IN PRACTICE

Management of Glycemia in Patients With Diabetes Mellitus and CKD

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INDEX WORDS: Diabetes mellitus; chronic kidney disease.

CASE PRESENTATION

A 57-year-old white man with hypertension, hypercholesterolemia, and a 12-year history of type 2 diabetes mellitus returned for follow-up. He was found to have microalbuminuria 4 years ago, presumed secondary to diabetes. He progressed to stage 2 chronic kidney disease (CKD) 2 years ago. He feels well except for 2 episodes of hypoglycemia in the last month. He denies symptoms of neuropathy, and a dilated-eye examination 3 months ago did not show retinopathy. He is administered simvastatin, 20 mg/d; lisinopril, 20 mg/d; metformin, 1,000 mg twice daily; and glyburide, 5 mg twice daily. On examination, his body mass index is 27 kg/m^2 and blood pressure is 118/70 mm Hg. Recent laboratory evaluations showed a creatinine level of 1.5 mg/dL (133 μmol/L; estimated glomerular filtration rate [GFR], 52 mL/min/1.73 m^2 [0.9 mL/s/1.73 m^2]), and hemoglobin A_{1c} (HbA_{1c}) level of 7.2%. Urine albumin-creatinine ratio was 100 mg/g. One year ago, he had a creatinine level of 1.3 mg/dL (115 μmol/L; estimated GFR, 61 mL/min/1.73 m^2 [1 mL/s/1.73 m^2]), HbA_{1c} level of 7.4%, and similar urine albumin-creatinine ratio. What advice should be given regarding his glycemic management?

INTRODUCTION

Diabetes is a leading cause of CKD worldwide,[1] and its increasing prevalence may explain much of the increase in prevalence of kidney failure.[2-4] Even when diabetes is not the cause of kidney disease, the coexistence of CKD and diabetes presents unique problems that need to be recognized and managed appropriately to optimize outcomes.

The objective of this article is to review the management of glycemia in patients with CKD and diabetes. We first provide an overview of glycemic management in patients with CKD, followed by a review of the appropriate use of available hypoglycemic agents in patients with CKD and diabetes, with emphasis on newer classes of agents. Methods for diagnosis of diabetic kidney disease are beyond the scope of this review and are covered by recent Kidney Disease Outcomes Quality Initiative guidelines.[1]

OVERVIEW OF GLUCOSE MANAGEMENT IN CKD

Glycemic Control and Clinical Outcomes in CKD

Diabetes and CKD often coexist because they share common causes, including aging, vascular inflammation, hypertension, and dyslipidemia. Based on large intervention trials, it is now well accepted that tight glycemic control in patients with both type 1 and type 2 diabetes reduces the risk of nephropathy, retinopathy, and neuropathy.[5-8] Notably, optimal glucose control decreases the risk of adverse kidney outcomes, including incident microalbuminuria (as much as 59%) and progression to macroalbuminuria (as much as 84%).[5-8] Although hyperglycemia is also associated strongly with macrovascular disease in observational trials, there are only limited data from trials supporting tight glycemic control as a risk-reduction intervention for patients with incident cardiovascular disease.[9] National guidelines in the United States recommend an HbA_{1c} level less than 6.5% to 7%[10,11] to prevent vascular complications in the general diabetes population; however, optimal glycemic targets for patients with diabetes and CKD have not been established because major trials did not include patients with more advanced CKD (stage $\geq$3). In observational studies, glycemic control had a favorable effect on progression of nephropathy in patients with advanced CKD, but there is lack of long-term trials showing that the rate of nephropathy was influenced by glycemic control in these patients.[12-15]

The importance of tight glycemic control in patients with end-stage renal disease is even more controversial.[16-18] Data from small observational studies suggested that poor glycemic con-

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trol predicted unfavorable outcomes, including mortality,[19-21] but larger studies showed no correlation between glycemia and clinical outcomes.[22] These conflicting results may be caused by the difficulty interpreting observational data in patients with end-stage renal disease because of multiple confounding factors.[23]

Glucose Metabolism and Monitoring of Glycemia in CKD

CKD is defined as either persistent structural kidney damage or GFR less than 60 mL/min/1.73 m^2 (<1 mL/s/1.73 m^2) for more than 3 months.[24] Patients with stages 1 and 2 CKD have relatively preserved kidney function (GFR ≥ 60 mL/min/1.73 m^2 [≥1 mL/s/1.73 m^2]). These patients may have microalbuminuria or macroalbuminuria, and nephrotic syndrome sometimes may occur. In these stages, no changes typically are required in hyperglycemia therapy; therefore, the review focuses mainly on patients with CKD stages 3 to 5.

Patients with stages 3 to 5 CKD (GFR <60 mL/min/1.73 m^2 [<1 mL/s/1.73 m^2]) often show several complications related to decreased kidney function, including worsening hypertension, anemia, hyperparathyroidism, and malnutrition. In patients with diabetes and CKD stages 3 to 5, issues related to both altered glucose metabolism and pharmacokinetics place them at risk of hyperglycemia, as well as hypoglycemia (Table 1). Therefore, it is important to monitor glycemia closely and decrease doses of medications appropriately with changes in kidney function in these patients.

