REVIEW ARTICLE

Management of Diabetic End-stage Renal Disease: Role of Hemodialysis

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ABSTRACT

Diabetes mellitus is now the most common cause of end-stage renal disease (ESRD) all across the globe, including India. In view of the alarming rise in numbers, renal failure due to type 2 diabetes has been termed a "medical catastrophe of worldwide dimensions." When a patient develops uremic symptoms he needs renal replacement therapy. The renal replacement therapies available for all patients with ESRD are: hemodialysis, chronic ambulatory peritoneal dialysis (CAPD) and renal transplantation. Kidney transplantation is the best option for patients with diabetic ESRD. The 5-year survival of transplant patients of 75-85% is far superior to the 5-year survival rate of around 25% on dialysis.

Keywords: Diabetes mellitus, end-stage renal disease, renal replacement therapies, hemodialysis, CAPD, renal transplantation

Diabetes mellitus is now the most common cause of end-stage renal disease (ESRD) all across the globe, including India. It is estimated that 30-50% of patients being initiated on renal replacement therapy (RRT) have diabetes as the cause of their ESRD[1] and most of these patients have type 2 diabetes. In view of the alarming rise in numbers, renal failure due to type 2 diabetes has been termed a "medical catastrophe of worldwide dimensions".[2] This article will discuss the management of diabetic ESRD specifically related to type 2 diabetes.

RENAL REPLACEMENT THERAPY

When a patient's kidney function, as measured by the calculated glomerular filtration rate, has reached <10 mL/min (ESRD) or the patient develops uremic symptoms they need RRT.

The RRTs available for all patients with ESRD are:

- Hemodialysis
- Chronic ambulatory peritoneal dialysis (CAPD)
- Renal transplantation.

Though these modalities are available for all patients with ESRD, there are significant differences in the morbidity and mortality of any given modality between the diabetic and nondiabetic ESRD population. We will discuss some of these issues, specifically the modality of hemodialysis.

HEMODIALYSIS FOR DIABETIC ESRD

Although hemodialysis prevents death from uremia, the patient survival on hemodialysis is poor, especially for patients with diabetes, being approximately 20-25% at 5 years as compared to 40-50% for other causes of ESRD.[3] This is worse than many cancers. The survival of patients on maintenance hemodialysis in India seems dismal for both, diabetic and nondiabetic populations.[4]

The important contributors for mortality in the diabetic dialysis population are: Cardiovascular disease, adequacy of dialysis and nutritional status.

- **Cardiovascular disease (CVD):** CVD is the most common cause of death accounting for more than one-half of the cases.[5] The main reason for such a high mortality rate, which is of cardiovascular origin in the majority of cases is that the cardiovascular conditions of patients with diabetes are already severely impaired when they start RRT, as demonstrated by the high prevalence of coronary artery disease, stroke, peripheral occlusive disease and amputations. This also explains why patients who have diabetes and are on RRTs are at higher risk of developing *de novo* CVD, particularly ischemic heart disease, which not only is more frequent but also has a more aggressive course than in nondiabetic patients. In view of this, aggressive

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measures to manage CVD need to be adopted in all diabetic patients even before they reach the stage of dialysis.

- **Adequacy of dialysis:** Adequacy of dialysis, which also plays an important role in CVD and nutrition (MIA or malnutrition inflammation atherosclerosis syndrome), is also a contributor to the poor outcome and diabetics, in particular, seem to be more sensitive than nondiabetics to inadequate dialysis.[6] The increase in mortality of these patients largely disappears if there is an improvement in the nutritional status as reflected by an increase in serum albumin and creatinine.[7] This is a major problem in India where for various reasons like financial constraints, lack of access and availability of good dialysis units causes most patients to have inadequate dialysis.[8] Whenever possible, it is very essential to monitor the adequacy of dialysis by using biochemical measures like urea reduction rates, Kt/V and clinical well-being of patients and to take measures to improve the adequacy of dialysis.
- **Nutrition in dialysis:** Nutrition in dialysis patients is closely linked to inadequate dialysis, which leads to anorexia and poor calorie and protein intake. This is reflected by poor serum albumin and creatinine levels, which are indicators for mortality in dialysis patients. The problems of diabetic gastroparesis and diabetic enteropathy compound the nutritional problems.

The help of a good dietician and measures to treat diabetic gastroparesis and enteropathy by motility agents, frequent small foods and appropriate use of broad-spectrum antibiotics to treat bacterial infections in diabetic enteropathy are needed to maintain adequate nutrition. It is to be noted that cisapride is best avoided in this population because of the risk of fatal arrhythmias.[9]

DIET IN DIABETIC PATIENTS ON DIALYSIS

The general recommendation for diet in dialysis patients is given in Table 1. The iron requirement of dialysis patients varies and will need to be addressed on a patient to patient basis. In general, water-soluble vitamins are routinely prescribed and calcitriol may be needed in some patients.

