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Managing diabetes in hospitalized patients with chronic kidney disease

ABSTRACT

Because few randomized trials have been done, little is known about appropriate glycemic control in hospitalized patients with chronic kidney disease (CKD) and diabetes mellitus. These patients are at high risk of hypoglycemia. It is prudent to monitor glucose closely, set less-stringent blood sugar goals, avoid oral antidiabetic agents, and possibly reduce insulin dosage.

KEY POINTS

Hemoglobin A_{1c} values are often unreliable in patients with end-stage renal disease; close monitoring by finger-stick testing or a continuous monitoring system is recommended during hospitalization.

Insulin is the preferred treatment for hospitalized patients with diabetes; oral antidiabetic agents should be avoided.

Blood glucose targets for hospitalized patients with diabetes or stress hyperglycemia should be less than 140 mg/dL before meals, and random values should be less than 180 mg/dL.

A basal-bolus insulin approach is flexible and mimics endogenous insulin release.

Many insulin-treated patients with type 2 diabetes and CKD stop needing insulin as kidney disease progresses.

MANAGING GLYCEMIC CONTROL in hospitalized patients with chronic kidney disease (CKD) and diabetes mellitus is a challenge, with no published guidelines. In this setting, avoiding hypoglycemia takes precedence over meeting strict blood glucose targets. Optimal management is essential to reduce hypoglycemia and the risk of death from cardiovascular disease.[1]

This article reviews the evidence to guide diabetes management in hospitalized patients with CKD, focusing on blood glucose monitoring, insulin dosing, and concerns about other diabetic agents.

■ FOCUS ON AVOIDING HYPOGLYCEMIA

CKD is common, estimated to affect more than 50 million people worldwide.[2] Diabetes mellitus is the primary cause of kidney failure in 45% of dialysis patients with CKD.

Tight control comes with a cost

Hyperglycemia in hospitalized patients is associated with a higher risk of death, a higher risk of infections, and a longer hospital stay.[3,4] In 2001, Van den Berghe et al[5] found that intensive insulin therapy reduced the mortality rate in critically ill patients in the surgical intensive care unit. But subsequent studies[6,7] found that intensive insulin therapy to achieve tight glycemic control increased rates of morbidity and mortality without adding clinical benefit.

Randomized clinical trials in outpatients have shown that tight control of blood glucose levels reduces microvascular and macrovascular complications in patients with type 1 diabetes.[8–10] In the Diabetes Control and Complications Trial,[9] compared with conventional therapy, intensive insulin therapy reduced the

Chronic kidney disease is a risk factor for hypoglycemia in hospitalized patients
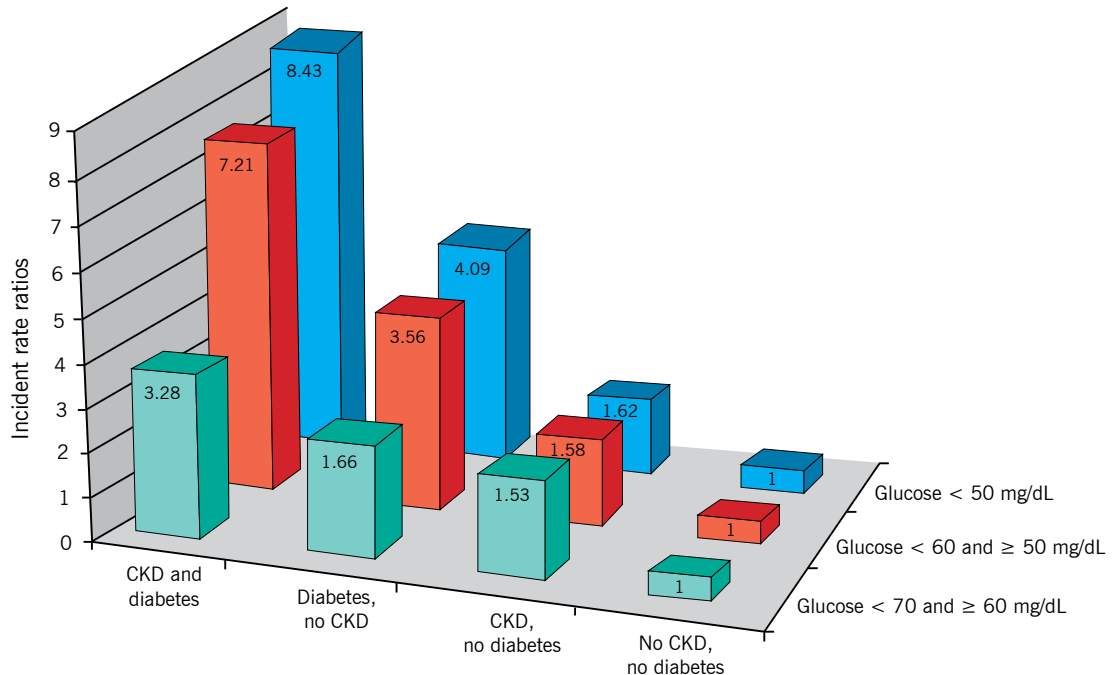
FIGURE 1. Incidence of hypoglycemic episodes in hospitalized patients with or without chronic kidney disease (CKD) and diabetes in a Veterans Administration study.[12] All differences compared with the reference group (no CKD, no diabetes) were statistically significant (*P* < .0001).

