CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will be familiar with special considerations in treating diabetes in patients with end-stage renal disease

KUMARPAL SHRISHRIMAL, MD, MS
Department of Hospital Medicine, Cleveland Clinic

PETER HART, MD
Division of Nephrology, Department of Medicine, Cook County Hospital, Chicago, IL

FRANKLIN MICHOTA, MD
Department of Hospital Medicine, Cleveland Clinic

Managing diabetes in hemodialysis patients: Observations and recommendations

ABSTRACT

Diabetes is challenging to manage in patients who have end-stage renal disease (ESRD), as both uremia and dialysis can complicate glycemic control by affecting the secretion, clearance, and peripheral tissue sensitivity of insulin. The authors summarize the available evidence and make practical recommendations.

KEY POINTS

Blood glucose levels can fluctuate widely due to various and opposing effects of ESRD and dialysis.

The hemoglobin A_{1c} level can be falsely high in ESRD, but it is still a reasonable measure of glycemic control in this population.

Most diabetes drugs are excreted at least in part by the kidney, so that patients in ESRD are at greater risk of hypoglycemia.

Insulin is the cornerstone of treatment, since most oral diabetes drugs are contraindicated or not recommended in this population. Insulin doses should be lowered in those with low glomerular filtration rates.

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Although diabetes is the most common cause of end-stage renal disease (ESRD) worldwide, accounting for 44.2% of ESRD patients in the US Renal Data System in 2005,[1] data are scarce on how diabetes should best be treated in patients in ESRD.

We do know that blood glucose levels need to be well controlled in these patients. Several observational studies and one nonrandomized interventional study[2–10] showed that higher levels of hemoglobin A_{1c} were associated with higher death rates in patients with diabetes and chronic kidney disease after adjusting for markers of inflammation and malnutrition.

However, ESRD significantly alters glycemic control, the results of hemoglobin A_{1c} testing, and the excretion of antidiabetic medications. The various and opposing effects of ESRD and dialysis can make blood glucose levels fluctuate widely, placing patients at risk of hypoglycemia—and presenting a challenge for nephrologists and internists.

In this review, we summarize the available evidence and make practical recommendations for managing diabetes in patients on hemodialysis.

GLUCOSE LEVELS MAY FLUCTUATE WIDELY

In ESRD, both uremia and dialysis can complicate glycemic control by affecting the secretion, clearance, and peripheral tissue sensitivity of insulin.

Several factors, including uremic toxins, may increase insulin resistance in ESRD, lead-

ing to a blunted ability to suppress hepatic gluconeogenesis and regulate peripheral glucose utilization. In type 2 diabetes without kidney disease, insulin resistance leads to increased insulin secretion. This does not occur in ESRD because of concomitant metabolic acidosis, deficiency of 1,25 dihydroxyvitamin D, and secondary hyperparathyroidism.[11,12] Hemodialysis further alters insulin secretion, clearance, and resistance as the result of periodic improvement in uremia, acidosis, and phosphate handling.

The dextrose concentration in the dialysate can also affect glucose control. In general, dialysates with lower dextrose concentrations are used and may be associated with hypoglycemia. Conversely, dialysates with higher dextrose concentrations are occasionally used in peritoneal dialysis to increase ultrafiltration, but this can lead to hyperglycemia.[10,13]

Thus, ESRD and hemodialysis exert opposing forces on insulin secretion, action, and metabolism, often creating unpredictable serum glucose values. For example, one would think that a patient who has insulin resistance would need more supplemental insulin; however, the reduced renal gluconeogenesis and insulin clearance seen in ESRD may result in variable net effects in different patients. In addition, ESRD and hemodialysis alter the pharmacokinetics of diabetic medications. Together, all of these factors contribute to wide fluctuations in glucose levels and increase the risk of hypoglycemic events.

Diabetes is the leading cause of ESRD worldwide

HEMOGLOBIN A_{1c} MAY BE FALSELY HIGH

Self-monitoring of blood glucose plus serial hemoglobin A_{1c} measurements are the standard of care in diabetic patients without renal failure.