Monitoring glycemia in individuals with decreased GFR also poses certain challenges, as listed in Table 1. Interfering and confounding factors may lead to falsely low or high levels of HbA_{1c}, the most commonly used measure of glycated hemoglobin. Thus, HbA_{1c} values should be interpreted with caution in patients with CKD and correlated with patient self-monitoring of blood glucose levels.

Table 1. Glycemia-Related Issues in Chronic Kidney Disease

Glucose metabolism and pharmacokinetics
Increased risk of hyperglycemia
Increased production and use of glucose[25]
Impaired glucose disposal[25]
Increased insulin resistance[26]
Increased risk of hypoglycemia
Impaired renal gluconeogenesis[25,27]
Decreased clearance of insulin[28-30]
Decreased clearance of oral hypoglycemic agents
Monitoring of glycemic control
Falsely increased hemoglobin A_{1c}
Carbamylation of erythrocytes interfering with hemoglobin A_{1c} assay[31]
Falsely decreased hemoglobin A_{1c}
Increased erythrocyte turnover (reduced life span)[32]
Use of erythropoietin[33]

HYPOGLYCEMIC MEDICATIONS IN CKD

Patients with type 1 diabetes and CKD require insulin, whereas patients with preexisting type 2 diabetes who develop progressive CKD often require a change in pharmacotherapy as GFR decreases. In patients with preexisting CKD who develop new-onset diabetes, most have type 2 diabetes, but a few may have type 1 diabetes or a predominantly insulin-requiring form of diabetes. Nearly all patients with CKD and established or new-onset diabetes require pharmacotherapy; however, lifestyle modifications remain a cornerstone of all successful diabetes management strategies. In patients with established type 2 diabetes, lifestyle changes improve glycemia and associated cardiometabolic risk factors, including albuminuria.[34]

Hypoglycemic therapy for patients with type 2 diabetes is aimed primarily at either decreasing insulin resistance, thereby decreasing insulin requirements, or increasing the available insulin to match insulin requirements.

In the next section, we review currently available hypoglycemic agents, emphasizing newer classes developed in the last decade (Tables 2 and 3).

Insulin Secretagogues

There are 3 subclasses of insulin secretagogues, and all require functioning pancreatic beta cells. Therefore, insulin secretagogues may not work well in patients with long-standing diabetes.[35]

Sulfonylureas

Agents in this class stimulate insulin secretion from the islet beta cell by binding to the sulfonylurea receptor 1 of the adenosine triphosphate–dependent potassium channel. Sulfonylureas are

Table 2. Noninsulin Hypoglycemic Agents for Management of Hyperglycemia in CKD

Class	Mechanism of Action	Drug (Brand) Name/ Approximate Cost for 30-d Supply (generic if available) of Starting Dose ($)	Clearance Mechanism	Expected Glycemic Efficacy (HbA_{1c} lowering; %)	Other Features or Concerns	Usual Dose	Use in CKD Stage 3	Use in CKD Stage 4	Use in CKD Stage 5/Dialysis	Comments
Insulin secretagogues										
SUs (second generation)	Bind to SU receptor 1 in pancreatic β cell and stimulate insulin release				Avoid first generation					
		Glyburide (Micronase, Diabeta, Glynase)/8	100% Liver metabolism to weakly active metabolites excreted in urine (50%) and bile/feces (50%)	1.5	High risk of hypoglycemia due to active metabolites that accumulate in CKD	NA	Avoid	Avoid	Avoid	
		Glipizide (Glucotrol, Glucotrol XL)/10	90% Liver metabolism to inactive metabolites excreted in urine/feces; 10% excreted unchanged in urine/feces	1.5	Small risk of hypoglycemia	2.5-10 mg/d	May use	May use	May use without adjustments	Preferred SU; low initial dosing and careful dose titration
		Glimepiride (Amaryl)/8	100% Liver metabolism to weakly active and inactive metabolites excreted in urine (60%) and feces (40%)	1.5	Small risk of hypoglycemia	1-4 mg/d	May use	May use	Use with caution	Low initial dosing and careful dose titration
Non-SU insulin secretagogues										
Meglitinides	Bind to SU receptor in pancreatic β cell (different than SU site) and stimulate insulin release	Repaglinide (Prandin)/ 125	100% Liver metabolism to inactive metabolites excreted in urine (10%) and feces (90%)	1.0	Low risk of hypoglycemia in CKD	0.2-2 mg with meals	May use	May use	No data for patients with creatinine clearance $<$20 mg/mL	Preferred glinide; low initial dosing and careful dose titration
D-Phenylalanine derivative	Bind to SU receptor in pancreatic β cells and stimulate insulin release	Nateglinide (Starlix)/ 120	85% Liver metabolism to weakly active metabolites excreted in urine (83%) and feces (10%); 15% excreted unchanged in urine	0.7	Risk of hypoglycemia due to decreased clearance in CKD and active metabolites	60-120 mg with meals	Use with caution	Use with caution	Use with caution, avoid if possible	Low initial dosing and careful dose titration
Incretin mimetic	Binds to GLP-1 receptors in pancreatic β cell and promotes glucose-dependent insulin secretion; decreases glucagon secretion and gastric emptying	Exenatide (Byetta)/200	Kidney metabolism, proteolytic degradation; excretion in urine	1.0% in combination with metformin or SU	Low risk of hypoglycemia; decreased clearance and increased side effects in CKD stages 4/5	5-10 μg SC twice daily 30 min before meals	May use	Not recommended	Not recommended	Not approved as monotherapy