Avoiding hypoglycemia takes precedence over meeting strict blood sugar targets

incidence of retinopathy progression (4.7 vs 1.2 cases per 100 patient-years, number needed to treat [NNT] = 3 for 10 years) and clinical neuropathy (9.8 vs 3.1 per 100 patient-years, NNT = 1.5 for 10 years). The long-term likelihood of a cardiovascular event was also significantly lower in the intensive treatment group (0.38 vs 0.80 events per 100 patient-years).[9]

Similarly, in the Epidemiology of Diabetes Interventions and Complications follow-up study, the intensive therapy group had fewer cardiovascular deaths.[11] On the other hand, the risk of severe hypoglycemia and subsequent coma or seizure was significantly higher in the intensive therapy group than in the conventional therapy group (16.3 vs 5.4 per 100 patient-years).[8]

CKD increases hypoglycemia risk

Moen et al[12] found that the incidence of hypoglycemia was significantly higher in patients with CKD (estimated glomerular filtration rate [GFR] < 60 mL/min) with or without diabetes, and that patients with both conditions were at greatest risk (**Figure 1**). Multiple factors contribute to the increased risk of hypoglycemia: patients with advanced CKD tend to have poor nutrition, resulting in reduced glycogen stores, and a smaller renal mass reduces renal gluconeogenesis and decreases the elimination of insulin and oral antidiabetic agents.

After the onset of diabetic nephropathy, progression of renal complications and overall life expectancy are influenced by earlier glycemic control.[8] Development of diabetic nephropathy is commonly accompanied by changes in metabolic control, particularly an increased risk of hypoglycemia.[13] In addition, episodes of severe hypoglycemia constitute an independent cardiovascular risk factor.[14]

Aggressive glycemic control in hospitalized patients, particularly those with advanced CKD, is associated with a risk of hypoglycemia

without overall improvement in outcomes.[15] Elderly patients with type 2 diabetes are similar to patients with CKD in that they have a reduced GFR and are thus more sensitive to insulin. In both groups, intensifying glycemic control, especially in the hospital, is associated with more frequent episodes of severe hypoglycemia.[16] The focus should be not only on maintaining optimal blood glucose concentration, but also on preventing hypoglycemia.