However, in diabetic patients with ESRD, elevated blood urea nitrogen causes formation of carbamylated hemoglobin, which is indistinguishable from glycosylated hemoglobin by electrical-charge-based assays and can cause the hemoglobin A_{1c} measurement to be falsely elevated. Other factors such as the shorter red life span of red blood cells, iron deficiency, recent transfusion, and use of erythropoietin-stimulating agents may also cause underestimation of glucose control.[14]

Despite these limitations, the hemoglobin A_{1c} level is considered a reasonable measure of glycemic control in ESRD. Glycated fructosamine and albumin are other measures of glycemic control with some advantages over hemoglobin A_{1c} in dialysis patients. However, they are not readily available and can be affected by conditions that alter protein metabolism, including ESRD.[15–18]

Self-monitoring of blood glucose and continuous glucose monitoring systems provide real-time assessments of glycemic control, but both have limitations. Self-monitoring is subject to errors from poor technique, problems with the meters and strips, and lower sensitivity in measuring low blood glucose levels. Continuous monitoring is expensive and is less reliable at lower glucose concentrations, and thus it needs to be used in conjunction with other measures of glucose control. For these reasons, continuous glucose monitoring is not yet widely used.

The guidelines of the 2005 National Kidney Foundation Kidney Disease Outcomes Quality Initiative did not clearly establish a target hemoglobin A_{1c} level for patients with diabetes and ESRD, but levels of 6% to 7% appear to be safe. The target fasting plasma glucose level should be lower than 140 mg/dL, and the target postprandial glucose level should be lower than 200 mg/dL.[19]

MOST ORAL DIABETES DRUGS ARE CONTRAINDICATED IN ESRD

Oral antihyperglycemic drugs include the insulin secretagogues (sulfonylureas and meglitinides), biguanides, thiazolidinediones, and alpha-glucosidase inhibitors (**TABLE 1**). Most of these drugs are contraindicated in ESRD.

Sulfonylureas

Sulfonylureas reduce blood glucose by stimulating the pancreatic beta cells to increase insulin secretion.

Sulfonylureas have a wide volume of distribution and are highly protein-bound,[20] but only the unbound drug exerts a clinical effect. Because of protein binding, dialysis cannot effectively clear elevated levels of sulfonylurea drugs. Furthermore, many ESRD patients take drugs such as salicylates, sulfonamides, vita-

TABLE 1

Non-insulin antihyperglycemic agents

AGENTS	MECHANISM	INITIAL DOSE	MAXIMUM DOSE	ADVERSE EFFECTS	USE IN RENAL FAILURE
Sulfonylureas	Increase insulin secretion by pancreatic beta cells			Hypoglycemia and weight gain	Metabolism is affected by renal failure, necessitating dosage reduction and eventually avoidance
Glyburide (Micronase)		2.5–5 mg/day	10 mg twice daily		Used at doses of 2.5–5 mg/day if GFR > 50 mL/minute Not safe
Glimeperide (Amaryl)		1 mg/day	8 mg/day		Not safe
Glipizide (Glucotrol)		5 mg/day or XL 5 mg/day	20 mg twice daily or XL 20 mg/day		Safe at dosage of 2.5–10 mg/day Extended-release form is not safe
Tolbutamide (Orinase)		500 mg twice daily	500 mg four times a day		Not used
Chlorpropamide (Diabinese)		100 mg/day	500 mg/day		Not used
Meglitinides	Increase insulin secretion by pancreatic beta cells			Hypoglycemia and weight gain	Can be used
Repaglinide (Prandin)		0.5 mg three times a day	4 mg three times a day		May be used with caution, but is best avoided
Nateglinide (Starlix)		120 mg three times a day	180 mg three times a day		Hepatically metabolized and active metabolites excreted by kidneys; hence, not safe
Biguanides	Decrease hepatic gluconeogenesis			No hypoglycemia or weight gain	Contraindicated when GFR is < 60 mL/minute
Metformin (Glucophage)		250 mg twice daily	850 mg three times daily		
Thiazolidinediones	PPAR-gamma agonists; lower insulin resistance and enhance peripheral disposal of glucose			Cause weight gain; no hypoglycemia	Metabolism not affected; caution in patients with congestive heart failure
Rosiglitazone (Avandia)		4 mg/day	8 mg/day		
Pioglitazone (Actos)		15 mg/day	45 mg/day		
Alpha-glucosidase inhibitors	Prevent digestion of carbohydrates			No hypoglycemia or weight gain	Contraindicated because of increased level of parent drug and metabolite
Acarbose (Precose)		25 mg three times daily	100 mg three times daily		
Miglitol (Glyset)		25 mg three times daily	100 mg three times daily		
GLP-1 analogues	Slow gastric emptying, increase postprandial insulin release, reduce glucagon release				
Exenatide (Byetta)		5–10 µg twice daily	10 µg twice daily	Nausea, vomiting, and weight loss	Contraindicated if GFR is < 30 mL/min, and in ESRD
'Gliptins'	Inhibit DPP-IV, enhance action of GLP-1			Gastrointestinal effects; risk of hypoglycemia if used with sulfonylureas	
Sitagliptin (Januvia)		25 mg/day	100 mg/day		50 mg/day if GFR is 30–50 mL/min, or 25 mg/day if GFR < 30 or in ESRD
Saxagliptin (Onglyza)		2.5 mg/day	5 mg/day	Headache, upper respiratory infection, urinary tract infection	2.5 mg/day if GFR < 50 mL/min and in hemodialysis patients; not studied in peritoneal dialysis

