of sulfonylurea use have been described in dialysis patients.[37] In patients with Stage 3–5 CKD, first-generation sulfonylureas should be avoided. Of the second-generation sulfonylureas, glipizide is recommended because its metabolites are not active, and there is a lower potential for development of hypoglycemia.[10]

Although the mechanisms are not clear, α-glucosidase inhibitors and metabolites may result in damage from cumulative dose effects and result in possible hepatic damage.[38] Therefore, this class of medications is not recommended for patients with a serum creatinine > 2 mg/dl.[10]

Metformin is in the biguanides class of oral hyperglycemic drugs, which does not exhibit the high risk of hypoglycemia associated with other drug classes used to treat diabetes. However, special care must be taken when it is used in patients with CKD. There is a risk of

development of lactic acidosis, even in patients with mild impairment of kidney function, again likely resulting from the accumulation of the drug and its metabolites.[39] Metformin is contraindicated in male patients with a serum creatinine > 1.5 mg/dl and in female patients with serum creatinine > 1.4 mg/dl.[10]

Recently, it has been suggested that thiazolidinediones (TZDs) may have a protective effect to either prevent or slow the progression of DKD independent from glycemic control.[40] Several small studies have reported a greater reduction in albuminuria in patients administered TZDs;[41,42] however, there has been no evidence to support an independent association between TZD use and actual prevention of DKD. This class of drugs undergoes hepatic metabolism. It has been demonstrated to be effective without increasing the risk of hypoglycemic episodes in patients with CKD, including those receiving dialysis,[24,43,44] and in patients who require therapy for glycemic control after kidney transplant.[45] No adjustment in dosing of TZDs is required for these patient groups. The known TZD side effect of fluid retention may be accentuated in patients with CKD.

In summary, the majority of drugs available to treat hyperglycemia, and especially first-generation sulfonylureas and α-glucosidase inhibitors, are affected by kidney function and therefore should be either avoided or used in reduced doses for patients with CKD. Metformin is contraindicated with even mild to moderate kidney disease, whereas TZDs do not require dose adjustments for kidney disease and may have an independent beneficial impact on the progression of DKD. A summary of available drug therapies for diabetes and dosing recommendations is presented in Table 2.

Management of Cardiovascular Comorbid Disease

Hypertension

Hypertension is commonly found in patients with DKD and is diagnosed by

Class	Drug	CKD Stage 3–5	Dialysis	Complication
First-generation sulfonylurea	Acetohexamide	Avoid	Avoid	Hypoglycemia
	Chlorpropamide	GFR 50–70 ml/min/1.73 m²: ↓ 50% GFR < 50 ml/min/1.73 m²: Avoid	Avoid	Hypoglycemia
	Tolazamide	Avoid	Avoid	Hypoglycemia
	Tolbutamide	Avoid	Avoid	Hypoglycemia
Second-generation sulfonylurea	Glipizide	No dose adjustment	No dose adjustment	
	Glyburide	Avoid	Avoid	Hypoglycemia
	Glimepiride	Low dose: 1 mg/day	Avoid	Hypoglycemia
α-Glucosidase inhibitors	Acarbose	SCr > 2 mg/dl: Avoid	Avoid	Possible hepatic toxicity
	Miglitol	SCr > 2 mg/dl: Avoid	Avoid	
Biguanide	Metformin	Contraindicated: Male: SCr > 1.5 mg/dl Female: SCr > 1.4 mg/dl	Avoid	Lactic acidosis
TZDs	Pioglitazone	No dose adjustment	No dose adjustment	Volume retention
	Rosiglitazone	No dose adjustment	No dose adjustment	Volume retention
Meglitinides	Repaglinide	No dose adjustment	No dose adjustment	
	Nateglinide	Initiate low dose: 60 mg	Avoid	Hypoglycemia
Incretin mimetic	Exenatide	No dose adjustment	No dose adjustment	
Amylin analog	Pramlintide	No dose adjustment GFR < 20 ml/min/1.73 m²: Unknown	Unknown	
Dipeptidyl-peptidase IV inhibitor	Sitagliptin	GFR 30–50 ml/min/1.73 m²: ↓ 25% GFR < 30 ml/min/1.73 m²: ↓ 50%	↓ 50%	Hypoglycemia

Table 2. Recommendations for Non-Insulin Hyperglycemia Drug Therapy for Patients With Moderate to Severe CKD

