

## Elderly Diabetic Patients on Peritoneal Dialysis

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*Diabetes mellitus is the fastest-growing cause of end-stage renal disease (ESRD) among patients requiring renal replacement therapy (RRT). While diabetes mellitus has become the leading cause of ESRD, the number of elderly patients who need dialysis has grown almost exponentially. Most elderly patients with diabetes are treated with hemodialysis; only a small percentage are treated with peritoneal dialysis (PD).*

*Elderly PD patients with diabetes have a lower survival rate than do nondiabetic patients and younger diabetic patients, perhaps because of the increased comorbidity seen in diabetic patients at dialysis initiation. Also, diabetic patients on RRT are at higher risk of developing de novo cardiovascular disease, one of the major causes of mortality.*

*In Canada, survival in elderly diabetic patients undergoing PD is similar to that in hemodialysis patients; in the United States, patients over 45 – 55 years of age with diabetes have experienced higher mortality on PD than on hemodialysis. It is important, however, to emphasize that survival on PD in these elderly patients has greatly improved in recent years. Fluid volume expansion may be one of the reasons for the higher mortality in elderly diabetic patients in some countries; but overall, PD remains a viable form of long-term RRT for elderly diabetic patients with ESRD.*

### Key words

Elderly patients, diabetes, hemodialysis, survival

### Introduction

Worldwide, among patients requiring renal replacement therapy (RRT), those with diabetes mellitus are the fastest-growing group (1–3). Because of the aging of the general population, the number of elderly patients who need dialysis has grown substantially.

Thus, in Canada, 53.3% of those who initiated RRT in 2008 were 65 years of age or older (3). At the same time, advances in the management of coronary artery disease and in critical care medicine, technological improvements in RRTs, and earlier initiation of dialysis has brought a progressive decline in the mortality rate of diabetic dialysis patients. These improvements have led to a substantial increase in number of prevalent dialysis patients with diabetes.

Despite the increasing numbers of these elderly patients—and especially those with diabetes—on peritoneal dialysis (PD), we know little about their clinical outcome. Most reports define as “old” individuals older than 60 or 65 years, but some registries define as “old” those older than 70 or 75 years. Moreover, possible risk factors that may affect outcome in these vulnerable patients have not been identified, and it is not known whether such factors are equally predictive in elderly patients with and without diabetes, on PD and on hemodialysis (HD).

The present paper describes our experience with a large number of elderly diabetic patients with end-stage renal disease (ESRD) treated with PD at the University Health Network in Toronto. It also reviews the literature concerning the long-term use of PD in elderly diabetic patients with ESRD.

### Discussion

#### *Characteristics of elderly diabetic patients*

The overall rate of new ESRD patients with diabetes in the United States was 159 per million population in 2006—50% higher than a decade earlier. Although the incidence of new diabetic patients requiring RRT had remained stable between 2001 and 2005, the prevalence rose by 2.5% in 2006 because of the continued increase in the incidence of diabetes in the general population (2).

Nearly one-half of new ESRD patients are over 65 years of age; 23% are 65 – 74 years of age, and 25.6% are over 75 years of age. Among these groups, the incidence of diabetes as a cause of renal disease has increased dramatically between 1985 and 2006.

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### *Elderly diabetic patients on dialysis*

Among 8619 diabetic patients on RRTs in Canada in 2008, 1151 were on PD (13.4%), 5527 were on HD (64%), and 1941 patients (22.5%) had received a renal graft (3).

In the United States, the use of PD in ESRD patients with diabetes has decreased. Thus, for the periods 1998 – 2002 and 2002 – 2006, the average annual change (rate per million) was 2.17% and 1.07% respectively in favor of HD, and for the same periods, PD declined by 5.11% and 4.47% annually (2). In a recent study of the prevalent PD population at our center, diabetic nephropathy was present in 38.8% of the patients (139 of 358), whose mean age ( $\pm$  standard deviation) was  $58.8 \pm 14.5$  years (4).

Several investigators have studied and compared the clinical outcomes of diabetic patients on PD with those of nondiabetic dialysis patients, or the outcome of diabetic patients on PD and on HD. However, only a small number of diabetic PD patients have been followed for more than 5 years, and only a few studies have reported on the long-term outcome of diabetic patients on PD. This paucity of data is especially true for elderly PD patients with diabetes mellitus as their primary kidney disease.

