International Journal of Diabetes in Developing Countries

Vol. 27 **Number 4** **October-December 2007**

C O N T E N T S

Glycemic control in patients of chronic kidney disease

K. V. S. Hari Kumar, K. D. Modi, Ratan Jha[1]

Departments of Endocrinology and [1]Nephrology, Medwin Hospitals, Hyderabad, Andhra Pradesh, India

The incidence of diabetes is assuming pandemic proportions all over the world and with improved health care systems there is an increase in life expectancy for diabetic patients, resulting in an increase in complications. Diabetes is the leading cause of end-stage renal disease and various factors help in delaying this complication. Glycemic control in chronic kidney disease (CKD) is very important but is often an overlooked aspect, especially when the patient is on renal replacement therapy.

KEY WORDS: Diabetes, glycemic control, kidney disease

Introduction

Optimum glycemic control in diabetic patients with chronic kidney disease (CKD) can retard disease progression and reduce overall morbidity and mortality.[1] Additionally it offers several other benefits [Table 1]. However, achieving good glycemic control in azotemic patients is a challenging task. Altered metabolism of various nutrients, uremia-related insulin resistance, electrolyte and acid-base imbalance, reduced clearance of administered drugs, and the means of renal replacement therapy (RRT) itself (e.g. dialysis or renal transplant) can cause wide fluctuations in blood glucose. Optimum use of dietary measures, oral hypoglycemic agents and insulin, along with a clear understanding of the deranged physiology, can help in achieving good glycemic control.

Table 1: Importance of glycemic control in chronic kidney disease patients

- Lowers infection rate
- Shortens hospital stay
- Retards progression of associated micro- and macrovascular complications
- Delays progression of nephropathy in proteinuria stage
- Lowers incidence of cardiovascular events
- Improves electrolyte control
- Decreases gastropathy and neuropathy
- Reduces thirst and fluid overload
- Improves overall wellbeing

Correspondence to **Dr K. V. S. Hari Kumar,** Dept. of Endocrinology, Medwin Hospitals, Chirag Ali Lane, Nampally, Hyderabad, AP, India.
E-mail: hariendo@rediffmail.com

This article discusses the factors influencing glycemic control in uremic patients and reviews the various measures available, in the context of the newer oral anti-diabetic agents and insulin analogues, to optimize the glycemic control in diabetic patients with CKD. It also highlights entities like post transplant and '*de novo*' diabetes in relation to CKD.

Altered Nutrient Metabolism in CKD Patients

Uremia alters the entire metabolism, including that of carbohydrate, proteins and lipids. It also causes electrolyte disturbances and upsets mineral and hormonal homeostasis. Directly or indirectly, glucose metabolism is disturbed by all these changes.

Carbohydrate metabolism in CKD

There is a combination of insulin resistance and reduced insulin clearance, leading to erratic blood glucose control. There is reduced early insulin release and peripheral insulin resistance, which leads to net under-utilization of glucose.[2] The agents causing insulin resistance are counter-regulatory hormones, dyselectrolytemia, uremic acidosis and 'toxic' metabolic intermediates or end products.

Protein metabolism in CKD

Uremia *per se* does not stimulate net protein catabolism. The ability to conserve protein is impaired with metabolic acidosis and concomitant illness. Overall, renal neoglucogenesis is reduced, which contributes to

fasting hypoglycemia. Dialysis promotes protein wasting at least partly because of obligatory protein and amino acid losses into the dialysate. A low-protein diet has a beneficial effect on insulin resistance in uremia.[3]

Lipid metabolism in CKD

The characteristic lipid abnormality in CKD patient is moderate hypertriglyceridemia and an overall increased level of free fatty acids, leading to lipotoxicity and insulin resistance. Changes in the action of insulin on lipolytic enzymes, possibly mediated via increased levels of parathyroid hormone, have been implicated.[4]

Altered Pharmacokinetics of Antidiabetic Agents in CKD

Uremia may affect insulin activity and the ability of the patient to maintain optimal glucose control. Once a patient's creatinine clearance declines, the clearance of insulin diminishes and the half-life is prolonged, resulting in decreased insulin requirement. The selection of oral agents used to control blood glucose must be done keeping in mind the issues of their prolonged half-lives (or that of their metabolites) and the potential for adverse drug events due to the accumulation of these agents in renal failure.

Sulfonylurea

Prolonged hypoglycemia, with its attendant morbidity and mortality, is a significant problem in patients with CKD treated with sulfonylureas. Glyburide has a relatively longer half-life and 50% of the drug is excreted unchanged in the urine. It has metabolites with hypoglycemic activity and has been associated with hypoglycemic reactions in patients with renal failure. Glipizide, gliclazide and glimepiride have inactive metabolites and are relatively safer to use in diabetic patients with CKD.[5]

Biguanides

Metformin acts by decreasing basal hepatic glucose production and enhancing peripheral insulin uptake. It is primarily cleared by the kidneys.[6] Diabetic patients are at a high risk for metformin-induced lactic acidosis due to their predisposition for renal dysfunction, impaired clearance and abnormal lactate metabolism. Hence, metformin use is contraindicated when the creatinine level is >1.5 mg/dl for males and >1.4 mg/dl for females.