(Continued)

Table 2 (Cont'd). Noninsulin Hypoglycemic Agents for Management of Hyperglycemia in CKD

Class	Mechanism of Action	Drug (Brand) Name/ Approximate Cost for 30-d Supply (generic if available) of Starting Dose ($)	Clearance Mechanism	Expected Glycemic Efficacy (HbA_{1c} lowering; %)	Other Features or Concerns	Usual Dose	Use in CKD Stage 3	Use in CKD Stage 4	Use in CKD Stage 5/Dialysis	Comments
DPP4 inhibitor	Inhibits DPP4, which inactivates endogenous incretins, thus increasing endogenous incretin levels	Sitagliptin (Januvia)/ 164	Excreted mostly unchanged in urine (87%) and feces (13%)	0.7	Low risk of hypoglycemia; decreased clearance when creatinine clearance <50 mL/min	100 mg/d	Reduce dose to 50 mg/d	Reduce dose to 25 mg/d	Reduce dose to 25 mg/d	
Amylin analogue	Inhibits glucagon release; slows gastric emptying	Pramlintide (Symlin)/ 115	Kidney metabolism to active metabolites excreted in urine	0.6% in combination with insulin	Risk of hypoglycemia	60-120 μg SC 3 times/ d with meals coadministered with insulin	May use; no dose adjustment necessary	May use; no dose adjustment necessary	No data	
Insulin sensitizers										
Biguanide	Decreases hepatic glucose production; increases insulin sensitivity	Metformin (Glucophage, Glumetza)/34	Excreted unchanged in urine	1.5	Risk of lactic acidosis	NA	Not recommended	Contraindicated	Contraindicated	
Thiazolidinediones	Improves insulin sensitivity; ligand for $PPAR_{\gamma}$ receptor				Low risk of hypoglycemia; promote fluid retention and precipitate CHF; not indicated in patients with New York Heart Association class III or IV cardiac status					No dose adjustments necessary
		Rosiglitazone (Avandia)/110	Extensive liver metabolism to weakly active metabolites; excreted in urine (64%) and feces (23%)	0.6-1.5	Concern for small increased risk of cardiovascular disease	4-8 mg/d	May use; no dose adjustments necessary	May use; no dose adjustments necessary	May use; no dose adjustments necessary	Recent reports of increased risk of cardiovascular disease
		Pioglitazone (Actos)/ 112	Extensive liver metabolism; active metabolites; excreted in urine (15%) and feces (85%)	0.6-1.5		15-45 mg/d	May use; no dose adjustments necessary	May use; no dose adjustments necessary	May use; no dose adjustments necessary	

(Continued)

Table 2 (Cont'd). Noninsulin Hypoglycemic Agents for Management of Hyperglycemia in CKD

Class	Mechanism of Action	Drug (Brand) Name/ Approximate Cost for 30-d Supply (generic if available) of Starting Dose ($)	Clearance Mechanism	Expected Glycemic Efficacy (HbA_{1c} lowering; %)	Other Features or Concerns	Usual Dose	Use in CKD Stage 3	Use in CKD Stage 4	Use in CKD Stage 5/Dialysis	Comments
Other										
α-Glucosidase inhibitors	Inhibits α-amylase, α-glucosidase enzyme limiting absorption of carbohydrates in small intestine			0.6						
		Acarbose (Precose)/ 79	Nearly 100% GI tract metabolism; excreted in urine (34%) feces (51%), $<$2% excreted in urine as drug or active metabolite		No data for patients with creatinine $>$ 2 mg/dL; should not be used in GI disease or increased transaminases	25-100 mg with meals	May use	Avoid	Avoid	
		Miglitol (Glyset)/66	No metabolism; absorbed systemically and excreted unchanged in urine (95%)		No data for patients with creatinine $>$ 2 mg/dL	25-100 mg with meals	May use	Avoid	Avoid	

Note: Stages 1 and 2 of CKD represent less severe abnormalities in kidney function, and in general, no changes are required in regard to hyperglycemia therapy. Efficacy in the general population. Prices from www.drugstore.com for lowest dose. To convert from creatinine clearance in mL/min to mL/s, multiply by 0.01667; to convert from creatinine in mg/dL to μmol/L, multiply by 88.4.