Table 1. Daily Dietary Recommendations for Dialysis Patients versus Nonuremics[a]

Factor	Nonuremic	HD	PD
Protein (g/kg)	0.8	1.2	1.2-1.5
Calories (sedentary; kcal/kg)	30	30[b]	30-40[b,c]
Protein (%)	15-20	15	15
Carbohydrate (%)	55-60	55-60[d]	55-60[c,d]
Fat (%)	20-30	Balance	Balance
Cholesterol (mg)	300-400	300-400	300-400
Polyunsaturated/Saturated fat ratio	2.0:1.0	2.0:1.0	2.0:1.0
Crude fiber (g)	25	25	25
Sodium (1 g = 43 mEq)	2-6 g	2 g + 1 g/LUO	2-4 g + 1 g/LUO
Fluids (L)	Ad lib 1 L/LUO	1 L + 1 L/LUO	1.0-2.5 L + 1 L/LUO
Potassium (1 g = 25 mEq)	2-6 g	2 g + 1 g/LUO	4 g + 1 g/LUO
Calcium (g)	0.8-1.2	Diet +1.2	Diet + 1.2
Phosphorus (g)	1.0-1.8	0.6-1.2	0.6-1.2
Magnesium (g)	0.35	0.2-0.3	0.2-0.3

[a]All intakes calculated on the basis of normalized body weight (i.e., the average body weight of normal persons of the same age, height and sex as the patient).
[b]These levels of caloric intake are rarely attained in practice.
[c]Includes glucose absorbed from dialysis solutions.
[d]Carbohydrate intake should be decreased in patients with hypertriglyceridemia.
HD = Hemodialysis; PD = Peritoneal dialysis; LUO = Liters of urine output per day.

BLOOD SUGAR CONTROL IN DIABETIC DIALYSIS PATIENTS

There are certain special problems about blood sugar control in dialysis patients.

Altered Insulin Metabolism

In uremic patients (both diabetic and nondiabetic), insulin secretion by the β-cells of the pancreas is reduced and the responsiveness of peripheral tissues (e.g., muscle) to insulin is depressed. On the other hand, the rate of insulin catabolism (renal and extrarenal) is decreased, and therefore, the half-life of any insulin present in the circulation is prolonged.

All of these abnormalities are only partially corrected after institution of maintenance dialysis therapy.

Increased Sensitivity to Insulin

In diabetic dialysis patients treated with exogenous insulin, the importance of reduced insulin catabolism overrides the impact of insulin resistance; when exogenous insulin is administered, its effect may be intensified and prolonged. Thus, smaller than usual doses should be given.

Insulin Therapy

Tight control of sugar is sometimes difficult to achieve in diabetic dialysis patients. Nevertheless, good glucose control is worthwhile with split doses of insulin preferably. The "amount of insulin" per day required for patients receiving maintenance hemodialysis is usually small; optimum control of glycemia is achieved by administration of long-acting insulin at two separate times during the day (split dosing) and by supplementing with regular insulin for meals as needed. The proportions of long-acting and regular insulin, as well as the total insulin doses vary widely among different patients. Hypoglycemia is quite common in diabetic dialysis patients usually due to reduced insulin catabolism and reduced intake or food and/or poor absorption.

A fasting serum glucose of <140 mg/dL and a postprandial value <200 mg/dL is a reasonable goal to achieve.

Oral Hypoglycemic Agents

Lack of clinical studies on use of oral hypoglycemic agents (OHAs) in dialysis patients restricts the use of these agents.

Nevertheless, these agents are useful adjuncts in the treatment of diabetics and are used by many nephrologists. The safety of sulfonylureas depends on their mode of metabolism and their half-life. Use of short-acting agents primarily metabolized by the liver is, in general, safer in dialysis patients. Acetohexamide, chlorpropamide and tolazamide are excreted to a large extent in the urine. These drugs should not be used in dialysis patients because their half-lives will be greatly prolonged in the absence of renal function, possibly resulting in severe and prolonged hypoglycemia. The excretion of glyburide is 50% hepatic, and prolonged hypoglycemia has been reported using this drug in dialysis patients. Metabolism of glipizide, tolbutamide and gliclazide is almost completely hepatic. Consequently, the last three drugs should be considered if an OHA is desired. Many drugs frequently used in dialysis patients either antagonize (phenytoin, nicotinic acid, diuretics) or enhance (sulfonamides, salicylates, warfarin, ethanol) the hypoglycemic action of sulfonylureas.

Metformin, a biguanide, is associated with increased incidence of lactic acidosis in dialysis patients and should not be used. Acarbose inhibits α-glucosidase in the enteric mucosa and moderates postprandial hyperglycemia. It may prove to be a useful adjunct to other diabetic medications in diabetic patients. Troglitazone and other thiazolidinediones sensitize the target tissues to insulin and may be of help in obese, type 2 diabetics with insulin resistance. However, the use of this class of drugs may be associated with the risk of severe hepatotoxicity.

In general, insulin use is preferable in diabetic dialysis patients but judicious use of appropriate OHAs can be done.