Glitazones

PPAR-γ agonists are insulin sensitizers and are useful in type 2 DM and CKD due to the fact that they are primarily metabolized at the hepatic level by cytochrome P450. Moreover, these compounds might improve uremia-associated insulin resistance. However, their propensity to increase fluid retention should be kept in mind.

Acarbose

α-Glucosidase inhibitors decrease postprandial glucose levels by delaying the digestion of carbohydrates and the absorption of glucose. In patients with renal impairment, plasma concentrations of acarbose have been shown to be proportionally increased and hence it is not advisable to use acarbose when serum creatinine is more than 2 mg/dl.[6] Miglitol is excreted primarily by the kidneys and should be used with caution in moderate to severe renal failure.

Meglitinides

Nonsulfonylurea secretogogues act by increasing the secretion of insulin. Nateglinide, which has active metabolites, is not considered safe in end-stage renal disease (ESRD) but repaglinide is safe and needs no dose adjustments in renal failure cases.[6]

Insulin

Approximately one-third of the body's insulin is removed by the kidneys. As a result, the patient with renal failure usually requires less insulin, secondary to a decreased insulin metabolism by the kidney.[7] Traditional insulin absorption profiles are erratic, creating fluctuations in glycemic control, and hence their onset of action and peak activity requires coordination of injection and meals. Futhermore, uremic patients are threatened by frequent hypoglycemic episodes when receiving traditional insulin treatment.

The action profile of rapid-acting insulin analogues affords more flexible treatment regimens, with a lower risk of hypoglycemia. Rapidly acting analogues like lispro and aspart are active within minutes and peak in about 1 h, mimicking normal mealtime insulin release.[8] Insulin analogue usage may not only facilitate the correction of hyperglycemia may but also decrease the risk of late hypoglycemic episodes. Long-acting analogues, such as glargine, provide a peak-less, continuous insulin release over 24 h that approximates a normal basal pattern and their role in CKD is under evaluation.

The measures to improve glycemic control in CKD patients are summarized in Table 2.

Table 2: Means to improve glycemic control in chronic kidney disease patients

Low protein diet	Reduce insulin resistance
Correction of acidosis	
Moderate exercise	
Selective sulfonylureas (glipizide, gliclazide, glimepiride)	Less active metabolic end products, leading to less hypoglycemia risk
Thiazolidinedione derivatives	Reduces insulin resistance; improves lipid profile
Rapid-acting insulin analogues	Less hypoglycemia
Use of meglitinides (repaglinide)	Metabolized by liver; can be used without dose adjustment

Monitoring Errors in CKD Patients

Glycemic monitoring carries immense importance in CKD patients in view of the fluctuating blood glucose levels. However, monitoring of various glycemic parameters may be fallacious due to uremia and disturbed metabolism.

HbA_{1c} (glycated Hb)

The use of longer-term measures of glycation like glycated hemoglobin is the cornerstone of assessing glycemic control. However, these test results are significantly flawed in the presence of uremia.[9] The factors causing pseudo-elevation of HbA_{1c} are the presence of carbamylated hemoglobin and acidosis. There can be low HbA_{1c} because of decreased RBC survival or due to frequent transfusion resulting in dilution of blood. Measurement of glycated albumin provides a better estimate of glycemic control in these patients.

Self-monitoring of blood glucose (SMBG)

The use of icodextrin-containing peritoneal dialysis (PD) fluid has brought new problems like spurious hyperglycemia, with falsely elevated serum glucose readings when using glucose dehydrogenase-pyrroloquinolinequinone (GDH-PQQ)-based assays in the glucometer.[10]

Serum creatinine in diabetic ketoacidosis

Patients with diabetic ketoacidosis show creatinine concentrations that are disproportionately elevated compared to the blood urea nitrogen level, which is compatible with true renal insufficiency. Investigations have shown that most of this elevation in creatinine is artifactual and caused by interference of acetoacetate in the automated methods for measuring creatinine.

Different Situations in CKD and Glycemic Management

Intensive diabetic management with the goal of achieving near-normoglycemia has been shown in various studies to delay the onset of microalbuminuria and progression from microalbuminuria to ESRD. Glycemic control is of less relevance for disease progression in ESRD patients; however, it has many proven benefits (other than retardation disease progression), as shown in Table 1.