Abbreviations: CKD, chronic kidney disease; HbA_{1c}, hemoglobin A_{1c}; SU, sulfonylurea; GLP-1, glucagon-like peptide 1; SC, subcutaneous; DPP4, dipeptidyl peptidase IV; NA, not applicable; CHF, congestive heart failure; GI, gastrointestinal; PPARγ, peroxisome proliferator-activated receptor γ.

Table 3. Available Types of Insulin by Comparative Action

Insulin Type	Onset	Peak (h)	Duration (h)	Comments
Prandial (bolus)				
Rapid acting analogues	5-15 min	1-2	3-4	Analogues associated with less hypoglycemic compared with regular human insulin. Preferred prandial insulin in CKD
Insulin lispro (Humalog) Insulin aspart (Novolog) Insulin glulisine (Apidra)				
Short acting	15-30 min	2-4	4-6	
Regular human (Humulin R/Novolin R)				
Inhaled insulin	10-20 min	1-3	2-5	Contraindicated if smoking or uncontrolled lung disease; dosing in milligrams instead of units (1 mg ≈ 3 units); pulmonary function testing required at baseline, 6 mo, and yearly thereafter
Basal (long-acting)				
Intermediate acting	2-4 h	5-7	10-20	
NPH human (isophane)				
Long acting				
Insulin glargine (Lantus)	1-2 h	No peak	24	Analogues cannot be mixed with other insulin; associated with less hypoglycemia compared with NPH insulin
Insulin detemir (Levemir)	1-2 h	No peak	18-20	
Premixed				
70/30 (70% NPH, 30% regular), Humulin/Novolin				Onset, peak, and duration of premixed insulins may vary from that predicted by the individual components
50/50 (50% NPH, 50% regular) Humulin				
Humalog 75/25 (75% NPL, 25% lispro) Novolog mix 70/30 (70% NPA, 25% aspart)				

Note: All insulin preparations available in the United States as U-100 (100 units/mL). Regular human insulin U-500 (500 units/mL) is also available for patients with severe insulin resistance. Production of human insulin Lente and Ultralente has been discontinued.

Abbreviations: NPH, neutral protamine Hagedorn (regular); NPL, neutral protamine lispro; NPA, neutral protamine aspart.

highly efficacious in the short term, but glycemic efficacy may be attenuated over time more than with other oral agents.[35] Sulfonylureas have been studied extensively and are associated with favorable vascular outcomes.[6] Because maximum doses of sulfonylureas may be less effective than moderate doses,[36] maximizing doses of sulfonylureas is not recommended. The main risk is hypoglycemia; therefore, low starting doses and slow titration are required.

First-generation sulfonylureas are rarely used in the United States and are not discussed here. Of the second-generation sulfonylureas, glyburide undergoes complete hepatic metabolism to 2 weakly active metabolites. These metabolites accumulate in patients with CKD, increasing the risk of hypoglycemia.[37-40] Therefore, it is recommended that glyburide be avoided in patients with CKD. Glimepiride undergoes complete hepatic metabolism to 2 metabolites, which

are excreted in urine and feces. The predominantly renally excreted metabolite has weak hypoglycemic activity[41] and may build up with renal impairment, increasing the risk of hypoglycemia, including prolonged hypoglycemia.[42-44] Glipizide undergoes near-complete hepatic biotransformation to inactive metabolites, and its half-life is unaffected by kidney function.[45] Accordingly, glipizide is the sulfonylurea of choice in patients with CKD. Hypoglycemia remains a risk with glipizide, but considerably less so compared with glyburide or glimepiride.[46]

Nonsulfonylurea Insulin Secretagogues (glinides)

Although glinides stimulate insulin secretion by binding to adenosine triphosphate–dependent potassium channels in the pancreatic β islet cell, they are chemically unrelated to sulfonylureas. Clinically, glinides are differentiated from sulfonylureas by a very short half-life and duration of action (3-4 hours) and therefore are administered shortly before meals. Glinides have modest glycemic efficacy and lack clinical outcome data; however, their relatively low risk of hypoglycemia gives them an advantage over sulfonylureas in patients with CKD and mild type 2 diabetes with predominantly postprandial hyperglycemia.

Repaglinide binds to a different site on the sulfonylurea receptor 1 subunit than sulfonylureas. It is completely metabolized by hepatic biotransformation and conjugation to inactive metabolites,[47] with no increase in hypoglycemia risk in patients with CKD.[48] Nateglinide binds to the same binding site on the sulfonylurea receptor 1 subunit as sulfonylureas. Approximately 15% of nateglinide is excreted unchanged in urine; the remainder is metabolized by the liver to weakly active metabolites and conjugates that are excreted in urine (80%) and feces (20%). In patients with advanced CKD, there is accumulation of an active metabolite of nateglinide, which may increase the risk of hypoglycemia[49-51]; therefore, caution is recommended when using this drug in patients with CKD.

