Diabetes mellitus and renal failure: Prevention and management

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Nowadays, diabetes mellitus (DM) and hypertension are considered as the most common causes of end-stage renal disease (ESRD). In this paper, other than presenting the role of DM in ESRD, glucose metabolism and the management of hyperglycemia in these patients are reviewed. Although in several large studies there was no significant relationship found between tight glycemic control and the survival of ESRD patients, it is recommended that glycemic control be considered as the main therapeutic goal in the treatment of these patients to prevent damage to other organs. Glycemic control is perfect when fasting blood sugar is less than 140 mg/dL, 1-h postprandial blood glucose is less than 200 mg/dL, and glycosylated hemoglobin (HbA1c) is 6-7 in patients with type 1 diabetes and 7-8 in patients with type 2 diabetes. Administration of metformin should be avoided in chronic renal failure (CRF) because of lactic acidosis, the potentially fatal complication of metformin, but glipizide and repaglinide seem to be good choices.

Key words: Chronic kidney disease, diabetes mellitus (DM), World Kidney Day

INTRODUCTION

End-stage renal disease (ESRD) is a condition in which the kidneys are no longer able to work properly in response to the needs of day-to-day life. ESRD usually occurs following chronic kidney disease and is one of the most important and life-threatening diseases. It imposes a huge mental and economic burden on societies.[1-18] Nowadays, diabetes and hypertension have become the most common causes of ESRD in both developed and developing societies.[4,5,19] In a study conducted in the USA, diabetes and hypertension were responsible for more than 50% of cases of ESRD,[19] and in a study conducted in Khuzestan, Iran, diabetes was the most common cause of disease and glomerulonephritis was responsible for about 10% of cases.[4]

According to the high prevalence of DM among patients with ESRD, there is a huge need to learn more about its prevention and management. Hence, other than presenting the role of DM in ESRD and the preventive choices, this paper was designed to review the glucose metabolism and management of hyperglycemia in these patients.

IMPACT OF DIABETES MELLITUS AND RENAL FAILURE ON EACH OTHER

DM is a metabolic disease that causes renal failure, and renal failure increases the need for insulin in diabetic patients.[4,20-31] The accumulation of uremic toxins and increased parathyroid hormone levels in patients with chronic renal failure (CRF) cause insulin resistance in tissues, particularly skeletal muscle tissues. This has been attributed to damage in the process after insulin binding to its receptors, which disturbs glucose metabolism and glycogen production.[20,21,24,27,30] It also seems that anemia caused by CRF has an impact on insulin resistance, and the correction of anemia by erythropoietin has been shown to increase insulin sensitivity in the body.[32]
Insulin secretion is also reduced in patients with CRF, which appears to be due to metabolic acidosis, elevated levels of parathyroid hormone, and decreased level of vitamin D.[33,34]

It should be noted that despite the decreased insulin secretion and impaired tissue sensitivity to insulin that occurs in patients with CRF, most nondiabetic CRF patients do not have hyperglycemia unless they are genetically predisposed.[20,24]

In advanced stages of CRF, when the glomerular filtration rate (GFR) become less than 15-20 cc/min, degradation and renal clearance of insulin decreases, which is clinically important in the treatment of patients with diabetes.[20] Although insulin resistance increases the insulin requirement, decreased insulin degradation reduces the need for administration of insulin in diabetic patients with advanced CRF or even resolves it in patients with type 2 diabetes. This may increase the risk of hypoglycemia. Renal replacement therapy, hemodialysis, and peritoneal dialysis relatively resolve this problem in most patients and based on the amount of clinical improvement, the insulin requirements change. Increased appetite and food intake resulting from the replacement therapy and alleviation of uremic symptoms also change insulin requirements.[24]

**IMPACT OF OXIDATIVE STRESS ON DIABETES MELLITUS AND RENAL FAILURE**

Under stressful conditions, reactive oxygen species (ROS) are overproduced, inducing oxidative stress. Hence, oxidative stress is due to an imbalance between free radical formation and antioxidant defense capacity.[35-41]

