EARLY-START DIALYSIS IN DIABETIC NEPHROPATHY

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he point at which dialysis is initiated is still largely an empirical decision that is influenced by a number of variables, many of which are not actually linked to the individual’s end-stage renal failure but rather to economic and social factors (1). The traditional approach has been to initiate dialysis only when conservative therapy fails to control uremic symptoms. However, delayed initiation of dialysis is associated with excess mortality, morbidity, and cost (2-5). A more proactive approach is to consider early initiation of dialysis to avoid the onset of uremic symptoms and their consequences. No controlled studies have been published demonstrating the benefits of early dialysis, but a number of observational studies support the concept of early-start dialysis (6).

In 1978, Bonomini and colleagues (2) demonstrated a superior outcome in patients who commenced dialysis before the appearance of uremic symptoms. They showed that the 5-year survival in 34 patients started on chronic dialysis at a time when their creatinine clearance was > 10 mL/min was 100%, compared to 85% in 158 patients with a creatinine clearance of < 5 mL/min at the time of initiation of dialysis. Bonomini’s group subsequently extended their observations out to a 12-year follow-up with 82 patients commencing dialysis early compared to 308 patients commencing dialysis late. Those who commenced early had lower mortality (survival rate 77% versus 51 %), lower hospital admissions, and better rehabilitation (7). In another study (8), an 88% 10-year survival rate was seen in patients who commenced dialysis with a creatinine clearance of 10 mL/min compared to a 55% 10-year survival in patients whose creatinine clearance was < 10 mL/min (the mean clearance being 4 mL/min). The level of residual renal function at the time of commencement of dialysis

has also been shown to be an independent predictor of patient outcome over a 6-month follow-up (9). A strong link exists between decreasing renal function and deteriorating nutritional status, with a low serum albumin being a strong indicator of poor outcome (10).

Churchill (6), in a recent evidence-based review of literature, found -despite the absence of properly conducted randomized clinical trials supportive evidence for the concept of early dialysis, which has been associated with improved survival. More importantly, the major factor influencing outcome was timely referral to nephrology services with good "total" pre-dialysis care, including attention to cardiovascular risk factors, nutrition, vascular access, and patient education. Sesso and Belasco (11) demonstrated a lower survival at 6 months for patients who were late referrals to a nephrology service. The outcomes obviously relate, in part, to the more severe degree of uremia and other related complications (5).

The impact of early compared to late referral on diabetic versus non diabetic renal disease has not been examined in detail. Diabetic patients have a poorer prognosis on renal replacement programs compared to non diabetic patients. Much of this situation is attributable to associated comorbidity -in particular, to underlying cardiovascular disease. However, the comorbidity in turn is adversely modified by persistent uremia.

In an attempt to obtain better data on the impact of early referral versus late referral to a nephrologist on the survival outcome for diabetic renal disease compared to non diabetic renal disease, data from the ANZDATA registry was analyzed. ANZDATA is a comprehensive registry for Australia and New Zealand, with a 100% reporting rate for all patients on renal replacement programs in the two countries.

ANZDATA data from October 1991 to March 1995 was analyzed. A total of 4735 patients were on renal replacement over this period of time. Survival analysis was undertaken for early referral versus late referral and diabetic versus non diabetic renal disease.
The analysis used Kaplan-Meier survival plots, and survival curves were compared with the log rank test. Early referral (ER) was defined as "duration of known renal failure under the care of a nephrologist > 6 months" and late referral (LR) was defined as "duration of known renal failure under the care of a nephrologist < 6 months". The initial analyses are from the day of first treatment regardless of treatment modality.

