Renal Replacement Therapy in Patients with Diabetes and End-Stage Renal Disease

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Abstract. The number of patients who have diabetes and ESRD and are being admitted to renal replacement treatment (RRT) is increasing dramatically worldwide, and in many countries, diabetes has become the single most frequent cause of ESRD. Although the prognosis of patients who have diabetes and are receiving RRT has greatly improved, survival and medical rehabilitation rates continue to be significantly worse than those of nondiabetic patients, mainly because of preexisting severely compromised cardiovascular conditions. The most common RRT modality in patients with diabetes is still hemodialysis, but it gives rise to a number of clinical problems, in particular difficulties in the management of the vascular access and high frequency of intradialytic hypotension. However, patients who have diabetes and are on peritoneal dialysis have to face a progressive increase in peritoneal permeability, loss of ultrafiltration, and peritoneal fibrosis, all phenomena being accelerated in patients with diabetes and ultimately leading to an increased technique failure. The results of observational studies and national registries, although conflicting, suggest that these two dialytic modalities are somehow comparable in terms of outcomes, whereas accumulating evidence shows that both survival and medical rehabilitation of patients with diabetes are significantly better after renal transplantation, which should be the first-choice option for patients who have diabetes and reach ESRD but unfortunately still accounts for only a limited proportion of RRT treatments in these patients.

The number of patients who have diabetes and ESRD and are being admitted to renal replacement treatments (RRT) is increasing dramatically, to the point that, during the past few years, in many countries, diabetes has or will soon become the most frequent single cause of ESRD. According to the United States Renal Data System (USRDS), the annual number of patients who have diabetes and are admitted to RRT in the United States more than doubled between 1995 and 2000 (from 19,155 to 41,685), and there was a striking increase in the percentage of incident ESRD patients with diabetes as the primary diagnosis (30.4% in 1987, 36.3% in 1992, and 45.2% in 2000) (1). The corresponding figures in other countries are lower (Figure 1) but show similar trends. In Italy, diabetes was the third most frequent known cause of ESRD in incident patients in 2000 (15.9%) after vascular nephropathies (20.6%) and chronic glomerulonephritis (16.7%) (2). In Lombardy, the percentage of patients with diabetes among patients who were newly admitted to RRT increased from 9% in 1983 to 11% in 1992 (3) and reached 17% in 1998. In Japan, this proportion increased from 21.3% in 1986 to 31.9% in 1995 (4).

There are various reasons for the increasing number of patients who have diabetes and are being admitted to RRT. First, as a result of the aging of the population, the prevalence of type 2 diabetes in the general population is increasing worldwide, because type 2 diabetes is a chronic degenerative disease and therefore is becoming more frequent with advancing age (it is forecasted that the number of patients with diabetes worldwide will reach 221 million by 2010, whereas they were 124 million in 1997). Furthermore, the survival of patients with diabetic nephropathy has significantly improved, thus allowing them to live long enough to develop ESRD. Finally, patients with type 2 diabetes, who are usually elderly, are now more readily admitted to RRT than in the past.

As a consequence of the increasing number of patients who have diabetes and are being admitted to RRT and of their improved survival, the prevalence of RRT patients with diabetes has also significantly increased worldwide: in the United States, the proportion of RRT patients with diabetes as the presumed cause of ESRD increased from 26.9% in 1991 to 30.6% in 1995 and to 36% in 2000 (1); in Lombardy, the same proportion increased from 4.6% in 1986 to 7.9% in 1996 and in Madrid from 7.4% in 1985 to 12.7% in 1997 to 1998 (5).

RRT Modalities: Impact on Prognosis

Thirty years ago, survival of patients who had diabetes and were on RRT was catastrophic (6). Although it has greatly improved since then, patients with diabetes continue to do significantly worse than nondiabetic patients. According to the USRDS, the adjusted 5-yr survival of patients who have diabetes and started RRT in 1995 was 33.6% (it was 24.5% for patients who started dialysis in 1985), significantly worse than that of patients in whom the primary cause of ESRD was hypertension (42.0%), glomerulonephritis (53.0%), or other renal diseases (43.0%) (1).