Predialysis CKD patient

The major considerations, in addition to glycemic control, are control of hypertension and dyslipidemia and improvement of the nutritional status of the patient. Adjustment of the drugs for hypertension and dyslipidemia is required. Glycemic control is achieved by using oral antidiabetic agents like insulin secretogogues, thiazolidinedione (TZD) alone or in combination therapy. Initiation of insulin therapy is beneficial because of the erratic absorption pattern of drugs in CKD, coupled with poor oral intake. Additionally, most oral drugs or their metabolites are excreted through the kidneys.

CKD patient on peritoneal dialysis

Conventional glucose-containing PD solutions result in diffusion of glucose into the circulation, exacerbating the risk of hyperglycemia and contributing to poor glycemic control. Progressive increase in peritoneal membrane permeability has been observed during long-term PD, which leads to rapid hyperglycemia. Some patients lose the osmotic effect of glucose quickly, but the large icodextrin molecules, which are not easily transported across the peritoneal membrane, maintain an osmotic gradient and prolong ultrafiltration; its use, however, may sometimes lead to spurious hyperglycemia.

The objective of insulin treatment is to maintain 'euglycemia' during the dwell time, to prevent postprandial or post-PD hyperglycemia, and to avoid delayed hypoglycemia. However, controversy exists about the route of insulin administration. Subcutaneous (SC) and intraperitoneal (IP) insulin therapy are both acceptable in PD, providing good glycemic control.[11] Major fluctuations of blood glucose, hyperinsulinemia and the formation of insulin antibodies can be prevented by intraperitoneal insulin administration. The increase in insulin requirement and increased frequency of peritonitis during intraperitoneal insulin administration has resulted in some centers preferring the SC route over the IP route.

Uremic diabetic patient, requiring maintenance hemodialysis

Hemodialysis (HD) is the most common RRT modality in patients with diabetes. Glycemic control is a major objective in HD patients with diabetes as the achievement of satisfactory glycemic control, even after the beginning of HD, was shown to have a positive impact on morbidity and survival.[12]

Patients undergoing HD frequently become hypoglycemic and sometimes may not be aware of it. These events have become more frequent with the current use of glucose-free bicarbonate dialysis solution. Post-dialysis hypoglycemia manifests with non-specific symptoms like headache, weakness and easy fatigability. Hypoglycemia can be prevented by decreasing the morning insulin dose, food intake prior to dialysis, or by addition of glucose to the dialysis fluid.[13] The addition of glucose to dialysis fluid shows advantages such as prevention of glucose loss, decreased risk for both hypoglycemia and incidence of headache and post-dialysis fatigue.

Diabetic CKD Patient with Acute Worsening of Renal Failure (Acute-on-chronic CKD)

The diabetic CKD patient in acute renal failure may experience changes in insulin requirements and should be carefully monitored. Most of the patients demonstrated a need for less insulin during their acute renal failure. Subsequently, as the patient's renal function improved, insulin requirements are increased. Other considerations to keep in mind when monitoring a diabetic patient with acute renal failure are the patient's poor daily caloric intake and the occurrence of emesis.[14]

Post-transplant diabetes mellitus

Post-transplant diabetes mellitus (PTDM) is a form of type 2 diabetes mellitus, which is thought to develop from increased insulin resistance due to corticosteroid use, impaired insulin production because of use of calcineurin inhibitors, or a combination of both and other factors. Improved appetite and weight gain following renal transplantation may also contribute to hyperglycemia.[15]

As standard post-transplant management is directly diabetogenic, it is not easy to achieve glycemic control following transplantation. Regimens to reduce steroid use or to replace them with less diabetogenic steroids such as deflazacort may reduce the incidence of hyperglycemia without compromising on immunosuppression. A healthy allograft kidney clears insulin and hypoglycemic drugs normally. Hence, these patients are managed with oral antidiabetic drugs or insulin as deemed necessary.

Thus, multiple factors that affect glycemic control during RRT are summarized in Table 3.

De novo diabetes mellitus

The detection of diabetes for the first time in known CKD patients, unrelated to the underlying disease, is *de novo* diabetes.[16] It may be asymptomatic because of the absence of osmotic diuresis and may predispose to a hyperosmolar state if the patient is on chronic ambulatory peritoneal dialysis (CAPD). The mechanisms associated with the development of *de novo* diabetes are incorrect diagnosis (pseudo *de novo* diabetes mellitus), unmasking of diabetes due to improved nutrition and increased glucose load during PD, natural evolution of the disease,