Incretin-Based Insulin Secretagogues

This is the newest class of hypoglycemic agents, developed as a result of improved understanding of the incretin effect on the pathophysiology of type 2 diabetes. The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose or nutrients in the gut.[52] The incretin effect is composed primarily of 2 peptides; glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1. Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP4), resulting in a very short half-life (minutes). The incretin pathway appears to be attenuated in patients with type 2 diabetes, making the pathway a target for the development of new pharmacological agents.[52] Currently, there are 2 approved agents in this class; exenatide, a glucagon-like peptide 1 receptor analogue resistant to DPP4 degradation, and sitagliptin, a selective DPP4 inhibitor.

Exenatide has only modest glycemic efficacy, but it is the only hypoglycemic agent associated with weight loss.[53] It is administered subcutaneously twice daily about 60 minutes before meals. Its main side effect is dose-dependent nausea and vomiting, but only 4% of patients stop the medication because of gastrointestinal side effects.[53] Exenatide is cleared primarily by the kidneys; however, dose adjustment is not required for patients with a creatinine clearance greater than 30 mL/min (>0.5 mL/s). In patients with CKD stage 4/5, clearance of exenatide is significantly decreased (~10% of normal), and its use is neither recommended nor well tolerated.[54]

Sitagliptin, currently the only available DPP4 inhibitor, has a modest hypoglycemic efficacy and generally is well tolerated, although there may be a small increased risk of urinary tract infections and nasopharyngitis.[53] Advantages of DPP4 inhibitors include a very low risk of hypoglycemia and lack of weight gain. Sitagliptin is administered orally once daily. Because it is excreted mostly unchanged in urine, lower doses are recommended in patients with CKD stages 3 to 5.[55,56] Long-term efficacy and safety of sitagliptin in patients with CKD have not been determined.

Pramlintide is an analogue of amylin, a hormone cosecreted with insulin from pancreatic beta cells in response to meals that contributes to postprandial glucose control.[57] Pramlintide is metabolized primarily by the kidney to active metabolites, but no change in dose is required at a creatinine clearance greater than 20 mL/min.[58] Because of its low glycemic efficacy, frequent

side effects (hypoglycemia and nausea), and somewhat complex administration, pramlintide is not commonly used in clinical practice.

Insulin Sensitizers

Biguanides

Metformin, the only biguanide available in the United States, decreases glucose levels primarily by decreasing hepatic glucose output and, to a lesser extent, promoting insulin-mediated glucose uptake in peripheral insulin-target tissues. Metformin is one of the most efficacious oral hypoglycemic agents and is associated with favorable clinical outcomes.[7] It is well tolerated, and its most common adverse effect is gastrointestinal disturbance, which can be avoided by starting with a low dose and titrating slowly.[59] Unless contraindicated, metformin is the oral hypoglycemic agent of choice as first-line therapy in patients with type 2 diabetes.[60] A life-threatening complication of metformin is the development of lactic acidosis, which is exceedingly rare and almost always seen in patients with significant comorbidity, including advanced kidney disease.[61] Metformin is excreted unchanged in urine, and the drug accumulates as renal function worsens, especially at GFRs less than 60 mL/min/1.73 m^2 ($<$1 mL/s/1.73 m^2), increasing the risk of lactic acidosis. Thus, patients with CKD stage 3 or higher should not be administered metformin.

Thiazolidinediones

Rosiglitazone and pioglitazone, the 2 available thiazolidinediones in the United States, enhance insulin action in insulin-target tissues through binding to peroxisome proliferator-activated receptor γ (nuclear transcription factors involved in glucose and lipid homeostasis). Thiazolidinediones have glycemic efficacy equivalent to sulfonylureas or metformin, with less hypoglycemia, but also have a slower onset of action (weeks to months). Therefore, these agents are not appropriate for patients with symptomatic hyperglycemia. The currently available thiazolidinediones do not share the hepatotoxicity that was associated with the first agent in the class, troglitazone, but rare isolated cases of idiosyncratic hepatotoxicity were reported. Weight gain is the most common adverse effect of thiazolidinediones, especially when coadministered with insulin or insulin secretagogues. This is caused by both fluid and fat accumulation. Thiazolidinediones may precipitate heart failure and therefore are contraindicated in patients with New York Heart Association class III or IV cardiac status and should be used with caution in patients with preexisting edema. Thiazolidinediones are metabolized extensively by the liver to metabolites with either very weak (rosiglitazone and pioglitazone) or moderate activity (pioglitazone). Pharmacokinetics of thiazolidinediones do not change with decreasing renal function, and no dose adjustment is required in patients with CKD.[62-64]

A recent meta-analysis combining data from 42 trials linked rosiglitazone to an increased risk of cardiovascular disease.[65] It is not clear whether this finding will be replicated in large trials specifically designed for cardiovascular disease outcomes and whether this represents a class effect.[66]