The main reason for such a high mortality rate, which is of cardiovascular origin in the majority of cases (7), 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 heart disease, stroke, peripheral occlusive disease, and amputations (8–10). This also explains why patients who have diabetes and are on RRT are at higher risk of developing de novo cardiovascular disease, particularly ischemic heart disease, which not only is more frequent but also has a more aggressive course than in nondiabetic patients (11).

Comparative survival analyses of patients who have diabetes and are on hemodialysis or peritoneal dialysis, although with conflicting results, have shown that the two dialytic modalities are substantially comparable in terms of patient outcome, when considering the whole diabetic population (12–14). The survival rates of patients who have diabetes and are on hemodialysis or peritoneal dialysis are also approximately similar. In the multicenter study by Maiorca et al. (15), 7-yr survival was not significantly different among patients with and without diabetes on the two modalities. According to the Catalonia Registry, 5-yr survival in patients with diabetes was 30% on hemodialysis and 25% on peritoneal dialysis (16). In a study by Locatelli et al. (17) of incident patients who lived in Lombardy, no significant difference was found in cardiovascular mortality or morbidity between patients on hemodialysis or peritoneal dialysis, even when the analysis was limited to patients with diabetes (Figure 2). It therefore can be concluded that there is not any a priori first-choice dialytic treatment modality for patients with diabetes and ESRD, and the decision to adopt hemodialysis or peritoneal dialysis should be made on medical grounds and, above all, on the wishes of the individual patients.

However, both survival and medical rehabilitation of patients with diabetes are significantly better after kidney transplantation. USRDS data show that the adjusted 5-yr survival in patients who had diabetes and received a kidney from a cadaveric or a living donor in 1995 was 75.2% and 83.0% respectively, far higher than the 29.2% 5-yr survival of patients who had diabetes and started dialysis in the same year (1). Although the survival of patients with diabetes and a kidney graft is worse than that of their nondiabetic counterparts (1), mainly as a result of a higher prevalence of pretransplantation cardiovascular disease, the gain in life expectancy after renal transplantation is proportionally much higher in patients with diabetes than without: in a retrospective observational study, Wolfe et al. (18) analyzed the reduction in the long-term risk of death achieved in the transplant recipients as compared with patients who remained on the waiting list for transplantation and found that it was greater in the subgroup of patients with diabetes (73%) than in those with glomerulonephritis (61%) or other causes of ESRD (62%). Although a selection bias affecting the patients who received a transplant could not be completely ruled out, these results suggest that renal transplantation should be considered the first-choice option also, and above all, in patients with diabetes.

**Hemodialysis**

Hemodialysis is still the most common RRT modality in patients with diabetes: in 2000, it was adopted in >80% of prevalent RRT patients with diabetes in Italy (2) and in >75% in the United States (1). The first problem to be faced when choosing hemodialysis for patients with diabetes is the vascular access, because advanced calcific atherosclerosis leads to frequently inadequate arterial inflow and eventually also to venous run-off problems. Indeed, patients with diabetes have worse access survival rates and more steal syndromes and often require a more proximal anastomosis (19,20). For these reasons, the creation of the vascular access must be considered at an earlier stage in patients with diabetes than without, and the
first choice must be a native arteriovenous fistula, which leads to more positive outcomes in patients with diabetes when careful attention is given to timely access creation, preoperative evaluations, surgical techniques, and surveillance program (19).