### *Survival of diabetic patients on PD*

Advanced age represents an important predictor of poor outcome in diabetic patients on continuous ambulatory PD (CAPD) (5). Patients with diabetes are at higher risk of developing other concurrent illnesses than are members of the general population, and among ESRD patients, comorbidity is more common in those with diabetes than in those without. Thus, the presence of conditions such as peripheral vascular disease, cardiovascular disease, cerebrovascular disease, hypoalbuminemia, malnutrition, and hyperparathyroidism at the initiation of dialysis may increase the mortality of diabetic patients on PD. Atherosclerotic vascular disease is common in people of all ages with diabetes, and heart disease in its various forms is the most frequent cause of death among diabetic patients (1). Furthermore diabetic patients on RRT are at higher risk of developing *de novo* cardiovascular disease, which is more frequent and more aggressive in them than in nondiabetic patients. Herzog *et al.* (6) reviewed 34,189 patients on long-term dialysis and found that long-term survival after acute myocardial infarction was poor and that patients

who were older or diabetic had a higher mortality rate than did patients without those characteristics. Also, several dialysis-related factors (Table I) may adversely affect the long-term survival of elderly PD patients with diabetes mellitus (7).

### *Experience at the University Health Network*

Among 139 diabetic PD patients studied during a mean follow-up of  $28.2 \pm 21.8$  months, Fang *et al.* (4) found 1-, 2-, 3-, and 5-year patient survival rates of 91%, 76%, 66%, and 47% respectively (Figure 1). Those outcomes are comparable to the outcomes reported by the U.S. Renal Data System (USRDS) for incident diabetic PD patients (85.7%, 67.9%, 52.5%, and 26.0% respectively), and the data reported by the Canadian Organ Replacement Register (CORR: 86.4%, 53.6%, and 31.3% at 1, 3, and 5 years).

To evaluate the influence of age on patient survival, Fang *et al.* further stratified the study group by age at the beginning of PD: younger (<65 years) and older ( $\geq 65$  years) diabetic patients, and younger (<65 years) and older ( $\geq 65$  years) nondiabetic patients. Figure 2 shows Kaplan–Meier survival curves for these four patient groups. Diabetic patients had a significantly poorer survival than did nondiabetic patients, both in the group younger than 65 and in patients 65 years of age or older. Furthermore, older patients had significantly poorer outcomes than did younger patients both with and without diabetes.

In a multivariate Cox regression analysis, age was the only significant factor that independently predicted outcome in diabetic patients after adjustment for other factors including sex, cardiac disease, serum albumin, blood pressure, HbA1c, and type of diabetes (4).

### *Survival for U.S. diabetic patients*

According to the latest USRDS data (2), the overall 5-year survival probability for incident patients during

TABLE I Factors affecting survival of elderly peritoneal dialysis patients with diabetes (7)

Comorbidity at dialysis initiation
Peritonitis
Ultrafiltration failure
Advanced glycosylated end-products (AGEs)
Adequacy of dialysis
Peritoneal membrane permeability
Residual renal function

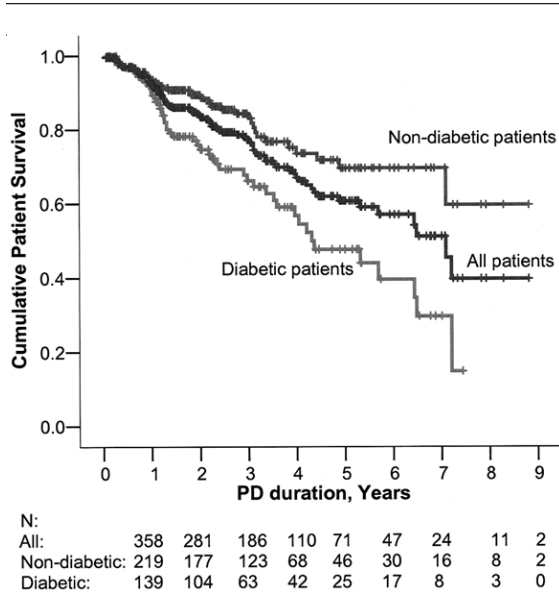


FIGURE 1 Kaplan–Meier survival curves for all patients and for diabetic and nondiabetic patients, stratified by number of patients being followed at various time points. Median actuarial patient survival was significantly shorter for diabetic patients than for nondiabetic patients (log rank: 14.117;  $p = 0.0001$ ) (4).

1997 – 2001 was 37%. Compared with data from the 1992 – 1996 period, the overall survival rate for incident patients in the later period rose by 7.2% (6.5% and 12.7% for HD and PD respectively). For patients with a primary diagnosis of diabetes, the survival rate rose 10.2% – 11.3%, although it remained lower than that for nondiabetic patients, and mortality continued to decline. Overall, hospitalization rates in dialysis patients have stabilized.

