CHOICE OF RENAL REPLACEMENT THERAPY IN PATIENTS WITH DIABETIC END STAGE RENAL DISEASE

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SUMMARY

Diabetic nephropathy is becoming the leading cause of end-stage renal disease (ESRD) worldwide. Although the prognosis of patients with diabetes and ESRD receiving Renal Replacement Therapy (RRT) has improved greatly, the presence of pre-existing cardiovascular disease means that the survival and medical rehabilitation of diabetics continue to be inferior to that of non-diabetics. RRT should be initiated earlier in patients with diabetes than in non-diabetics and the main choices of modalities are: 1) haemodialysis (HD), 2) Peritoneal dialysis (PD), 3) Kidney transplantation alone (KTA) or 4) simultaneous kidney and pancreas transplantation (SPKT). The most common modality of RRT utilised in the diabetic patient remains HD but this method is associated with many clinical problems, in particular the managment of vascular access and frequent intradialytic hypotension. There is accumulating evidence demonstrating that both survival and medcal rehabilitation of patients with diabetes and ESRD is superior after renal transplantation with or without pancreas transplantation.

KEY WORDS

- **Diabetes mellitus**
- **Renal Replacement Therapy**
- **End-Stage Renal disease**

BIODATA

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INTRODUCTION

The number of patients with diabetes and end-stage renal disease (ESRD) being admitted to Renal Replacement Therapy (RRT) is increasing dramatically, to the extent that in the last decade diabetes has become the most common single cause of ESRD in the United States, Europe, Latin America and even in Asia (1).

There are several reasons for the increasing number of diabetics with ESRD requiring RRT. First, the prevalence of diabetes, particularly type 2 diabetes in the general population is increasing, mainly due to ageing of the population worldwide. Furthermore, patients with diabetes nephropathy have an improved survival with a greater chance of developing ESRD. Finally patients with diabetic ESRD (usually the elderly) are now being accepted more readily for RRT programmes where formerly they had been excluded. Data from the United States Renal Data System (USRDS) show that in 2000 more than 40% (45.2%) of incident ESRD patients were diabetics (2). The figures for Europe and Asia are lower but show a similar trend.

NATURAL HISTORY OF DIABETIC NEPHROPATHY

The earliest clinical evidence of nephropathy is microalbuminuria (incipient) nephropathy. Without specific interventions ~80% of subjects with type 1 diabetes who develop sustained microalbuminuria evolve to overt nephropathy over a period of 10 –15 years. ESRD develops in 50% of type 1 individuals with overt nephropathy within 10 years and 75% by 20 years (3).

A higher proportion of individuals with type 2 diabetes are found

to have microalbuminuria and overt nephropathy shortly after diagnosis, because diabetes is actually present for many years before the diagnosis is established. Moreover, the presence of co-existing vascular disease and hypertension in type 2 diabetes may indicate that albuminuria may be less specific for the presence of diabetic nephropathy and in this group of patients it is not always clear whether renal failure is due solely to or even caused by diabetes (4). Without specific interventions, 20-40% of type 2 diabetic patients with microalbuminuria progress to overt nephropathy, but at 20 years after onset of overt nephropathy, only ~20% will have progressed to ESRD. Once the glomerular filtration rate (GFR) begins to fall, the actual rates of GFR deterioration is highly variable from one individual to another, but overall, they may occur at a frequency similar to that seen in type 1 diabetes (5).

However, the greater risk of dying from associated coronary artery disease in the older population with type 2 diabetes may prevent many with earlier stages of nephropathy from progressing to ESRD. As therapies and interventions for coronary artery disease continue to improve, more patients with type 2 diabetes may be expected to survive long enough to develop renal failure. In children with pre-pubertal onset of diabetes, renal disease (and microvascular complications) tends to accelerate during puberty (6).

CHOICE OF RRT IN DIABETES MELLITUS: IMPACT ON PROGNOSIS

RRT should be initiated earlier in diabetics than in non-diabetics. ESRD options should be discussed when creatinine clearance falls to 20 – 30ml/min and RRT should be started at a GFR of 10 –15ml/min.

There are reasons for going for RRT earlier in diabetics such as

a. diabetics become symptomatic at higher GFR due to poor renal reserves;
b. retinopathy has been observed to progress rapidly one to two years prior to start of dialysis and RRT should be initiated before the loss of lean mass due to uraemia induced catabolism.