'Burnt-out' diabetes

Paradoxically, patients with end-stage renal disease and type 2 diabetes often experience altered glucose homeostasis with markedly improved glycemic control. They may attain normoglycemia and normalization of hemoglobin A_{1c}, a condition known as "burnt-out" diabetes. Its precise mechanism is not understood and its significance remains unclear (**Table 1**).[17]

■ HEMOGLOBIN A_{1c} CAN BE FALSELY HIGH OR FALSELY LOW

Hemoglobin A_{1c} measurement is used to diagnose diabetes and to assess long-term glycemic control. It is a measure of the fraction of hemoglobin that has been glycated by exposure to glucose. Because the average lifespan of a red cell is 120 days, the hemoglobin A_{1c} value reflects the mean blood glucose concentration over the preceding 3 months.

But hemoglobin A_{1c} measurement has limitations: any condition that alters the lifespan of erythrocytes leads to higher or lower hemoglobin A_{1c} levels. Hemoglobin A_{1c} levels are also affected by kidney dysfunction, hemolysis, and acidosis.[18]

Falsely high hemoglobin A_{1c} levels are associated with conditions that prolong the lifespan of erythrocytes, such as asplenia. Iron deficiency also increases the average age of circulating red cells because of reduced red cell production. For patients in whom blood glucose measurements do not correlate with hemoglobin A_{1c} measurements, iron deficiency anemia should be considered before altering a treatment regimen.

Falsely low hemoglobin A_{1c} levels are associated with conditions of more rapid erythrocyte turnover, such as autoimmune hemolytic anemia, hereditary spherocytosis,

TABLE 1

Possible causes of normoglycemia or hypoglycemia in dialysis patients who previously required insulin

Decreased renal clearance of insulin

Decreased hepatic clearance of insulin

Impaired renal insulin degradation

Increased insulin half-life for reasons other than renal or hepatic conditions

Decline in renal gluconeogenesis

Deficient catecholamine release

Other impacts of uremia on glucose homeostasis

Diminished food intake because of problems such as anorexia, diabetic gastroparesis

Protein-energy wasting (malnutrition-inflammation complex)

Loss of body weight and fat mass

Comorbid conditions

Hypoglycemia during hemodialysis treatments

Effects of peritoneal dialysis on glucose metabolism

Prescribed medications

Imposed dietary restrictions

Low hemoglobin A_{1c} owing to confounding by uremia or anemia

Kovesdy CP, Park JC, Kalantar-Zadeh K. Glycemic control and burnt-out diabetes in ESRD. Semin Dial 2010; 23:148–156. Copyright John Wiley and Sons, 2010; used with permission.

and acute blood loss anemia. In patients with CKD, recombinant erythropoietin treatment lowers hemoglobin A_{1c} levels by increasing the number of immature red cells, which are less likely to glycosylate.[19]

Morgan et al[20] compared the association between hemoglobin A_{1c} and blood glucose levels in diabetic patients with moderate to severe CKD not requiring dialysis and in diabetic patients with normal renal function and found no difference between these two groups, suggesting that hemoglobin A_{1c} is reliable in this setting. But study results conflict for patients on dialysis, making the usefulness of hemoglobin A_{1c} testing for those patients less clear. In one study, hemoglobin A_{1c} testing underestimated glycemic control,[20] but other

TABLE 2

Pharmacokinetic profile of insulin preparations in healthy people

Insulin	Onset of action	Peak effect	Duration	Frequency of administration
Glargine	2 hours	No peak	24 hours	Once daily
Detemir	2 hours	3–9 hours	12–24 hours	Once or twice daily
Neutral protamine Hagedorn	1–2 hours	4–8 hours	12–18 hours	Once or twice daily
Lispro, glulisine, aspart	5–15 minutes	1–2 hours	4–6 hours	Before or after each meal
Regular	30 minutes	2–4 hours	6–8 hours	With meals or every 6 hours for patients on continuous tube feeding

studies found that glycemic control was overestimated.[21,22]

Alternatives to hemoglobin A_{1c}
Other measures of long-term glycemic control such as fructosamine and glycated albumin levels are sometimes used in conditions in which hemoglobin A_{1c} may not be reliable.