#### Technique survival among diabetic patients on PD

As with patient survival, technique failure is a greater risk for diabetic patients than for nondiabetic patients (4). The 1-, 2-, 3-, and 5-year technique survival rates were 90%, 83%, 67%, and 58% in diabetic patients and 94%, 87%, 77%, and 70% in nondiabetic patients respectively. But those results are better than the technique survival rates for diabetic PD patients in our group's previous report: 93%, 72%, and 44% for the first, third, and fifth years of CAPD respectively (7). They are also better than the results reported by the CORR, which found technique survival rates of 60% and 42% for

the second and fifth years of dialysis (4), and better than the rates reported from the United States [62.6% and 41.4% at the second and fifth years among 40,000 patients initiating PD during 2000 – 2003 (8)]. An earlier evaluation of PD using the U.S. data had concluded that age and diabetes did not appear to influence PD technique success (9).

#### Elderly diabetic patients on PD and HD

Several studies of dialysis populations with varying proportions of diabetic patients have attempted to compare long-term clinical outcomes for PD and HD. They yielded conflicting results even after adjustments for patient characteristics and comorbidity, with some studies showing no difference in mortality between the two dialysis modalities, and others showing higher mortality in PD than in HD.

#### STUDIES THAT SHOWED NO DIFFERENCE IN MORTALITY

Most of the studies that showed no difference in mortality have arisen from analyses of the CORR. Analyses in three separate periods showed the same results. In the early period, Fenton *et al.* (10) compared mortality rate ratios (RRs) for HD and for CAPD or continuous cycling PD (CCPD) in 11,970 ESRD dialysis patients and reported that the overall RR for PD relative to HD was 0.73 [95% confidence interval (CI): 0.62 to 0.87]. This lower mortality on PD was less pronounced among patients over 65 years of age: in diabetic patients 0 – 64 years of age, the RR for PD/HD was 0.73 (95% CI: 0.62 to 0.87), and in diabetic patients 65 years of age and older, it was 0.88 (95% CI: 0.73 to 1.06).

In a subsequent analysis, Schaubel *et al.* (11) used Poisson regression to evaluate trends in mortality among 17,900 patients receiving PD in Canada, adjusting for age, race, sex, primary renal diagnosis, follow-up time, and type of PD (CAPD or CCPD versus intermittent PD). They found a significant reduction in adjusted mortality RR by calendar period using 1981 – 1985 as the reference period (RR: 1): 1986 – 1989 RR: 0.81 (95% CI: 0.75 to 0.87); 1990 – 1993 RR: 0.73 (95% CI: 0.67 to 0.78); 1994 – 1997 RR: 0.63 (95% CI: 0.58 to 0.67). This improvement in mortality was fairly consistent across patient subpopulations, except for diabetic patients more than 65 years of age from 1986 – 1989. For diabetic patients 65 years of age and older, using 1981 – 1985 as the reference period (RR: 1), the 1986 – 1989 RR was 1.01

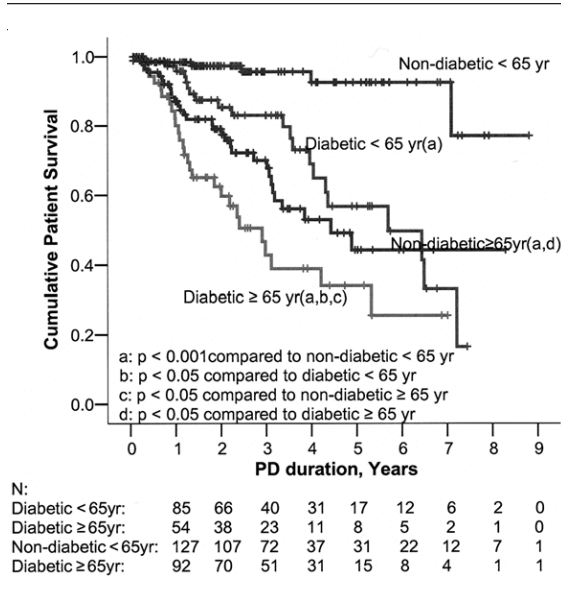


FIGURE 2 Kaplan–Meier survival curves for diabetic and nondiabetic patients, stratified by age and by number of patients being followed at various time points. Comparisons between the four groups showed that diabetic patients experienced significantly worse survival than did nondiabetic patients, both for those under 65 years of age and for those 65 years of age or older. On the other hand, older patients experienced significantly worse outcomes than did younger patients, whether with or without diabetes (4).