These considerations could help to decrease the overall mortality in diabetics. Although, data from the USRDS indicates that survival of diabetic patients on RRT has improved greatly as compared to 30 years ago (7) patients with diabetes continue to do significantly worse than non-diabetic patients (2). One of the main reasons for the higher mortality rate is the increased cardiovascular risk profile and events in patients with diabetes (8).

These patients not only have a higher prevalence of macroangiopathy at the start of RRT (9) but are also at a greater risk for developing ***de novo*** cardiovascular disease with a poorer outcome in comparison with non-diabetic patients (10).

CHOICE OF RRT MODALITIES IN DIABETES ESRD

The different available modalities of RRT are: haemodialysis (HD); peritoneal dialysis (PD); kidney transplantation alone (KTA) or simultaneous pancreas and kidney transplantation (SPKT).

Comparative analyses concerning survival of diabetic patients undergoing HD or PD report conflicting results, but seem to show that the two dialytic methods are comparable in terms of outcome and survival (11,12).

In view of these findings we can conclude that there does not seem to be a first choice dialysis treatment modality for patients with diabetic ESRD and the decision of choice between these two methods should be based on medical grounds and the individual wish of the patient.

However, kidney transplantation with or without simultaneous pancreas transplantation is the premier modality of treatment in patients with diabetes and ESRD as demonstrated by the longer survival and improved morbidity and medical rehabilitation post renal transplantation in diabetics (2). On the other hand, the post renal transplantation survival of patients with diabetes appears to be worse than that of their non-diabetic counterpart (2) mainly due to pre-transplantation coronary artery disease. However, pure long-term graft survival was reported to be equally good in diabetic versus non-diabetic transplant recipients (13).

Moreover, the gain in life expectancy after kidney transplantation is proportionally higher in patients with diabetes than without. Wolfe et. al. (14) reported in a retrospective observational study that the reduction in long-term risk of death achieved in transplant recipients as compared to patients on the waiting list was greater in the group with diabetes (73%) than in those with glomerulonephritis (61%) or other causes of ESRD (62%). Recent data from Ventstrom et al (15) confirmed survival benefit with a solitary kidney transplant for patients with diabetes and kidney failure patients when compared to patients on the waiting list. These findings could be extended to simultaneous pancreas and kidney transplantation in contrast to the group undergoing pancreas after kidney (PAK) transplantation or solitary pancreas transplantation where the group on the waiting list had a much better prognosis and survival rate (15). These results together suggest that renal transplantation with or without simultaneous pancreas transplantation should be considered the first choice option, above all, in patients with diabetes.

MODALITIES

HAEMODIALYSIS (HD)

HD is still the most common RRT in patients with diabetes with > 75% in US in 2000 (2). There are several issues that need to be taken into consideration when choosing HD as the mode of

treatment in diabetic patients with ESRD. The first problem is that of vascular access, because of the existence of advanced atherosclerosis leading to frequent inadequacies in blood flow for the placement of arteriovenous (A-V) fistulas. Indeed diabetic patients have the worst access survival rates, suffer higher rates of steal syndrome and often require a more proximal anastomosis (16).

Therefore measures should be taken in order to decrease the morbidity and mortality in patients with diabetes with emphasis on instructions and treatment in the pre-dialysis period regarding patient compliance (such as metabolic control, smoking and hypertension) which influence the development and progression of complications during maintenance HD (17). Timely access creation with, as first choice, a native A-V fistula, with careful attention given to pre-operative evaluations, surgical techniques and surveillance programme provides better outcomes in patients with diabetes (16).

As a result of autonomic dysfunction due to polyneuropathy (PNP), vascular damage and impaired left ventricle compliance diabetic patients are more prone to intradialytic hypotension making optimal removal of fluid overload more difficult. This means that diabetics have a greater tendency for overhydration in the interdialysis period, ultimately leading to worse blood pressure control requiring a higher proportion of antihypertensive treatment (18). Prescribing longer and smoother dialysis procedures may circumvent these problems in the patients with diabetes, helped by discontinuing antihypertensive therapy before dialysis sessions.

Glycaemic control is also very important and poor glycaemic control in both type 1 (19) and type 2 (20) has been shown to be a strong predictor of cardiovascular morbidity, mortality and long term dialysis survival.