Other Medications

α-Glucosidase Inhibitors

Drugs in this class target postprandial hyperglycemia by inhibiting the intestinal breakdown of oligosaccharides, thereby delaying digestion of ingested carbohydrates. This class of medications has lower glycemic efficacy compared with other hypoglycemic classes, but in a trial of patients with glucose intolerance, the α-glucosidase inhibitor acarbose was reported to decrease the risk of cardiovascular disease events.[67] Because carbohydrates are not absorbed, they remain in the colon to be digested by colonic bacteria. Therefore, gastrointestinal disturbances, such as abdominal pain, flatulence, and diarrhea, are major limitations encountered in approximately 50% of patients. Initiation at the lowest available dose and slow titration to the maximum dose attenuates gastrointestinal side effects; however, side effects frequently are unacceptable to patients, leading to discontinuation. Acarbose is metabolized nearly completely and exclusively within the gastrointestinal tract, with less than 2% of an oral dose recovered as active drug or metabolites in urine.[68] A second α-glucosidase inhibitor, miglitol, is absorbed systemically and excreted unchanged in urine.

α-Glucosidase inhibitors are excellent agents for monotherapy in obese patients with postprandial hyperglycemia or early mild diabetes. However, given their modest glycemic efficacy, their frequent gastrointestinal effects, and the lack of studies in patients with kidney disease, α-glucosidase inhibitors have a limited role in the treatment of type 2 diabetes in patients with CKD. They may be used in patients with stage 3 CKD, but should be avoided in those with stages 4 and 5 because they were not studied in patients with serum creatinine values greater than 2 mg/dL ($>$177 μmol/L).[69]

Insulin

Insulin is the most effective therapy for patients with diabetes, but there is considerable resistance to its use by patients and health care providers for a variety of reasons, including the need for subcutaneous injection, concern for weight gain, and hypoglycemia.[70] Fortunately, the availability of newer insulin analogues enables clinicians to provide more physiological insulin therapy, and new delivery methods and glucose monitoring techniques have facilitated acceptance of intensive insulin treatment.[71]

Insulin therapy is governed by certain principles, including: (1) individualizing approach, (2) administrating adequate amounts of insulin, (3) providing physiological therapy through administration of both basal (long-acting) and prandial (bolus) insulin, and (4) monitoring and adjusting frequently based on individual responsiveness to therapy. An understanding of the pharmacokinetic profile of available insulin preparations is important in designing effective insulin regimens while minimizing the risk of hypoglycemia.

There are many formulations of basal and prandial insulin available for subcutaneous administration. These preparations can be divided into 4 main classifications: rapid-acting insulin analogues, short-acting insulin (regular human), intermediate-acting insulin (human), and long-acting insulin analogues. Insulin analogues, designed by means of recombinant DNA technology, have structural modifications in the amino-acid sequence of human insulin, resulting in improved (more physiological) time profiles.

Prandial (bolus) Insulin Preparations. Regular insulin has been used for years as prandial insulin. Its main disadvantage is its relative (compared with newer rapid-acting analogues) delayed onset of action, necessitating subcutaneous administration 30 to 45 minutes before a meal starts. Because this rarely happens in practice, insulin levels rarely correlate with carbohydrate intake, resulting in a less predictable postprandial glucose response compared with more rapid-acting analogues and greater risk of delayed hypoglycemia.

Rapid-acting insulin analogues differ from human insulin by 1 to 2 amino-acid substitutions,[71] which result in rapid absorption within 15 minutes after subcutaneous injection. Rapid-acting analogues were designed to mimic the physiological secretion of insulin after a meal, and they are administered within 15 minutes before a meal starts, although they also can be administered immediately after the meal in patients with unpredictable eating patterns.

Recently, human regular insulin became available in a powdered form aerosolized through a special inhaler device.[72] Inhaled insulin has a pharmacokinetic profile between regular and rapid-acting analogues and typically is used as prandial insulin. Glycemic efficacy is slightly less than with subcutaneous insulin, with a similar risk of hypoglycemia compared with subcutaneous insulin.[72] The long-term safety and efficacy of inhaled insulin is not yet known. It is contraindicated in active smokers and patients with unstable lung disease. There has been a small and reversible change in lung function associated with use of inhaled insulin, and frequent monitoring of lung function is required. Unlike subcutaneous insulin, dosing of inhaled insulin is in milligrams instead of units (with 1 mg $\approx$ 3 units). Use of inhaled insulin may be appropriate in patients who are opposed to injections and who would otherwise delay appropriate and timely therapy with injectable insulin. The effect of renal impairment on inhaled insulin has not been studied.[73]

Basal (long-acting) Insulin Preparations. Neutral protamine Hagedorn (NPH) is an intermediate-acting insulin with a peak effect approximately 8 to 10 hours after injection, but with significant intrapatient variation. NPH is prefer-

able in patients with morning fasting hyperglycemia, but often has to be administered twice daily to meet basal insulin requirements. NPH insulin is the preferred long-acting insulin for patients administered glucocorticoids, but the timing of administration must coincide with glucocorticoid dosing to prevent hypoglycemia.