Table 3: Glycemic control during renal replacement therapy

Mode of dialysis	Problem	Remedial measures
Peritoneal dialysis	Hyperglycemia	• Use of non-glucose PD solutions (like icodextrin), adjusting insulin dosage at higher levels
	Spurious hyperglycemia	• Prefer glucometer that works on glucose oxidase method rather than glucose dehydrogenase method whenever icodextrin-based PD fluid is used
Hemodialysis	Hypoglycemia	• Predialysis snacks
		• Reduce morning insulin dose by 50% on dialysis day
		• Addition of glucose to dialysate solution
Post-transplant	Hyperglycemia (common)	• Reduce steroid use and early withdrawal
		• Use of less diabetogenic steroids like deflazacort
		• Use of mycophenolate mofetil as the immunosuppressive agent
		• Avoid tacrolimus use in HCV co-infection
		• Consider simultaneous pancreas and kidney transplantation
		• Keep in mind the possibility of 'post-transplant diabetes' and '*de novo* diabetes' in newly detected cases
	Hypoglycemia (sometimes)	• Decrease doses of insulin as insulin sensitivity improves

Table 4: Medications that increase glucose intolerance

Antihypertensives	Immunosuppressive	Miscellaneous
Thiazides	Prednisone	Phenytoin
Betablockers	Cyclosporine	Niacin
Minoxidil	Tacrolimus	

and a common underlying autoimmune mechanism causing both diabetes mellitus and nephropathy. The management involves use of oral hypoglycemic agents and insulin, depending on the creatinine clearance.

Commonly Used Drugs in CKD Affecting Glycemic Control

Numerous medications used in CKD are associated with glucose intolerance, namely diuretics, antihypertensive drugs, immunosuppressive agents and seizure medications.[17] On the other hand, carbohydrate tolerance is improved by ACE inhibitors in some patients. The various drugs that increase glucose intolerance are given in Table 4.

To summarize, tight glycemic control offers several benefits in CKD patients but achieving this is a daunting task. Altered metabolism, insulin resistance, the drugs used in CKD patients, and reduced clearance of insulin/oral antidiabetic agents are the factors leading to swings in glycemic levels. The use of selective oral antidiabetic agents with end-metabolic products that are less active and rapid-acting insulin analogues help in reducing hypoglycemic events. Post-transplant diabetes mellitus and *de novo* diabetes mellitus are the conditions to be kept in mind while treating CKD patients.

References

1. Manske CL. Hyperglycemia and intensive glycemic control in diabetic patients with chronic renal disease. Am J Kidney Dis 1998;32:S157-71.
2. Fröhlich J, Schollmeyer P, Gerok W. Carbohydrate metabolism in renal failure. Am J Clin Nutr 1978;31:1541-6.
3. Rigalleau V, Blanchetier V, Combe C, Guillot C, Deleris G, Aubertin J, *et al*. A low-protein diet improves insulin sensitivity of endogenous glucose production in predialytic uremic patients. Am J Clin Nutr 1997;65:1512-6.
4. Trevisan R, Dodesini AR, Lepore G. Lipids and renal disease. J Am Soc Nephrol 2006;17:S145-7.
5. Yale JF. Oral antihyperglycemic agents and renal disease: New agents, new concepts. J Am Soc Nephrol 2005;16:S7-10.
6. KDOQI. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis 2007;49:S12-154.
7. Mak RH, DeFronzo RA. Glucose and insulin metabolism in uremia. Nephron 1992;61:377-82.
8. Ersoy A, Ersoy C, Altinay T. Insulin analogue usage in a haemodialysis patient with type 2 diabetes mellitus. Nephrol Dial Transplant 2006;21:553-4.
9. Ansari A, Thomas S, Goldsmith D. Assessing glycemic control in patients with diabetes and end-stage renal failure. Am J Kidney Dis 2003;41:523-31.
10. Disse E, Thivolet C. Hypoglycemic coma in a diabetic patient on peritoneal dialysis due to interference of icodextrin metabolites with capillary blood glucose measurements. Diabetes Care 2004;27:2279.
11. Quellhorst E. Insulin therapy during peritoneal dialysis: Pros and cons of various forms of administration. J Am Soc Nephrol 2002;13: S92-6.
12. Morioka T, Emoto M, Tabata T, Shoji T, Tahara H, Kishimoto H, *et al*. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care 2001;24:909-13.
13. Sangill M, Pedersen EB. The effect of glucose added to the dialysis fluid on blood pressure, blood glucose and quality of life in hemodialysis patients: A placebo-controlled crossover study. Am J Kidney Dis 2006,47:636-43.
14. Naschitz JE, Barak C, Yeshurun D. Reversible diminished insulin requirement during acute renal failure. Postgrad Med J 1983;59: 269-71.
15. Van Hooff JP, Christiaans MH, van Duijnhoven EM. Evaluating mechanisms of post-transplant diabetes mellitus. Nephrol Dial Transplant 2004;19:vi8-12.
16. Catalano C. Diabetes in dialysis patients: when diabetes is not diabetic nephropathy. Nephrol Dial Transplant 1996;11: 938-41.
17. Triplitt C. Drug interactions of medications commonly used in diabetes. Diabetes Spectrum 2006;19:202-11.

Source of Support: Nil, **Conflict of Interest:** None declared.