Figures 1 and 2 show the survival graphs. For the total population, there was a significant difference in survival, with survival being better in the ER group (5-year survival: 47.69% ± 2.56% LR versus 55.99% ± 0.9% ER, p < 0.001; Figure 1). The difference was due to the poor survival of non diabetic late referrals compared to early referrals (p < 0.01); moreover, the total number of diabetic late referrals was low, at only 12.5% of the late referrals. There was no statistical difference in survival at 5 years in the diabetic groups between early and late referral (Figure 2), reflecting the overall poorer prognosis for this group with renal failure. As in other reported registries, survival of non diabetic patients was better than that of diabetic patients (Figure 2). This effect is more striking for latereferal diabetic patients compared to non diabetic patients (5-year survival: 27.01% ± 17; 6.73% diabetic patients versus 50.86% ± 17; 2.73% non diabetic patients). Unfortunately, data on residual renal function, nutritional status, and comorbidity for these groups was not recorded. Technique survival for mode of dialysis at 90 days demonstrated no difference between PD and HD for late-referral diabetic patients, but a better outcome for diabetic patients on HD in the early referral group (p < 0.001).

As has been reported elsewhere, there is a trend to commence renal replacement therapy earlier - particularly in diabetic patients - on the basis of observational studies and clinical experience, despite the absence of properly controlled trials. In New Zealand, where the incidence of diabetes is high, this tendency is also evident. Data was obtained from three New Zealand units on all new patients entering renal replacement therapy in 1997. The diagnosis of renal disease, late or early referral status, dialysis modality, and plasma creatinine at the time of first dialysis were collected. Creatinine clearance was calculated using the Cockcroft and Gault formula (12). There were 64 patients in total, with 25% of patients having diabetes, predominantly type II diabetes. The average creatinine clearance at the time of commencement of dialysis for the diabetic patients was 11.7 ± 1.0 mL/min compared to 8.4 ± 1.7; 0.6 mL/min for the non diabetic patients (p < 0.004). The average creatinine clearance at commencement of dialysis for early referrals was 8.3 ± 17; 0.6 mL/min versus 6.3 ± 17; 0.7 mL/min for late referrals. Obrador and Pereira (10)
reported a similar trend from the United States Renal Data System with lower plasma creatinine levels at the onset of dialysis in diabetic patients.

On the basis of reported studies, some of which are discussed above, the National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) guidelines have suggested that starting PD at a relatively high level of residual renal function is linked to better nutritional state and hence survival (13,14). Adequacy of dialysis with a recommended weekly Kt/V urea of 2.0 is associated with a better outcome. A weekly Kt/V urea of 2.0 approximates a glomerular filtration rate (GFR) of between 9 and 14 mL/min; therefore, it has been suggested that early incremental dialysis to maintain total clearances (residual renal function plus dialysis clearances) equal to a weekly Kt/V urea of 2.0 will be associated with a better long-term outcome (14). However, it is essential to remember the patient. The delivery of renal replacement therapy is not just the achievement of "adequacy" as defined by a numerical figure; rather, it is the quality of life and total health of the patient that is important, and diabetic patients are no exception.

An essential part of providing good renal replacement therapy is early referral to a nephrologist. A number of studies demonstrate the benefits of early referral and initiation of an integrated renal replacement program (2,3,6,10). For the diabetic population, this approach is even more critical. Rather than consider early-start "dialysis" in diabetic patients (15), we, as nephrologists, should be considering more active, early nephrological management of diabetic patients with greater cooperation with diabetologists as part of the holistic management of this group of patients. The total pre-dialysis care package is essential to plan, for diabetic patients, the optimal renal replacement program that will improve quality of life and reduce mortality.

In planning the optimal renal replacement program for a diabetic patient, there is no randomized controlled study that examines which modality is best: hemodialysis compared to peritoneal dialysis, or dialysis compared to transplantation. The dialysis modality will be influenced by the nephrologist's bias, the patient's health status and knowledge of options at the time of referral, social and economic reasons, underlying comorbidity, and the perceived need to preserve residual renal function.

ACKNOWLEDGMENTS

Brian Livingston and Alex Disney of the Australian and New Zealand Dialysis and Transplant Registry, The Queen Elizabeth Hospital, Adelaide, South Australia, kindly provided the data and statistical analyses presented.

The data reported here have been supplied by the Australian and New Zealand Dialysis and Transplant Registry. The interpretation and reporting of the data are the responsibility of the author and in no way should be seen as an official policy or interpretation of the Australian and New Zealand Dialysis and Transplant Registry.

REFERENCES