Adapted from Ref. 10; SCr, serum creatinine

a blood pressure measurement > 130/80 mmHg, as defined by the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[46] Prevalence of hypertension is estimated to range from 30 to 96%, with higher prevalence found to be associated with greater levels of proteinuria.[10] Hypertension that is not controlled leads to a higher risk of cardiovascular events including death, increasing proteinuria, and progression of kidney disease.[47] The cornerstone of medical therapy for hypertension, especially in patients with CKD, is treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitor or ARB therapy has been demonstrated to slow the progression of proteinuria in patients with either type 1 or type 2 diabetes and microalbuminuria; however, no randomized clinical trials have shown impact on development of more advanced CKD or mortality in this population.[10]

In patients with type 1 diabetes and macroalbuminuria, ACE inhibitor therapy was shown to reduce albuminuria and also slow the rate of loss of GFR in the Collaborative Study Group captopril trial.[48] There is inconclusive and conflicting evidence about whether ACE inhibitor therapy has the same impact of prevention of progression of DKD in patients with macroalbuminuria and type 2 diabetes.[49,50] However, there is strong evidence that ARBs are effective at slowing DKD in hypertensive patients with type 2 diabetes. The two primary trials that have demonstrated this finding are the Irbesartan Diabetes Nephropathy Trial[51] and the Reduction of Endpoints in Non-Insulin-Dependent Diabetes with the Angiotensin II Antagonist Losartan trial.[52] In these studies, the use of an ARB compared to placebo resulted in a 16–20% risk reduction in the primary composite end point of worsening serum creatinine, development of end-stage renal disease, or death from any cause. Clinical trial evidence for the use of ARBs in patients with type 1 diabetes and hypertension is lacking. Therefore, for patients with type 1 diabetes, ACE inhibitor therapy is preferred, although ARBs may be used for patients who are intolerant of ACE inhibitors.[10]

Although ACE inhibitors and ARBs suppress the renin-angiotensin system, serum aldosterone remains elevated, and this has been suggested to contribute to the progression of CKD. A few small studies have reported that use of spironolactone, an aldosterone receptor antagonist, may be associated with a reduction of proteinuria and slower progression of kidney disease.[53,54] The use of an aldosterone antagonist, especially in combination with an ACE inhibitor or ARB, increases the possible development of hyperkalemia; therefore, close monitoring must be performed.

While ACE inhibitors and/or ARBs are preferred in patients with diabetes and kidney disease, many patients will require up to four medications to achieve blood pressure goals.[55] The combination of agents may include β-blockers, calcium channel blockers, and diuretics. As decline in kidney function progresses, the effect of thiazide diuretics for blood pressure control may lessen and the potential for electrolyte disturbances may increase. Therefore, it is generally recommended that, for patients with an eGFR < 30 ml/min/1.73 m^2, thiazide diuretics should be replaced with loop diuretics.[46]

Hyperlipidemia

Cardiovascular disease is common in patients with both diabetes and kidney disease. Risk factor modification, including management of dyslipidemia, is a key component of care for this patient population. Lipid levels should be measured annually, with a target LDL cholesterol level < 100 mg/dl for patients with CKD stages 1–4.[10] In a study of nearly 20,000 patients, those with diabetes and CKD who received pravastatin compared to placebo were found to have a 25% relative risk reduction of cardiovascular disease events.[56] Most clinical trials exclude patients with severe CKD; therefore, it is challenging to make recommendations for that population. One of the most influential studies to evaluate the impact of statin therapy in dialysis patients is the Deutsche

Diabetes Dialyse Studie (4D). The 4D trial was a multicenter, double-blind, placebo-controlled prospective study evaluating 1,255 patients with diabetes who were receiving hemodialysis.[57] This study did not find a significant difference in cardiovascular outcomes between statin therapy and placebo. This was a surprise result because previous observational studies suggested a benefit of statin therapy.[58,59] Although the explanation of why no difference was found is unclear, the current recommendation is not to initiate statin therapy in patients with type 2 diabetes who are receiving dialysis. However, those patients who were already receiving statins before dialysis initiation may continue therapy.

Consideration of dosing of drugs for dyslipidemia therapy must also take into account severity of kidney disease. No dosage adjustments are required for bile acid sequestrants, niacin, ezetimibe, atorvastatin, or pravastatin. Reduced dosing of fibric acid derivatives, fluvastatin, lovastatin, rosuvastatin, and simvastatin should be considered in patients with Stage 4 or 5 CKD.