Insulin glargine has changes in amino-acid content that shift its isoelectric point and reduce its aqueous solubility at physiological pH (subcutaneous space). These changes lead to the formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration of insulin in the circulation over 24 hours without a pronounced peak. This profile allows once-daily dosing as basal insulin.

Insulin detemir has a unique mechanism of action. After injection, it binds to albumin and then is distributed slowly to target tissues as it dissociates. Similar to glargine, insulin detemir has no pronounced peak and is used as basal insulin, but often requires twice-daily administration to meet basal insulin requirements. Given its mechanism of action, insulin detemir is not a good choice for a patient with nephrotic syndrome.

Premixed (fixed-ratio) Insulin Preparations

These preparations of insulin, administered twice daily before breakfast and dinner, are potentially convenient alternative options to basal-prandial combinations. However, premixed insulin also is often less effective because of its inflexibility, and it has significant interindividual variability.

Insulin Delivery

Insulin administration with syringes is still the most common delivery method; however, several pen-like devices are available that allow improved convenience and accuracy of administration. Insulin pens hold as many as 300 units of insulin and are available either prefilled (disposable) or as durable devices that use cartridges. The patient determines the dose by dialing a knob and injects the insulin through a needle (specifically designed for pens, sold separately) by pushing a button. Despite their added expense, pen use is the preferred method for insulin administration. For motivated patients, an insulin pump provides an alternate route of insulin administration that is effective and safe.

Compared with patients with normal kidney function, patients with impaired kidney function have lower insulin requirements. In the latter group, regular human insulin shows a higher maximal concentration and longer half-life, whereas rapid-acting analogues maintain similar maximum concentration and half-life and are less likely to cause hypoglycemia compared with patients with normal kidney function.[28] Thus, rapid-acting insulin analogues are preferred to regular human insulin in patients with CKD. Similarly, long-acting insulin analogues are also preferred to NPH. In general, as GFR decreases, insulin requirements decrease by as much as half, especially after initiation of dialysis therapy.[29] Therefore, in patients requiring insulin, clinicians should monitor kidney function closely and adjust insulin doses appropriately as GFR decreases.

SPECIAL CONSIDERATIONS

Diabetes After Kidney Transplantation

The development of diabetes after kidney transplantation is a common occurrence, with a reported incidence as high as 50%.[74,75] The high risk of diabetes after transplantation is population and treatment specific. First, the population of patients undergoing kidney transplantation often shares the same risk factors for developing diabetes as the general population, such as aging, obesity, and ethnic origin.[75-77] Next, several immunosuppressive agents are specifically associated with the development of diabetes. Among immunosuppressant medications, glucocorticoids, with both chronic and pulse administration, are well recognized to increase diabetes risk in a dose-dependent fashion by increasing insulin resistance.[77] Withdrawal of glucocorticoid therapy ameliorates insulin resistance and improves diabetes; however, withdrawal of glucocorticoid therapy clearly can be undertaken only with careful monitoring of graft function.[78] Calcineurin inhibitors, particularly tacrolimus, also are associated with posttransplantation diabetes. The exact mechanism of diabetes induced by calcineurin inhibitors is not known, but it is believed that these agents are directly toxic to

pancreatic β cells, resulting in impaired insulin secretion. They also appear to increase peripheral insulin resistance.[75] The effect of calcineurin inhibitors may occur at any time during therapy, and ongoing surveillance for diabetes is required. Diabetes may not be reversible upon discontinuation.

Patients are at greatest risk for diabetes in the first 6 months after transplantation. Six percent to 9% of patients develop diabetes in the first half year after surgery. The prevalence increases linearly thereafter, with 13%, 20%, and 30% of patients developing diabetes 5, 10, and 15 years after transplantation, respectively.[80] Although it may take years to develop, the development of diabetes is associated with impaired graft function and survival. As many as 50% of patients with posttransplantation diabetes develop graft failure within 4 years, as opposed to 18% without diabetes.[80] It is well known that improved glycemic control reduces microvascular complications (discussed previously); therefore, nephrologists taking care of patients with posttransplantation diabetes have a unique opportunity for primary prevention of diabetic nephropathy (in the new kidney) through tight glycemic control. Treatment of patients with posttransplantation diabetes follows the same principles outlined for patients with type 2 diabetes; namely, lifestyle changes followed by progressive stepwise use of medications, taking into consideration the patient's kidney function. Any medication can be used, but metformin should generally be avoided in transplant recipients showing some degree of kidney function impairment because acute renal failure is not uncommon in these individuals. Studies of kidney transplant recipients were performed with repaglinide,[79] rosiglitazone,[80] and pioglitazone,[81] and all were found to be safe and effective. Short-acting sulfonylureas and α-glucosidase inhibitors also can be used cautiously. Thiazolidinediones may be preferable in patients administered glucocorticoids because they ameliorate insulin resistance. However, they are associated with significant weight gain and risk of heart failure.