Another major problem for patients who have diabetes and are on maintenance hemodialysis is intradialytic hypotension, which is far more common than in patients without diabetes for a number of reasons, including autonomic dysfunction as a result of polyneuropathy, vascular damage, impaired left ventricular compliance, and the susceptibility of patients with diabetes to overhydration in the interdialytic interval. The high frequency of intradialytic hypotension makes it particularly difficult to reach the targeted dry weights in patients with diabetes, ultimately leading to worse BP control, as documented by the higher proportion of hemodialysis patients with diabetes requiring antihypertensive treatment (50 versus 27.7%) (21). Every effort therefore should be made to avoid the development of intradialytic hypotension in patients with diabetes by discontinuing antihypertensive therapy before dialysis sessions and, when necessary, by prescribing longer dialysis sessions with lower ultrafiltration rates.

Glycemic control is another major objective in hemodialysis patients with diabetes, as the achievement of a satisfactory glycemic control, even after the beginning of hemodialysis, was shown to have a positive impact on morbidity and survival (22). Furthermore, hyperglycemia causes thirst and high fluid intake, as well as an osmotic shift of water and potassium from the intracellular to the extracellular space, thus contributing to circulatory congestion and hyperkalemia. For these reasons, insulin should be administered without reservation also to patients who have diabetes and are on hemodialysis, whereas a dialysate containing glucose at a concentration of 11 mmol/L should be used, because it protects against the development of hypoglycemic and intradialytic hypertensive episodes without affecting glycemic control (23).

**Peritoneal Dialysis**

Although survival is substantially equivalent in patients who have diabetes and are on hemodialysis or peritoneal dialysis and there may be some good reasons for initially offering peritoneal dialysis to patients with diabetes (including, above all, difficulties in creating a vascular access), only a small proportion of patients with diabetes receive peritoneal dialysis. In Italy, only approximately 10% of the prevalent RRT patients with diabetes in 2000 were receiving peritoneal dialysis (2), and an even smaller percentage (6%) was recorded in the United States in the same year (1). However, wide differences existing between countries suggest that the selection of treatment is more influenced by cultural, logistic, and reimbursement policies than by medical considerations.

The major problems of patients who are on peritoneal dialysis are the progressive increase in peritoneal membrane permeability to small solutes, the loss of ultrafiltration, and the development of peritoneal fibrosis. These phenomena, promoted by severe or recurrent peritonitis and by the use of
conventional glucose-containing peritoneal dialysis solutions and ultimately leading to technique failure, seem to be accelerated in patients with diabetes, thus explaining why the risk of technique failure, which is greater in peritoneal dialysis than in hemodialysis patients, is even higher in patients with diabetes than without (24). In this context, the use of nonglucose peritoneal dialysis solutions, such as icodextrin, or those in multichambered bags may be particularly promising.

Transplantation

Although for the reasons mentioned above renal transplantation is the first-choice RRT option for patients who have diabetes and reach ESRD, it unfortunately still accounts for only a limited proportion of RRT treatments in these patients: only 16% of the United States prevalent patients who have diabetes and are on RRT in 2000 received a transplant, the majority of them having type 1 diabetes (1). The situation is even worse in other countries such as Italy, where, in the same year, the percentage of patients who had diabetes and were on RRT and had undergone transplantation was 8.4% among men and 6% among women (2).

A particularly promising strategy for patients with type 1 diabetes and ESRD is simultaneous pancreas and kidney transplantation (SPKT), as suggested by recent observational studies that have indeed reported a significant survival advantage for SPKT recipients with type 1 diabetes over cadaver kidney transplant recipients, whereas the results of the comparison with living donor kidney transplant recipients have not been unequivocal (25,26). Furthermore, it also should be remembered that SPKT improves the quality of life and a number of secondary complications of diabetes, including gastric and bladder function, metabolic impairment, and autonomic polyneuropathy (27,28).

It therefore is clear that renal transplantation, possibly combined with simultaneous pancreas transplantation in patients with type 1 diabetes, should now be the primary objective for all patients who have diabetes and reach ESRD and that every effort should be made to increase the use of this RRT modality in patients with diabetes.

References