GFR = glomerular filtration rate; ESRD = end-stage renal disease; DPP-IV = dipeptidyl peptidase; GLP-1 = glucagon-like peptide-1; PPAR-gamma = peroxisome proliferator-activated receptor gamma

min K antagonists, beta-blockers, and fibric acid derivatives, which may displace sulfonylureas from albumin, thus increasing the risk of severe hypoglycemia.

The first-generation sulfonylureas—chlorpropamide (Diabinese), acetohexamide (Dymelor), tolbutamide (Orinase), and tolazamide (Tolinase)—are almost exclusively excreted by the kidney and are therefore contraindicated in ESRD.[21] Second-generation agents include glipizide (Glucotrol), glimepiride (Amaryl), glyburide (Micronase), and gliclazide (not available in the United States). Although these drugs are metabolized in the liver, their active metabolites are excreted in the urine, and so they should be avoided in ESRD.[22]

The only sulfonylurea recommended in ESRD is glipizide, which is also metabolized in the liver but has inactive or weakly active metabolites excreted in the urine. The suggested dose of glipizide is 2.5 to 10 mg/day. In ESRD, sustained-release forms should be avoided because of concerns of hypoglycemia.[23]

Meglitinides

The meglitinides repaglinide (Prandin) and nateglinide (Starlix) are insulin secretagogues that stimulate pancreatic beta cells. Like the sulfonylureas, nateglinide is hepatically metabolized, with renal excretion of active metabolites. Repaglinide, in contrast, is almost completely converted to inactive metabolites in the liver, and less than 10% is excreted by the kidneys.[24,25] The meglitinides still pose a risk of hypoglycemia, especially in ESRD, and hence are not recommended for patients on hemodialysis.[24,25]

Plasma glucose values can be unpredictable in diabetic patients with ESRD

Biguanides

Metformin (Glucophage) is a biguanide that reduces hepatic gluconeogenesis and glucose output. It is excreted essentially unchanged in the urine and is therefore contraindicated in patients with renal disease due to the risks of bioaccumulation and lactic acidosis.[22]

Thiazolidinediones

The thiazolidinediones rosiglitazone (Avandia) and pioglitazone (Actos) are highly potent, selective agonists that work by binding to and activating a nuclear transcription factor, specifically, peroxisome proliferator-activated receptor gamma (PPAR-gamma). These drugs do not bioaccumulate in renal failure and so do not need dosing adjustments.[26]

The main adverse effect of these agents is edema, especially when they are combined with insulin therapy. Because of this effect, a joint statement of the American Diabetes Association and the American Heart Association recommends avoiding thiazolidinediones in patients in New York Heart Association (NYHA) class III or IV heart failure.[27] Furthermore, caution is required in patients in compensated heart failure (NYHA class I or II) or in those at risk of heart failure, such as patients with previous myocardial infarction or angina, hypertension, left ventricular hypertrophy, significant aortic or mitral valve disease, age greater than 70 years, or diabetes for more than 10 years.[27]

In summary, although ESRD and dialysis do not affect the metabolism of thiazolidinediones, these agents are not recommended in ESRD because of the associated risk of fluid accumulation and precipitation of heart failure.