Albumin also undergoes glycation when exposed to glucose. Glycated albumin appears to be a better measure of glycemic control in patients with CKD and diabetes than serum fructosamine,[23] which has failed to show a significant correlation with blood glucose levels in patients with CKD.[24] However, because serum albumin has a short half-life, glycated albumin reflects glycemic control in only the approximately 1 to 2 weeks before sampling,[25] so monthly monitoring is required.

Glycated albumin levels may be reduced due to increased albumin turnover in patients with nephrotic-range proteinuria and in diabetic patients on peritoneal dialysis. Several issues remain unclear, such as the appropriate target level of glycated albumin and at what stage of CKD it should replace hemoglobin A_{1c} testing. If an improved assay that is unaffected by changes in serum albumin becomes available, it may be appropriate to use glycated albumin measurements to assess long-term glycemic control for patients with CKD.

In general, therapeutic decisions to achieve optimum glycemic control in patients with diabetes and CKD should be based on hemoglobin A_{1c} testing, multiple glucose measurements, and patient symptoms of hypoglycemia or hyperglycemia. The best measure for assessing glycemic control in hospitalized patients with CKD remains multiple blood glucose testing daily.

■ INSULIN THERAPY PREFERRED
Although several studies have evaluated inpatient glycemic control,[26–29] no guidelines have been published for hospitalized patients with diabetes and CKD. Insulin therapy is preferred for achieving glycemic control in acutely ill or hospitalized patients with diabetes. Oral hypoglycemic agents should be discontinued.

Regardless of the form of insulin chosen to treat diabetes, caution is needed for patients with kidney disease. During hospitalization, clinical changes are expected owing to illness and differences in caloric intake and physical activity, resulting in altered insulin sensitivity. Insulin-treated hospitalized patients require individualized care, including multiple daily blood glucose tests and insulin therapy modifications for ideal glycemic control.

For surgical or medical intensive care patients on insulin therapy, the target blood glucose level before meals should be 140 mg/dL, and the target random level should be less than 180 mg/dL.[15,26–29]

Basal-bolus insulin
Sliding-scale therapy should be avoided as the only method for glycemic control. Instead,

Glycated albumin reflects glycemic control for only about 1 to 2 weeks

TABLE 3

Suggested starting doses of basal insulin (glargine or detemir) for hospitalized patients

Type of diabetes	Insulin dose (U/kg/day)				
	Normal renal function	GFR 10–50 mL/min	GFR < 10 mL/min	Age > 70	Body mass index < 19 kg/m²
Type 1	0.2	0.15	0.1	0.15	0.15
Type 2	0.25	0.15	0.1	0.15	0.15

NOTE: For patients who are eating, give an equivalent amount as short-acting insulin (eg, for a 100-kg patient with a GFR of 30 mL/min, give 15 units basal once per day and 5 units short-acting insulin with each meal).

scheduled subcutaneous basal insulin once or twice daily combined with rapid- or short-acting insulin with meals is recommended.

Basal-bolus insulin therapy, one of the most advanced and flexible insulin replacement therapies, mimics endogenous insulin release and offers great advantages in diabetes care. Using mealtime bolus insulin permits variation in the amount of food eaten; more insulin can be taken with a larger meal and less with smaller meals. A bolus approach offers the flexibility of administering rapid-acting insulin immediately after meals when oral intake is variable.

Individualize insulin therapy

Optimizing glycemic control requires an understanding of the altered pharmacokinetics and pharmacodynamics of insulin in patients with diabetic nephropathy. **Table 2** shows the pharmacokinetic profiles of insulin preparations in healthy people. Analogue insulins, which are manufactured by recombinant DNA technology, have conformational changes in the insulin molecule that alter their pharmacokinetics and pharmacodynamics. The rapid-acting analogue insulins are absorbed quickly, making them suitable for postprandial glucose control.