The result of this oxidative stress would be the induction of chronic hard-to-cure diseases such as diabetes,[42-47] hypertension,[48,49] cardiovascular disorders,[50-52] cancer,[53-60] cognitive diseases,[61-64] and pain,[65-69] or exacerbation of some other diseases such as infectious disorders.[70-79]

Oxidative stress also plays a crucial role in the development of diabetic kidney disease.[80-85] The number of patients with diabetic kidney disease is increasing worldwide. Increase in the level of ROS, which induces oxidative stress, has been considered the major cause of renal failure. Other than diabetes, renal failure itself also increases oxidative stress.[86] There are a number of macromolecules that have been shown to be implicated in the increased generation of ROS, including specific defects in the polyol pathway, glycolysis, advanced glycation, xanthine oxidase, reduced nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase, and uncoupling of nitric oxide synthase, which are the contributors of diabetic kidney disease. The morphologic characteristics of diabetic nephropathy include tubular atrophy, glomerular hypertrophy, arteriolar thickening, basement membrane thickening, mesangial expansion, and interstitial fibrosis, which are among the microvascular complications of diabetes.[87]

The increase in ROS is due to both increased production and decreased and/or inadequate antioxidant availability or function. Recent research studies have determined that both high glucose-induced changes in antioxidant function and high glucose-induced cellular ROS production contribute to the diabetes induction of renal failure. Treatments that target one or more diabetes-induced alterations for the regulation of ROS might lead to effective protection against or treatment of diabetic kidney disease. In this regard, the use of antioxidants seems to be effective in diabetes and protection against kidney disease.[88-90]

**ROLE OF ANTIOXIDANTS IN CONTROL OF DIABETES AND KIDNEY DISEASE**

Buffering the generation of ROS or consumption of these compounds might be a promising therapeutic approach to ameliorate diabetes and/or renal damage.[90-93]

Antioxidants have been shown to be effective in a lot of ROS-induced diseases.[94-105] The role of antioxidant therapy in diabetes and/or renal failure in humans is not clear, but there are a number of preclinical reports showing the effectiveness of antioxidants in the prevention and treatment[106-113] of diabetes[13,109,114-116] as well as renal failure.[117]

Antioxidants with plant origins have been shown to be a better choice for this purpose and a lot of plants exhibit antioxidant activity. In this regard, it is better that we try using plants that have shown good results for controlling both DM and kidney disease.[118-123]

**NEW APPROACHES FOR CONTROL OF RENAL FAILURE**

Control of diabetes and early treatment for the risk factors of diabetes are very important in preventing or delaying nephropathy. Control of hypertension with medications that modulate the renin-angiotensin system (RAS) has been shown to decrease the incidence as well as progression of diabetic kidney disease.[122] The consumption of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists reduces the incidence of ESRD in patients with type II DM.[122] Interestingly, the effects of angiotensin II receptor antagonists and ACEIs are independent of any antihypertensive property, which suggests a direct renal effect.

Furthermore, several new approaches, including the consumption of antifibrotic agents, endothelin receptor
Although glimepiride is metabolized by the liver, its active metabolites are excreted by the kidneys. Glimepiride is similar to glibenclamide in this aspect. 

**Sulfonylureas**

Sulfonylureas, which are widely used to treat type 2 diabetes, stimulate insulin secretion from pancreatic beta cells. These drugs inhibit the adenosine triphosphate (ATP)-dependent channels by binding to their receptors in pancreatic beta cells, leading to calcium influx and stimulation of insulin secretion. Thus, sulfonylureas are only effective in diabetic patients with some remaining beta cell function. These drugs have been reported to increase tissue sensitivity to insulin, but the clinical importance of this effect is negligible. Sulfonylureas usually lower blood glucose levels by 20% and HbA1c levels by 1.5-2%. These drugs are usually used in patients whose weight is normal or slightly increased. These drugs should not be used in patients who are losing weight, or are ketotic despite adequate caloric intake. In these cases, insulin should be used.