Alpha-glucosidase inhibitors

The alpha-glucosidase inhibitors acarbose (Precose) and miglitol (Glyset) slow carbohydrate absorption from the intestine. The levels of these drugs and their active metabolites are higher in renal failure,[22] and since data are scarce on the use of these drugs in ESRD, they are contraindicated in ESRD.

GLP-1 ANALOGUES AND 'GLIPTINS,' NEW CLASSES OF DRUGS

Glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin release from pancreatic beta cells and inhibits inappropriate postprandial glucagon release. It also slows gastric emptying and reduces food intake. Dipeptidyl peptidase IV (DPP-IV) is an active ubiquitous enzyme that deactivates a variety of bioactive peptides, including GLP-1.

Exenatide (Byetta) is a naturally occurring GLP-1 analogue that is resistant to degradation by DPP-IV and has a longer half-life. Given subcutaneously, exenatide undergoes minimal systemic metabolism and is excreted in the urine.

No dose adjustment is required if the

TABLE 2

Insulin preparations: Considerations in hemodialysis patients

INSULIN PREPARATION	ONSET OF ACTION	PEAK ACTION	EFFECTIVE DURATION	DOSING CHANGE IN RENAL FAILURE
Rapid-acting				Reduce dose by 25% when glomerular filtration rate (GFR) is 10–50 mL/min, and by 50% when GFR < 10 mL/min
Regular	30–60 min	2–3 hr	8–10 hr	
Lispro (Humalog)	5–15 min	30–90 min	4–6 hr	
Aspart (NovoLog)	5–15 min	30–90 min	4–6 hr	
Long-acting				Reduce dose by 25% when GFR is 10–50 mL/min, and by 50% when GFR is less than 10 mL/min
Neutral protamine Hagedorn (NPH)	2–4 hr	4–10 hr	12–18 hr	
Glargine (Lantus)	2–4 hr	None	20–24 hr	
Detemir (Levemir)	3–4 hr	3–14 hr	6–23 (19.9) hr	
Premixed				Reduce dose by 25% when GFR is 10–50 mL/min, and by 50% when GFR is less than 10 mL/min
70/30 human mix	30–60 min	3–12 hr	12–18 hr	
70/30 aspart mix	5–15 min	30–90 min	12–18 hr	
75/25 lispro mix	5–15 min	30–90 min	12–18 hr	

glomerular filtration rate (GFR) is greater than 30 mL/min, but exenatide is contraindicated in patients undergoing hemodialysis or in patients who have a GFR less than 30 mL/min (TABLE 1).

Sitagliptin (Januvia) is a DPP-IV inhibitor, or "gliptin," that can be used as initial pharmacologic therapy for type 2 diabetes, as a second agent in those who do not respond to a single agent such as a sulfonylurea,[28] metformin,[29–31] or a thiazolidinedione,[32] and as an additional agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control.[28] Sitagliptin is not extensively metabolized and is mainly excreted in the urine.

The usual dose of sitagliptin is 100 mg orally once daily, with reduction to 50 mg for patients with a GFR of 30 to 50 mL/min, and 25 mg for patients with a GFR less than 30 mL/min.[33] Sitagliptin may be used at doses of 25 mg daily in ESRD, irrespective of dialysis timing (TABLE 1).

Other drugs of this class are being developed. Saxagliptin (Onglyza) was recently approved by the US Food and Drug Administration and can be used at a dosage of 2.5 mg daily after dialysis.

Sitagliptin has been associated with gastrointestinal adverse effects. Anaphylaxis, angioedema, and Steven-Johnson syndrome have been reported. The risk of hypoglycemia increases when sitagliptin is used with sulfonylureas.

Few oral diabetes drugs can be used in ESRD

ESRD REDUCES INSULIN CLEARANCE

In healthy nondiabetic people, the pancreatic beta cells secrete half of the daily insulin requirement (about 0.5 units/kg/day) at a steady basal rate independent of glucose levels. The other half is secreted in response to prandial glucose stimulation.