Evaluation for Complications of CKD

Anemia in CKD is defined as a hemoglobin value < 13 g/dl for males and < 12 g/dl for females, and annual evaluation is recommended.[60] Correction of anemia to levels of 11–12 g/dl in dialysis patients has been associated with improved quality of life, fewer hospitalizations, and a lower risk of mortality; however, studies in patients with CKD (pre-dialysis) are lacking.[61] Two recent clinical trials, the Cardiovascular Risk Reduction in Early

Anemia Treatment With Epoetin Beta study and the Correction of Hemoglobin and Outcomes in Renal Insufficiency study, suggested that hemoglobin levels > 12 g/dl did not improve measures of quality of life and may increase the risk of cardiovascular events.[62,63] Additional clinical studies are ongoing to try to provide guidance in this complex area.

Abnormal calcium and phosphorus metabolism may also be present in patients with CKD. These measures, along with measurement of intact-para-thyroid hormone (i-PTH), may identify bone disease related to CKD. Bone disease may lead to poor bone structure resulting from high or low turnover, and this may result in a higher risk of fracture. Frequency of measurement of calcium, phosphorus, and i-PTH is described in Table 3.[64] The target serum phosphorus goal is < 5.5 mg/dl in patients with Stage 5 CKD and < 4.6 mg/dl in Stage 3–4 CKD.[64] In addition, if the i-PTH is abnormal, an evaluation for vitamin D deficiency should be sought, with measurement of 25-hydroxy vitamin D.

Nutritional Considerations in Diabetes and CKD

Patients with CKD may have complications that are significantly influenced by dietary intake. These conditions include hyperkalemia, hyperphosphatemia, and hypertension. If present, diet modification recommendations should then include a reduction of foods with high levels of potassium, phosphorus, and sodium. Given the restrictions already required because of diabetes, the complexity of dietary counseling often warrants interaction with a registered

Table 3. KDOQI Recommendations for Frequency of Measurement of Markers of Bone Health in CKD

Classification	i-PTH	Target i-PTH	Serum Calcium and Phosphorus
Stage 3	12 months	35–70 pg/ml	12 months
Stage 4	3 months	70–110 pg/ml	3 months
Stage 5	3 months	150–300 pg/ml	1 month

Table 4. Summary of Recommendations for Care of Patients With Diabetes and CKD

Management Issue		Outcome/Action
Diagnosis		Urinalysis for protein Serum creatinine – eGFR
Measurement of glycemic control		A1C Blood glucose meter
Medications	Insulin	May need to decrease dose
	Oral hyperglycemic agents	May need to decrease dose or discontinue use
Comorbid diseases	Blood pressure	ACE inhibitors/ARBs
	Hyperlipidemia	May need to decrease dose
Complications of CKD		Anemia, hyperphosphatemia, hyperparathyroidism
Nutrition		Avoid high protein intake; reduce sodium intake; reduce potassium intake; reduce phosphorus intake

dietitian who is trained in both diabetes and kidney disease for individualized recommendations. Frequent contact with a registered dietitian may improve dietary intake goals and clinical outcomes in patients with CKD.[65] Multidisciplinary management is often a cornerstone in the successful management plan for patients with diabetes.

Reduction of dietary protein intake to 0.8 g/kg body weight for CKD Stages 1–4 is recommended to try to reduce albuminuria and reduce the rate of loss of kidney function.[10] This is much lower than the 1.04 g/kg body weight of protein consumed by the majority of adults in the United States.[66] Several studies have shown a reduction of albuminuria in patients with CKD who are following a low-protein diet, and this was found to be most effective in patients with type 1 diabetes.[67–69] Thus, for patients with CKD, high-protein diets are not recommended.

Conclusions

CKD and diabetes are common diseases that affect a large proportion of the population. Depending on the severity of the CKD, drug regimens, including those for glycemic control, and dietary intake may require adjustments (Table 4). Aggressive identification and treatment of risk factors for cardiovascular disease as well as complications of CKD are recommended given the very high risk of adverse cardiovascular events in patients with both diabetes and CKD. Multidisciplinary care, including teamwork among physicians, nurses, pharmacists, dietitians, and social workers, may provide the optimal system for maximizing the care of complex chronic disease patients.

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