Today, second-generation sulfonylureas including glibenclamide, gliclazide, glipizide, and glimepiride have largely replaced with the first generation including chlorpropamide, tolazamide, and tolbutamide.

Chlorpropamide and tolbutamide are substantially excreted by the kidney in patients with normal renal function, but in patients with chronic kidney disease, the elevated serum levels caused by these drugs may cause severe hypoglycemia. Active metabolites of glibenclamide are also excreted by the kidney and increased serum levels caused by them have been observed in patients with renal failure. Although glimepiride is metabolized by the liver, its active metabolites are excreted by the kidneys. Glimepiride is similar to glibenclamide in this aspect.

Although glipizide is metabolized in the liver, its inactive metabolites are renally excreted. Therefore, glipizide is considered the oral hypoglycemic drug of choice from this group of drugs for patients with CRF. It is recommended that drug dosage should be reduced to approximately 50% if the GFR is less than 50 cc/min. The recommended initial dose for patients with normal renal function is 2.5-5 mg per day and the maximum dose is 20-40 mg per day in some references. The recommended dose for patients with renal failure is 2.5-10 mg per day.

A low dose of glibenclamide can be given to patients with a GFR above 50 cc/min, but it should be avoided entirely in patients with acute renal failure.

It should be noted that some drugs such as beta blockers, salicylates, and warfarin can separate sulfonylureas from the bonded proteins, which increases the amount of these drugs in blood; thus their glucose-lowering effects.
Biguanides
The only available drug in the biguanides class is metformin. Biguanides reduce glucose production and release by the liver, increase insulin-stimulated glucose uptake by all peripheral tissues such as muscles, and decrease plasma levels of free fatty acids, and thus gluconeogenesis.

Like sulfonylureas, metformin typically reduces fasting plasma glucose levels by 20% and HbA1C by 1.5%. The most common side effects of metformin are gastrointestinal disorders, including a metallic taste in the mouth, mild anorexia, nausea, and diarrhea, which cause treatment to be discontinued in 5% of cases. The most serious side effect of metformin is lactic acidosis, which happens rarely.[136,137]

The important factors that affect these complications are kidney, liver, and heart failures and kidney failure is the most important of them. This drug is usually excreted unchanged by the kidney, and its administration to patients with renal failure can cause drug retention and lactic acidosis. It is recommended to be avoided when GFR is less than 60 cc/min or serum creatinine is greater than 5.1 for men and 4.1 for women.[138-140]

Thiazolidinediones
Thiazolidinediones improve insulin sensitivity by increasing glucose utilization in the liver, skeletal muscle, and adipose tissues; suppress hepatic production of glucose through binding to peroxisome proliferator-activated receptors (PPARs); and increase insulin secretion through improvement of pancreatic beta cell function.[132,134]

Rosiglitazone and pioglitazone, the two main drugs of the thiazolidinedione family display strong protein-binding capacity, especially for albumin. Both these drugs and their metabolites are not retained in kidney failure; however, they can cause heart failure in patients receiving insulin.[132,133]

In a study, rosiglitazone increased mortality from cardiovascular diseases in dialysis patients. The administration of these drugs should be avoided in patients with ESRD, especially if they also have heart failure.[141]

Alpha-glucosidase inhibitors
The alpha-glucosidase inhibitors such as acarbose and miglitol reduce postprandial hyperglycemia by delaying the absorption of carbohydrate from the small intestine. The plasma levels of acarbose and its metabolites increase in patients with renal failure, but their relationship with an increased risk of hypoglycemia has not been established. Miglitol is also significantly excreted by the kidneys and expected to increase in the serum of patients with renal failure, so their administration is not recommended in patients with renal insufficiency.[134]

Meglitinides
Nateglinide and repaglinide are relatively new drugs in the meglitinides class that are used to treat diabetes. They are short-acting blood glucose-lowering medicines. Although their structural features and receptors are different from sulfonylurea, they also increase insulin secretion from pancreatic beta cells through ATP-dependent potassium channels.[134]

The recommended dose of repaglinide for people with normal renal function who have not previously received blood glucose-lowering agents is 50 mg before meals and the maximum dose is 40 mg before every meal. The suggested dose of nateglinide is 120 mg before every meal.