Changes in GFR are associated with altered pharmacokinetics and pharmacodynamics of insulin,[30,31] but unlike for oral antidiabetic agents, these properties are not well characterized for insulin preparations in patients with renal insufficiency.[13,32–36]

CKD may reduce insulin clearance. Rave

et al[32] reported that the clearance of regular human insulin was reduced by 30% to 40% in patients with type 1 diabetes and a mean estimated GFR of 54 mL/min. They found that the metabolic activity of insulin lispro was more robust than that of short-acting regular human insulin in patients with diabetic nephropathy. In another study, patients with diabetes treated with insulin aspart did not show any significant change in the required insulin dosage in relation to the renal filtration rate.[34] Biesenbach et al[33] found a 38% reduction in insulin requirements in patients with type 1 diabetes as estimated GFR decreased from 80 mL/min to 10 mL/min. Further studies are required to better understand the safety of insulin in treating hospitalized patients with diabetes and renal insufficiency.

Few studies have compared the pharmacodynamics of long-acting insulins in relation to declining renal function. The long-acting analogue insulins have less of a peak than human insulin and thus better mimic endogenous insulin secretion. For insulin detemir, Lindholm and Jacobsen found no significant differences in the pharmacokinetics related to the stages of CKD.[35] When using the long-acting insulins glargine or detemir, one should consider giving much lower doses (half the initial starting dosage) and titrating the dosage until target fasting glucose concentrations are reached to prevent hypoglycemia.

Table 3 summarizes recommended insulin dosage adjustments in CKD based on the literature and our clinical experience.

Hospitalization alters insulin sensitivity because of illness and differences in intake and activity

Considerations for dialysis patients

Subcutaneously administered insulin is eliminated renally, unlike endogenous insulin, which undergoes first-pass metabolism in the liver.[13,37] As renal function declines, insulin clearance decreases and the insulin dosage must be reduced to prevent hypoglycemia.

Patients on hemodialysis or peritoneal dialysis pose a challenge for insulin dosing. Hemodialysis improves insulin sensitivity but also increases insulin clearance, making it difficult to determine insulin requirements. Sobngwi et al[38] conducted a study in diabetic patients with end-stage renal disease on hemodialysis, using a 24-hour euglycemic clamp. They found that exogenous basal insulin requirements were 25% lower on the day after hemodialysis compared with the day before, but premeal insulin requirements stayed the same.

Peritoneal dialysis exposes patients to a high glucose load via the peritoneum, which can worsen insulin resistance. Intraperitoneal administration of insulin during peritoneal dialysis provides a more physiologic effect than subcutaneous administration: it prevents fluctuations of blood glucose and the formation of insulin antibodies. But insulin requirements are higher owing to a dilutional effect and to insulin binding to the plastic surface of the dialysis fluid reservoir.[39]

■ GLYCEMIC CONTROL FOR PROCEDURES

No guidelines have been established regarding the optimal blood glucose range for diabetic patients with CKD undergoing diagnostic or surgical procedures. Given the risk of hypoglycemia in such settings, less-stringent targets are reasonable, ie, premeal blood glucose levels of 140 mg/dL and random blood glucose levels of less than 180 mg/dL.

Before surgery, consideration should be given to the type of diabetes, surgical procedure, and metabolic control. Patients on insulin detemir or glargine as part of a basal-bolus regimen with rapid-acting insulin may safely be given the full dose of their basal insulin the night before or the morning of their procedure. However, patients on neutral protamine Hagedorn (NPH) insulin as a part of their basal-bolus regimen should receive half of their usual dose due to a difference in pharmacokinetic profile compared with insulin glargine or detemir.

In insulin-treated patients undergoing prolonged procedures (eg, coronary artery bypass grafting, transplant):

- Discontinue subcutaneous insulin and start an intravenous insulin infusion, titrated to maintain a blood glucose range of 140 to 180 mg/dL
- Subcutaneous insulin management may be acceptable for patients undergoing shorter outpatient procedures
- Supplemental subcutaneous doses of short- or rapid-acting insulin preparations can be given for blood glucose elevation greater than 180 mg/dL.