(95% CI: 0.76 to 1.33); the 1990 – 1993 RR was 0.74 (95% CI: 0.57 to 0.97); and the 1994 – 1997 RR was 0.70 (95% CI: 0.54 to 0.91).

In a more recent analysis of Canadian data, Yeates *et al.* compared PD with HD using both an intent-to-treat (ITT) and an as-treated (AT) analysis after adjusting for sex, age, dialysis vintage, primary renal diagnosis, and Charlson comorbidity index. Between 1991 and 2000, diabetic patients numbered 9871 (30.5% of the study population). For diabetic patients older than 65 years, the corresponding RRs were 0.88 (nonsignificant) with the ITT model and 1.04 (nonsignificant) with AT model (12).

Finally, Termorshuizen *et al.* (13) from Amsterdam studied mortality data according to treatment modality for 742 HD and 480 PD patients. Diabetes mellitus was present in 168 HD (22.6%) and 87 PD (18.1%) patients. The authors reported no significant difference in adjusted mortality rates between HD patients and PD patients 60 years of age and older, with or without diabetes mellitus, during a period of 3 – 24 months.

STUDIES THAT SHOWED HIGHER MORTALITY FOR ELDERLY DIABETIC PATIENTS ON PD OVER HD, OR VARYING MORTALITY

Most of the studies that showed higher mortality for elderly diabetic patients on PD come from the United States. Vonesh *et al.* (14) found that the death RR for PD over HD varied significantly according to sex and age. Thus, for the average male diabetic patient, there was little or no difference in risk between PD and HD, using 1989 – 1993 as the reference period: 1989 – 1991 RR: 1.02 (*p* = nonsignificant); 1990 – 1992 RR: 1.05 (*p* = nonsignificant); 1991 – 1993 RR: 1.08 (*p* < 0.01). For diabetic patients under the age of 50 years, those treated with PD had a significantly lower risk of death than did those treated with HD (1989 – 1993: 0.84 ≤ RR ≤ 0.89, *p* < 0.005). Over the same period, female diabetic patients treated with PD had a higher risk than did those treated with HD (1.18 ≤ RR ≤ 1.19, *p* < 0.001), as did diabetic patients over the age of 50 years (1.28 ≤ RR ≤ 1.30, *p* < 0.001).

Collins *et al.* (15), also from United States, showed a lower PD/HD mortality in diabetic PD patients younger than 55 years (RR for women: 0.88; RR for men: 0.86). The risk of all-cause death for female diabetic patients 55 years of age and older was 1.21 for CAPD and CCPD over HD, and the risk of death was not different (1.03) in men over 55 years of age on CAPD or CCPD as compared with their HD counterparts.

Winkelmayer *et al.* (16), who studied 2503 patients, 537 (21.5%) of whom started RRT on PD and 1966 (78.5%) of whom started on HD, reported higher mortality among elderly diabetic patients (older than 65 years) on PD in first 90 days, but similar mortality rates for both PD and HD after 180 days.

A more recent study of 16,643 dialysis patients from the Dutch End-Stage Renal Disease Registry compared survival on HD and PD (17). An initial survival advantage was found for PD over HD, that in the older diabetic population was reversed. These authors performed a time analysis stratified into three periods: more than 3 months to 6 months, more than 6 months to 15 months, and more than 15 months. For the first period, the mortality hazard ratio (HR) for PD over HD in patients 70 years of age and older with diabetes as the primary renal disease was 0.95 (95% CI: 0.64 to 1.39). The HRs for the second period were generally higher. After 15 months, the HR for 70-year old diabetic patients was 1.42 (95% CI: 1.23

to 1.65). Conversely, for diabetic patients 40 years of age, the HRs for PD over HD were 0.40 (95% CI: 0.23 to 0.68), 0.59 (95% CI: 0.44–0.81), and 1.06 (95% CI: 0.88–1.26) for the three periods from shortest to longest. Thus, in younger patients, PD was associated with superior survival in the first 15 months of RRT, independent of whether diabetes was the original renal disease. Among older patients, this association was present only for the first few months and only in patients whose underlying renal disease was not diabetes. Independent of underlying renal disease, PD was associated with higher mortality after 15 months in patients older than 70 years of age.