Secreted into the portal system, insulin passes through the liver, where about 75% is metabolized, with the remaining 25% metabolized by the kidneys. About 60% of the insulin in the arterial bed is filtered by the glomerulus, and 40% is actively secreted into the nephric tubules.[34] Most of the insulin in the tubules is metabolized into amino acids, and only 1% of insulin is secreted intact.

For diabetic patients receiving exogenous insulin, renal metabolism plays a more significant role since there is no first-pass metabolism in the liver. As renal function

starts to decline, insulin clearance does not change appreciably, due to compensatory peritubular insulin uptake.[35] But once the GFR drops below 20 mL/min, the kidneys clear markedly less insulin, an effect compounded by a decrease in the hepatic metabolism of insulin that occurs in uremia.[36] Thus, despite the increase in insulin resistance caused by renal failure, the net effect is a reduced requirement for exogenous insulin in ESRD.[37]

A variety of insulin preparations are available, including rapid-acting, intermediate-acting, and long-acting forms and premixed combinations, each with its specific onset, peak, and duration of action (TABLE 2). To our knowledge, no study of neutral protamine Hagedorn (NPH) insulin or other long-acting insulins has been done in patients with ESRD, and very few studies have described the use of insulin analogues in ESRD.

Aisenpreis et al[38] showed that the pharmacokinetic profile of insulin lispro (Humalog), which has a short onset of action and a short duration of action, may not only facilitate the correction of hyperglycemia but may also decrease the risk of late hypoglycemic episodes, which is of increased relevance in hemodialysis patients.

Reduce the insulin dose by 25% if the GFR is < 50 mL/min, and 50% if it is < 10 mL/min

On the basis of the available evidence,[39,40] we recommend a long-acting insulin such as insulin glargine (Lantus) or NPH insulin for basal requirements, along with a rapid-acting insulin analogue such as lispro or insulin aspart (NovoLog) before meals two or three times daily.

When the GFR drops to between 10 and 50 mL/min, the total insulin dose should be reduced by 25%; once the filtration rate is below 10 mL/min, as in ESRD, the insulin dose should be decreased by 50% from the previous amount.[41,42]

The newer insulins such as glargine and lispro are more favorable than NPH and regular insulin, but they cost more, which can be an obstacle for some patients.

OBSERVATIONS AND RECOMMENDATIONS

After reviewing the available evidence for the use of diabetic therapy in ESRD, we offer the following observations and recommendations:

- Glycemic control and monitoring in ESRD are complex.
- Patients with ESRD are especially susceptible to hypoglycemia, so diabetic drug therapy requires special caution.
- ESRD patients need ongoing diabetes education, with an emphasis on how to recognize and treat hypoglycemia.
- Diabetic pharmacotherapy in ESRD should be individualized. The targets of therapy are a hemoglobin A_{1c} value between 6% and 7%, a fasting blood glucose level less than 140 mg/dL, and a postprandial glucose level less than 200 mg/dL.
- Of the oral antidiabetic drugs available, glipizide, sitagliptin, and saxagliptin may be used in ESRD. Glipizide, starting with 2.5 mg daily, should be reserved for ESRD patients with a hemoglobin A_{1c} value less than 8.5%.
- Thiazolidinediones may cause fluid overload and thus should be avoided in ESRD.
- We recommend a long-acting insulin (glargine or NPH) for basal requirements, along with rapid-acting insulin before meals two or three times daily.
- The newer basal insulin (glargine) and rapid-acting insulin analogues (lispro or aspart insulin) are more favorable than NPH and regular insulin, but their higher cost could be an issue.
- Some patients may prefer a premixed insulin combination for convenience of dosing. In that case, NPH plus lispro insulin may be better than NPH plus regular insulin.
- For ESRD patients with type 1 diabetes, insulin therapy should be started at 0.5 IU/kg, which is half the calculated dose in patients without renal failure.
- For ESRD patients with type 2 diabetes, insulin therapy should be started at a total daily dose of 0.25 IU/kg.
- Further adjustments to the regimen should be individualized based on self-monitored blood glucose patterns.
- We recommend consulting an endocrinologist with expertise in managing diabetes in ESRD.

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***ADDRESS**: Kumarpal Shrishrimal, MD, MS, Department of Hospital Medicine, S70, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail shrishk@ccf.org.*