■ AVOID ORAL AGENTS AND NONINSULIN INJECTABLES

Oral antidiabetic agents and noninsulin injectables (**Table 4**) should generally be avoided in hospitalized patients, especially for those with decompensated heart failure, renal insufficiency, hypoperfusion, or chronic pulmonary disease, or for those given intravenous contrast. Most oral medications used to treat diabetes are affected by reduced kidney function, resulting in prolonged drug exposure and increased risk of hypoglycemia in patients with moderate to severe CKD (stages 3–5).

Metformin, a biguanide, is contraindicated in patients with high serum creatinine levels (> 1.5 mg/dL in men, > 1.4 mg/dL in women) because of the theoretical risk of lactic acidosis.[40]

Sulfonylurea clearance depends on kidney function.[41] Severe prolonged episodes of hypoglycemia have been reported in dialysis patients taking these drugs, except with glipizide, which carries a lower risk.[41,42]

Repaglinide, a nonsulfonylurea insulin secretagogue, can be used in CKD stages 3 to 4 without any dosage adjustment.[43]

Thiazolidinediones have been reported to slow the progression of diabetic kidney disease independent of glycemic control.[44] Adverse effects include fluid retention, edema, and congestive heart failure. Thiazolidinediones should not be used in patients with New York Heart Association class 3 or 4 heart failure,[45]

Periprocedural blood glucose targets should be looser

TABLE 4

Oral and injectable noninsulin antidiabetic agents

Drug	Mechanism of action	Advantages	Side effects and disadvantages	Use in chronic kidney disease
Biguanide metformin	Insulin sensitizer Decreases hepatic glucose production	No hypoglycemia [a] No weight gain	Gastrointestinal Vitamin B_{12} deficiency Lactic acidosis	Contraindicated if serum creatinine > 1.5 mg/dL in men and 1.4 in women in US (in most other countries may use if glomerular filtration rate [GFR] ≥ 30 mL/min)
Sulfonylureas glyburide, glipizide, glimepiride	Stimulate insulin release Decrease postprandial glucose	Less expensive	Hypoglycemia Weight gain	Due to risk of hypoglycemia, must be used with caution (short-acting glipizide preferred)
Meglitinides repaglinide, nateglinide	Stimulate insulin release Decrease postprandial glucose		Hypoglycemia Weight gain Expensive	Safer than sulfonylureas
Thiazolidinediones pioglitazone	Insulin sensitizer in muscle and adipose tissue	No hypoglycemia [a]	Weight gain Edema Bone fractures	Safe but can cause fluid retention, limiting its use in chronic kidney disease
Alpha-glucosidase inhibitors acarbose, miglitol	Slow carbohydrate absorption, decrease postprandial glucose	No hypoglycemia [a]	Gastrointestinal	Contraindicated if serum creatinine > 2 mg/dL
GLP-1 receptor agonists exenatide, liraglutide, albiglutide	Activate GLP-1 receptor Increase insulin Decrease glucagon Decrease gastric emptying, increase satiety	Weight loss No hypoglycemia [a]	Gastrointestinal Pancreatitis Medullary thyroid cancer Expensive	Contraindicated if GFR < 30 mL/min
Dipeptidyl peptidase-4 inhibitors sitagliptin, saxagliptin, linagliptin, alogliptin	Inhibit breakdown of GLP-1 Increase insulin Decrease glucagon	No hypoglycemia [a]	Pancreatitis Expensive	Safe Require dose reduction except linagliptin
Dopamine agonist bromocriptine	Stimulates dopamine receptors	No hypoglycemia [a]	Hypotension	Unknown
Bile acid sequestrant colesevelam	Unknown	No hypoglycemia [a]	Constipation Increases triglycerides	Unknown
SGLT2 inhibitors canagliflozin, dapagliflozin, empagliflozin	Inhibit sodium-glucose cotransporter-2 (SGLT2), reducing glucose reabsorption and increasing urinary glucose excretion	No hypoglycemia [a]	Mycotic infections Urinary tract infections	Contraindicated if GFR < 45 mL/min

[a] No hypoglycemia when used alone, but may cause hypoglycemia when used with insulin or sulfonylureas.

and so should not be prescribed in the hospital except for patients who are clinically stable or ready for discharge.