Specific problems of hemodialysis in diabetic patients:

- Difficulty in creating and maintaining a vascular access because of severe peripheral vascular disease (PVD) in older diabetic patients.
- Inability to tolerate volume shifts giving rise to hypotension during hemodialysis because of autonomic neuropathy and CVD.
- Risk of infection.
- Progression of diabetic retinopathy.

In view of all these problems, meticulous planning and appropriate management should start in the predialysis period well before dialysis is anticipated and would involve a special diabetic team consisting of an Ophthalmologist, Vascular Surgeon, Podiatrist, Endocrinologist, Cardiologist, Neurologist and Dietician to help the nephrology team in keeping the patient as fit as possible even before they reach dialysis.

TIMING OF DIALYSIS IN DIABETIC ESRD

In general, most nondiabetic patients are initiated on dialysis when the creatinine clearance is <10 mL/min.

In diabetic patients, dialysis may have to be initiated at creatinine clearance even >15 mL/min.[9] The reasons for this being:

- Renal functions deteriorate rapidly in this group
- Hypertension is very difficult to control with severe renal failure
- Most patients have CVD with volume overload
- Uremic symptoms may manifest earlier than non-diabetic patients.

In spite of these recommendations, dialysis is usually started as an emergency in most Indian patients because of uremia, pulmonary edema or severe hyperkalemia because of poor awareness, financial constraints and lack of facilities for dialysis.[4,8]

ROLE OF CAPD

CAPD is another modality of treatment in diabetic ESRD. Though it has its advantages and disadvantages, the following factors decide the modality of dialysis:

- Comorbid conditions
- Family and home support
- Financial support
- CVD and PVD leading to poor vascular access for dialysis
- Hemodynamic stability
- Availability of hemodialysis centers.

CAPD is 30-50% more expensive than hemodialysis in India and is generally used for patients who do not have access to hemodialysis, have severe chronic heart failure (CHF), hemodynamic instability, poor vascular access and are not candidates for transplantation. The patient and the family should be motivated and have adequate financial support. Table 2 gives the comparison between the two modalities of dialysis.

Table 2. Dialysis Modalities for Diabetics

Modality	Advantages	Disadvantages
Hemodialysis	Very efficient	Risky for patients with advanced cardiac disease
	Frequent medical follow-up (in center)	Multiple arteriovenous access surgeries often required; risk of severe hand ischemia
	No protein loss to dialysate	High incidence of hypotension during dialysis session
		Predialysis hyperkalemia
		Prone to hypoglycemia
CAPD	Good cardiovascular tolerance	Peritonitis, exit site and tunnel infection risks similar to those in nondiabetic dialysis patients
	No need for arteriovenous access	Protein loss to dialysate
	Good control of serum potassium	Increased intra-abdominal pressure effects (hernias, fluid leaks, etc.)
	Good glucose control, particularly with use of intraperitoneal insulin; less severe hypoglycemia	Schedule not convenient for helper if one is required (e.g., for a patient with physical disability like blindness, stroke, etc.)
CCPD	Good cardiovascular tolerance	Protein loss to dialysate
	No need for arteriovenous access	
	Good control of serum potassium	
	Good glucose control with use of intraperitoneal insulin	Very very expensive
	Good for patients with disability	
	Peritonitis risk slightly less than for CAPD	

CAPD = Continuous ambulatory peritoneal dialysis; CCPD = Continuous cycling peritoneal dialysis.

SURVIVAL ON HEMODIALYSIS AND PERITONEAL DIALYSIS

There have been conflicting data about the survival of patients on CAPD compared to hemodialysis. Initial data from Michigan suggested an advantage for CAPD.[10] However, most studies after adjustment for comorbid condition, have not found a statistically significant survival difference between the two modalities.[11]

TRANSPLANTATION

Kidney transplantation is the best option for patients with diabetic ESRD. The 5-year survival of transplant patients of 75-85%, though less than that of nondiabetic ESRD, is still far superior to the 5-year survival rate of around 25% on dialysis.[3,12] Though in general healthier patients go on to transplant and sicker patients remain on dialysis the survival rates are better, even when these are factored in. Transplantation is also associated with a better quality-of-life and high degree of rehabilitation.

The pre- and post-transplant care of diabetic patients is generally similar to that of nondiabetics. However, in view of the high prevalence of CVD in this population, meticulous attention has to be paid to screen these patients for CVD prior to the transplantation.[13]

RECOMMENDATIONS FOR TREATMENT OF DIABETIC ESRD PATIENTS

Kidney transplant remains the best option of RRT for patients with diabetic ESRD in all suitable candidates. Recommendations for those not suitable for transplantation-

CAPD is recommended for patients with:

- Poor vascular access because of PVD
- Severe CVD with hemodynamic instability during hemodialysis
- Nonavailability of hemodialysis centers
- Good family and financial support
- Motivated patients.

Hemodialysis is the treatment for all the rest which is the treatment available for the vast majority of patients with diabetic ESRD in India who are not candidates for transplantation. In view of the multiple associated comorbid conditions, a multidisciplinary approach is needed to prevent and manage the complications of vascular diseases, malnutrition and retinopathy in diabetic dialysis patients.

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