After the initiation of HD, insulin therapy must be adjusted respecting the impaired glucose use and prolongation of insulin half-life. Infections and necroses due to PNP and peripheral vascular disease need to be appropriately and aggressively tackled. Regular chiropody may prevent amputations in the diabetic dialysis population.

PERITONEAL DIALYSIS (PD)

Although survival is substantially equivalent in patients who have diabetes and are on HD or PD, there may be several good reasons for initial PD for diabetic patients. PD offers equal or better survival for younger patients during the early years of dialysis and is a viable alternative for patients with difficulties with vascular access (21). Better control of blood pressure can be maintained on PD mainly due to a slower shift of fluid across the peritoneal membrane maintaining a steady state, with a higher sodium loss.

Other possible advantages could be better control of anaemia and a possible slower rate of decline of residual renal function. PD may offer multiple lifestyle advantages with more flexibility and independence with less dietary constraints. PD technique survival has been reported to be similar (21) or inferior (22) between the diabetic and non-diabetic dialysis population. However, only a low percentage of patients with diabetes and ESRD appear to receive PD with wide differences existing between countries suggesting that selection criteria is influenced rather by cultural, logistic and reimbursement policies than by medical considerations.

The major problem confronted during PD in patients with diabetes is the increasing risk of peritoneal fibrosis. PD may accelerate changes in peritoneal membrane structure and function in diabetes. Severe and recurrent peritonitis and the use of conventional PD solutions containing high glucose and glucose degradation products are implicated in PD technique failure.

Increase in peritoneal expression of vascular endothelial end products (VEGF) and transforming factors ß-1 and excessive accumulation of advanced glycosylation end products (AGEs) may be involved in the progressive increase in peritoneal membrane permeability to small solutes, loss of ultrafiltration and peritoneal fibrosis (21). Therefore, utilization of non-glucose peritoneal dialysis solutions such as icodextrin and low glucose degradation products such as those in multi-chambered bags may prevent or delay alteration in function and hence be of interest for patients with diabetes.

TRANSPLANTATION

Renal transplantation is ***the*** modality of choice for treatment of ESRD in patients with diabetes for reasons already mentioned above. However it still accounts for only a limited proportion of RRT treatment in these patients.

The major limiting factor is the shortage of available renal allografts (23) and current research is concentrating on the possibility of the use of xenografts and the development of immune tolerance that will reduce the requirement of immunosuppressive drugs (24).

A particularly promising strategy for patients with type 1 diabetes and ESRD is simultaneous pancreas and kidney transplantation (SPKT), as suggested by several recent observational studies reporting a significant survival advantage for SPKT recipients over patients on the waiting list (15) and cadaver kidney transplant recipients with less equivocal results being reported in comparison to living donor kidney transplant recipients, mainly due to confounding factors such as multiple donor and recipient variables (25).

Thus, it remains unclear whether the pancreas transplant adds to the clear survival advantage conferred by a kidney transplant

for patients with diabetes and kidney failure. Moreover there appears to be uncertainty over whether quality of life is really enhanced post SPK as compared to KTA alone. Direct comparison between SPK and KTA transplant patients demonstrated improved perception about diabetes related issues, however general QOL benefits beyond those conferred by successful kidney transplantation were less apparent (26).

Superiority of newer procedures such as portal-enteric drainage utilized in SPK transplantation over systemic venous and bladder drainage may provide further differences in QOL and should be evaluated in long-term studies (27).

CONCLUSION

Renal transplantation, possibly combined with simultaneous pancreas transplantation (in patients with type 1 diabetes) should be the primary objective for patients with diabetes and ESRD due to improved survival, lessened morbidity and better rehabilitation.

However, at present this is a much under utilized option for a very limited proportion of patients with diabetic ESRD. HD and CAPD may be preferred in elderly patients, or patients with active systemic malignancy or severe cognitive disorders. Individual decisions need to taken in difficult cases such as HIV, hepatitis B and C infection. The choice of method of dialysis (HD or PD) in patients unable to undergo transplantation or awaiting transplantation is dependent on several factors such as the nature of associated co-morbid conditions, patient convenience, physician's bias, financial and reimbursement issues and mortality statistics. Ultimately efforts should be made to increase the use of renal transplantation as the modality of choice to treat patients with diabetes and ESRD.

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