Quick-release bromocriptine, a dopamine receptor agonist, has been shown to be effective in lowering fasting plasma glucose levels and hemoglobin A_{1c}, and improving glucose tolerance in obese patients with type 2 diabetes, although its usefulness in hospitalized patients with diabetes is not known.[46,47]

Dipeptidyl peptidase inhibitors. Sitagliptin and saxagliptin have been shown to be safe and effective in hospitalized patients with type 2 diabetes.[48] However, except for linagliptin, dose reduction is recommended in patients with CKD stage 3 and higher.[49–52]

GLP-1 receptor agonists. Drugs of this class are potent agents for the reduction of glucose in the outpatient setting but are relatively contraindicated if the GFR is less than 30 mL/min, and they are currently not used in the hospital.

■ BLOOD GLUCOSE MONITORING IN HOSPITALIZED PATIENTS

Bedside blood glucose monitoring is recommended for all hospitalized patients with known diabetes with or without CKD, those with newly recognized hyperglycemia, and those who receive therapy associated with high risk for hyperglycemia, such as glucocorticoid therapy and enteral and parenteral nutrition. For patients on scheduled diets, fingerstick blood glucose monitoring is recommended before meals and at bedtime. In patients with no oral intake or on continuous enteral or parenteral nutrition, blood glucose monitoring every 4 to 6 hours is recommended. More frequent monitoring (eg, adding a 3:00 AM check) may be prudent in patients with CKD.

Continuous glucose monitoring systems use a sensor inserted under the skin and transmit information via radio to a wireless monitor. Such systems are more expensive than conventional glucose monitoring but may enable better glucose control by providing real-time glucose measurements, with levels displayed at 5-minute or 1-minute intervals. Marshall et al[53] confirmed this technology's accuracy and precision in uremic patients on dialysis.

Most oral antidiabetic agents increase the risk of hypoglycemia in moderate to severe CKD

Considerations for peritoneal dialysis

For patients on peritoneal dialysis, glucose in the dialysate exacerbates hyperglycemia. Dialysis solutions with the glucose polymer icodextrin as the osmotic agent instead of glucose have been suggested to reduce glucose exposure.

Glucose monitoring systems measure interstitial fluid glucose by the glucose oxidase reaction and therefore are not affected by icodextrin. However, icodextrin is converted to maltose, a disaccharide composed of two glucose molecules, which can cause spuriously high readings in devices that use test strips containing the enzymes glucose dehydrogenase pyrroloquinoline quinone or glucose dye oxidoreductase. Spurious hyperglycemia may lead to giving too much insulin, in turn leading to symptomatic hypoglycemia.

Clinicians caring for patients receiving icodextrin should ensure that the glucose monitoring system uses only test strips that contain glucose oxidase, glucose dehydrogenase-nicotinamide adenine dinucleotide, or glucose dehydrogenase-flavin adenine dinucleotide, which are not affected by icodextrin.[54]

■ IMPROVING QUALITY

Hospitalized patients face many barriers to optimal glycemic control. Less experienced practitioners tend to have insufficient knowledge of insulin preparations and appropriate insulin dosing. Also, diabetes is often listed as a secondary diagnosis and so may be overlooked by the inpatient care team.

Educational programs should be instituted to overcome these barriers and improve knowledge related to inpatient diabetes care. When necessary, the appropriate use of consultants is important in hospitalized settings to improve quality and make hospital care more efficient and cost-effective.

No national benchmarks currently exist for inpatient diabetes care, and they need to be developed to ensure best practices. Physicians should take the initiative to remedy this by collaborating with other healthcare providers, such as dedicated diabetes educators, nursing staff, pharmacists, registered dietitians, and physicians with expertise in diabetes management, with the aim of achieving optimum glycemic control and minimizing hypoglycemia. ■

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