Although nateglinide is metabolized by the liver, its active metabolites are excreted by the kidney. In renal failure, active metabolites accumulate and cause hypoglycemia, so this drug should be used carefully or not prescribed in patients with renal failure.[142,143]

Repaglinide is also metabolized by the liver, but less than 10% of its metabolites are eliminated renally. Thus its use may be allowed in patients with ESRD.[139] A study showed that the risk of hypoglycemia for patients with ESRD receiving this drug was higher than that for patients with normal renal functions. Therefore the recommended starting dose of this drug for patients with renal failure is 0.5 mg per day and it should be increased carefully if a higher dose is required.[144]

Insulin
The renal and hepatic metabolism of insulin is decreased in CRF, so its recommended dose should be reduced in the following manner:[133,134]

When the GFR is above 50 mL/min, no dose reduction is required. When the GFR is 10-50 mL/min, the insulin dose should be reduced to approximately 75%. When the GFR is less than 10-50 mL/min, the dose should be reduced to approximately 50%. These adjustments are general, and insulin dosage adjustments should be based on regular blood glucose measurements. It should be noted that correction of uremia with dialysis on the one hand reduces insulin resistance and on the other hand increases insulin degradation; the ultimate effect of these on glycemic control in patients is different and glycemic control should be based on the final effect.[138,145-161]

CONCLUSION
In early stages of renal failure, insulin secretion and resistance in peripheral tissues, primarily in skeletal muscle, is reduced, and in advanced stages of renal failure, renal
clearance is reduced. These facts are clinically important in the treatment of diabetes. Although insulin resistance increases the insulin requirement, decreased insulin degradation reduces the need for administration of insulin in diabetic patients with advanced CRF, which increases the risk of hypoglycemia.

Severe hyperglycemia in oliguric or anuric ESRD patients is not associated with features of osmotic diuresis, which is seen in patients without renal failure, but it can cause hyponatremia, hyperkalemia, and acute increase in the intravascular volume.

In several large studies on ESRD patients, there was no correlation between increased survival and tight blood glucose control of patients. It is suggested that the incidence of hypoglycemia was significantly higher in patients receiving strict glycemic control. It is recommended that blood sugar control be considered an important goal in the treatment of ESRD diabetic patients to prevent additional damage to other organs including the eyes, kidneys, and heart.

The factors determining perfect glycemic control are the following: Fasting blood sugar less than 126 mg/dL, 1-h postprandial blood glucose less than 200 mg/dL, and HbA1c 7-6 in patients with type 1 diabetes and 7-8 in patients with type 2 diabetes.

Glipizide, an oral hypoglycemic agent, is administered at a daily dose of 2.5-10 mg in patients with CRF. Although thiazolidines and their metabolites are not retained in kidney failure, they can lead to edema and cardiac failure, particularly in patients receiving insulin. Their use has been prohibited in patients with advanced renal failure, particularly if they also have heart failure. Repaglinide is mainly metabolized by the liver, and less than 10% of its metabolites are excreted by the kidneys. Thus its use in ESRD patients may be allowed with meticulous care and with regard to the risk of hypoglycemia. Lactic acidosisis a rare but potentially fatal complication of metformin, so the administration of this drug should also be avoided in CRF patients. Insulin can be administered subcutaneously or intraperitoneally in patients on peritoneal dialysis with safety and accurate monitoring. DM induces renal failure, which increases oxidative stress and oxidative aggravate them. Therefore, the use of antioxidants, especially the ones which are effective in treating these two diseases, should be beneficial.

**Acknowledgments**

There was no financial support for this manuscript.

**Financial support and sponsorship**

There was no funding for this manuscript.

**Conflicts of interest**

Neither MRK nor HN has any conflicts to disclose.

**AUTHOR'S CONTRIBUTION**

MRK drafted the manuscript and performed the literature search. HN provided critical revisions of the manuscript.

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