#### *Registry and prospective cohort studies*

Recently Vonesh *et al.* systematically reviewed six large-scale registry studies and three prospective cohort studies, conducted in the United States, Canada, Denmark, and the Netherlands, that compared mortality among ESRD patients receiving HD or PD (18). Generally, PD was associated with equal or better survival among nondiabetic patients and younger diabetic patients in all four countries. However, among older diabetic patients, results varied by country. Among older diabetics, the Canadian and Danish registries found no difference in survival between PD and HD; but in the United States, HD was associated with better survival only among diabetic patients 45 years of age and older.

Because most of the worse results for diabetic patients on PD arise from U.S. data, there is a need to exclude statistical and methodologic biases, and the effect of particular patient selection criteria. Consequently, the 90-day rule of the USRDS might favor the modality with the worst short-term outcome, or it might favor frail patients such as those with cardiac failure or coronary artery disease, conditions frequently present in older diabetic patients (19). Other important determinants for final outcome may include the higher prevalence of overweight diabetic patients on PD in the United States, the size of the center and its level of excellence in the care of people with diabetes, and the education and follow-up programs for patients using PD as a self-care home dialysis modality.

#### *Possible reasons for the reported differences*

Difference in fluid homeostasis might be an underlying reason for the differences in mortality between

diabetic and nondiabetic patients and between diabetic patients on PD and HD. Fluid overload is the main cause of death in ESRD patients on dialysis, and fluid control is potentially more difficult in PD patients, who in early years were erroneously advised that fluid restriction was less important for them than for patients undergoing HD. Also, it may be difficult to restrict fluid intake in poorly controlled diabetes, given that hyperglycemia may then stimulate the thirst mechanism.

Tang *et al.* (20), who compared differences between diabetic and nondiabetic patients during the first year of PD after implementing strict fluid control, emphasized the critical value of strict volume control for diabetic patients on PD. At the initiation of treatment, diabetic patients had significantly higher extracellular volume and systolic blood pressure and lower serum albumin than did the nondiabetic patients, but 1 year later, the authors found no statistical difference in these parameters between the two groups. These authors believe that restricting salt and water intake can prevent fluid overload in diabetic PD patients; such restriction also reduces the need for hypertonic exchanges and prevents hyperglycemia and long-term peritoneal membrane damage in the patients. Use of icodextrin may also help to maintain better fluid balance, because this agent has been shown to produce higher ultrafiltration in diabetic patients than in nondiabetic patients on PD (21).

Fluid overload in diabetic PD patients may be a result of ultrafiltration loss (18) secondary to the development of high transport characteristics (22), which may be linked to enhanced inflammation and to neoangiogenesis (23). Fluid overload may also be a result of the high and high-average peritoneal transport characteristics that are more frequently seen in older diabetic patients (20). Diabetes mellitus has been reported (24) to be significantly more frequent among high transporters (60%) than among low transporters (16.6%). Among 224 diabetic PD patients at the Toronto Western Hospital, the distribution of permeability properties were 21% high, 48% high-average, 29% low-average, and 2% low (25).

Nakamoto *et al.* (26) confirmed that high peritoneal membrane transport and protein permeability are higher among diabetic PD patients; the hypoproteinemia observed in those authors' diabetic patients has been attributed to the higher permeability of the membrane to protein.

Van Laecke *et al.* (19), who discussed the possible reasons for the higher mortality of elderly female diabetic patients on PD as compared with HD, suggested that the reasons might be differences in treatment practices and experience with PD as compared with HD, and the effects of the different treatment modalities on factors related to inflammation, insulin resistance, and hormone balance.

Finally, conflicting results of epidemiologic studies on differences in outcome for diabetic patients on HD or PD can partly be explained by factors such as patient selection bias, center experience, center bias, incomplete case-mix stratification, small patient numbers, and the use of prevalent instead of incident patients in the analyses (27,28). Overall mortality studies that compared patient survival between PD and HD yielded comparable results, although important differences were observed within selected subgroups of patients, particularly those defined by age and by the presence or absence of diabetes (18).

### Conclusions

Studies conducted to establish long-term outcome in elderly diabetic patients undergoing chronic RRT have been inconclusive. However, in comparisons with younger patients, older age has constantly been shown to be a negative factor associated with lower survival in both diabetic and nondiabetic dialysis patients. Also, the higher incidence of comorbidity in elderly diabetic patients at dialysis initiation—onto either PD or HD—may increase the risk of morbidity and mortality. Short-term patient and technique survival (3 – 5 years) for diabetic patients on PD has greatly improved over recent years.

Peritoneal dialysis remains a viable form of long-term RRT for elderly diabetic patients with ESRD.

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