Despite oral pharmacotherapy options, many kidney transplant recipients will require insulin. In these patients, balancing glucocorticoids with therapy is critical; for example, a patient receiving a single dose of prednisone in the morning should be treated with NPH insulin once in the morning. In the same patient, insulin glargine or NPH insulin at bedtime may precipitate morning hypoglycemia. Finally, alternative-day glucocorticoid use, commonly prescribed in posttransplantation patients, offers no proven benefit over daily use and complicates glycemic management; therefore, alternative-day glucocorticoid regimens are discouraged in patients with posttransplantation diabetes.

Diabetes in Patients Receiving Kidney Replacement Therapy

The benefits of intensive glucose control in patients receiving kidney replacement therapy are not well documented. Although good glycemic control can no longer affect renal outcomes, it may decrease the progression of retinopathy, neuropathy, and cardiovascular disease. However, tight glycemic control often is difficult in these patients and carries a high risk of hypoglycemia. Although diabetes therapy must be reevaluated in all patients at the time of initiation of kidney replacement therapy, there currently is no consensus about the proper way to manage hyperglycemia in this setting.[82]

Diabetes in Patients on Hemodialysis Therapy. Based on data from specific studies or predictions from their molecular structure, clearance of most hypoglycemic agents is not significantly affected by hemodialysis.[83] In patients receiving hemodialysis, long-acting sulfonylureas are not appropriate because they are more likely to cause hypoglycemia. Short-acting sulfonylureas may be used at low doses. Thiazolidinediones can also be used without dose adjustment. However, in most patients, insulin will be the most appropriate therapy. Rapid-acting insulin analogues are cleared quickly and can be used safely. Long-acting basal insulin can be used in conjunction with rapid-acting analogues, although at low doses to not precipitate hypoglycemia. One major issue specific to hemodialysis patients is that eating patterns often change on dialysis days. Patients may miss meals or eat atypical foods because dialysis sessions often overlap with typical meal times. Other patients may be so fatigued after dialysis that they miss meals later in the day. In these situations, patients treated with secretagogues or mealtime insulin should tailor use of these medications based on

their typical eating patterns surrounding dialysis sessions. For example, a patient who typically misses breakfast on a dialysis day should hold the morning dose of secretagogues or breakfast-time insulin, and a smaller dose of oral secretagogues or insulin could be considered with the afternoon meal. Basal insulin dose does not need to be decreased or withheld on dialysis days assuming that total daily intake remains relatively constant.

Diabetes in Patients on Peritoneal Dialysis Therapy. Peritoneal dialysis poses additional challenges in the management of glycemia, primarily because of systemic absorption of glucose typically found in peritoneal dialysate and varying dialysis regimens. Accordingly, matching insulin dosing with blood glucose levels can be difficult. For patients receiving subcutaneous insulin and continuous ambulatory peritoneal dialysis, a subcutaneous regimen similar to that for patients on hemodialysis therapy could be used, with long-acting basal insulin and rapid-acting insulin with meals. Insulin requirements will likely be greater for most patients on continuous ambulatory peritoneal dialysis therapy because of the glucose in dialysate. For patients on intermittent peritoneal dialysis therapy or such therapies as continuous cycler-assisted peritoneal dialysis, in which glucose absorption fluctuates, use of an insulin preparation with an action profile that matches the length of time of the dialysis treatment is preferred. For example, twice-daily NPH could be used for basal needs, with a greater dose given at bedtime to match the greater glucose absorption from the overnight cycling, and a lower dose given in the morning to match the slow absorption from the daylong dwell. Bolus insulin or an oral agent would also be needed for control of postprandial glucose levels.

Intraperitoneal insulin is an alternative option for patients on peritoneal dialysis therapy[84] because insulin is absorbed rapidly and possibly more evenly through the peritoneum than with subcutaneous administration. Disadvantages to using intraperitoneal insulin include an increased time requirement to instill the insulin before the dialysis solution, a possible increase in insulin requirements because of dilution and the possible binding of insulin to the dialysis catheter, and the possibility of peritonitis from the insulin.[85] In patients with type 2 diabetes using insulin, rosiglitazone was shown to decrease insulin requirements in patients on continuous ambulatory peritoneal dialysis therapy by about 21%; therefore, adding a thiazolidinedione may be an additional option.[86]

CASE REVIEW

The patient discussed in the vignette at the opening of the review had recently progressed to stage 3 CKD. At this time, metformin therapy should be discontinued. In addition, he is having symptomatic hypoglycemia, which likely is secondary to decreased clearance of glyburide in the setting of worsening kidney function. Glyburide could be changed to glipizide, repaglinide, or sitagliptin, all less likely to cause hypoglycemia. The patient will need a second agent because the HbA_{1c} level was already greater than goal with 2 agents and metformin has now been discontinued. Pioglitazone would be a reasonable choice if an oral agent is desired. Alternatively, insulin therapy is appropriate at this point and may be the most effective and economical option. Insulin therapy would begin with basal insulin (NPH, glargine, or detemir at bedtime), followed by a rapid-acting analogue with meals.

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