Risk factors for mortality in diabetic peritoneal dialysis patients

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Abstract

Background. It is well established that the survival rate of diabetic end-stage renal disease patients remains the lowest among all primary diagnoses probably because of higher prevalence of cardiovascular diseases (CVD) associated with diabetes. This study was designed to evaluate the impact of CVD and other risk factors individually or in combination on mortality in diabetic peritoneal dialysis (PD) patients.

Methods. In a retrospective study, 213 incident PD patients [118 had diabetes mellitus (DM), 94 were female, mean age 55 ± 13 years] underwent initial assessment of nutritional status, comorbid disease (CMD) survey, residual renal function (RRF), dialysis adequacy and peritoneal transport characteristics at a mean of 9 days (range, 3–24 days) after start of PD and were then followed for 30 ± 24 months (range, 3–115 months). Of 213 patients, 154 patients were reassessed after a mean of 11 months (range, 6–19 months). Nutritional status was assessed by subjective global assessment and other methods. CMD was graded by Davies index and included DM, CVD, liver disease and respiratory disease.

Results. On Kaplan–Meier analysis, patient survival was significantly lower in female DM patients compared to other groups. The 3-year patient survival rate was 46, 70, 82 and 83% for female DM, male DM, male non-DM and female non-DM, respectively (P=0.003). On Cox proportional hazards multivariate analysis including all patients, old age, presence of CVD or protein-energy wasting (PEW), low serum albumin concentration and low RRF were independent predictors of mortality but not DM per se or female gender. In DM patients, old age, female gender, presence of CVD or PEW and low RRF were independent predictors of mortality while old age was the only risk factor in non-DM patients. After adjustment for age, gender and RRF, DM patients with both CVD and PEW had a risk of mortality that was 3.3 times that of DM patients without CVD and PEW. In DM patients without CVD and PEW, patient survival was not different from that of non-DM patients without CVD and PEW.

Conclusions. DM per se was not a risk factor for mortality in this group of PD patients. Instead, the higher mortality rate in diabetic PD patients, in particular among female patients, was mainly attributable to concurrent morbidity such as CVD and PEW, together with low RRF.

Keywords: cardiovascular disease; diabetes; mortality; peritoneal dialysis; protein-energy wasting

Introduction

Diabetes mellitus (DM) is the leading cause of end-stage renal diseases (ESRD) in many countries. In Korea, patients with DM accounted for 44.9% of all incident dialysis population in 2007 [1]. Although the survival rate of ESRD patients continues to improve, it remains markedly reduced compared to the general population [2]. The survival of diabetic ESRD patients remains the lowest among all primary diagnoses probably because of a higher prevalence of a cardiovascular diseases (CVD) associated with diabetes. Protein-energy wasting (PEW) is also prevalent in DM and may contribute to high mortality in diabetic peritoneal dialysis (PD) patients.

Recent studies suggest that female gender may also be associated with lower patient survival in ESRD [2,3]. The reported risk ratio of mortality is higher in women than in men [2,3] but the results are conflicting [4,5]. Little is known, however, about the reason(s) for a gender difference in mortality in diabetic ESRD patients.

The purpose of this study was to evaluate the impact of CVD and other risk factors including PEW and gender on mortality in diabetic PD patients.

Materials and methods

Patients

A total of 213 consecutive patients initiating PD at Soon Chun Hyang University Hospital, Seoul, Korea between September 1994 and December 2005 were included in the study. All patients underwent assessment of nutrition, adequacy of dialysis, residual renal function (RRF), peritoneal transport characteristics and comorbid diseases (CMD) survey on average of 9 days (range, 3–24 days) after initiating PD therapy. One hundred and
Predictors of mortality in diabetes

Table 1. Clinical characteristics at start of PD (n=213)

<table>
<thead>
<tr>
<th>Gender (male:female)</th>
<th>119:94</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), years</td>
<td>55.4 ± 12.8 (23–83)</td>
</tr>
<tr>
<td>Automated peritoneal dialysis</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>Icodextrin</td>
<td>7 (3.3%)</td>
</tr>
<tr>
<td>Protein-energy wasting</td>
<td>86 (40.4%)</td>
</tr>
<tr>
<td>Prevalence of comorbid diseasesa</td>
<td>138 (64.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>118 (55.4%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>48 (22.5%)</td>
</tr>
<tr>
<td>Other diseases</td>
<td>14 (6.6%)</td>
</tr>
<tr>
<td>Prevalence of comorbidity gradeb</td>
<td>None, n (%) 75 (35.2%), Intermediate, n (%) 135 (63.4%), Severe, n (%) 3 (1.4%)</td>
</tr>
</tbody>
</table>

aA total of 138 patients had one or more comorbid diseases for a total of 180 events.
bComorbidity was graded by Davies index [11].

nineteen patients were male (56%), and mean age was 55 ± 13 years (range, 23–83 years). Of 213 patients included in the analysis, 83 patients were new on dialysis and 130 were on temporary haemodialysis (HD) for 3–12 weeks after the PD catheter was inserted subcutaneously. Of 213 patients, 154 patients were reassessed at a mean of 11 months (range, 6–19 months). Of 59 patients excluded in reassessment, 17 patients died (nine patients were female DM, four patients were male DM, two patients were female non-DM and two patients were male non-DM; P=0.13).

The nutritional status of the patients was assessed by subjective global assessment (SGA) [6] and calculation of normalized protein equivalent of total nitrogen appearance (nPNA) [7]. Biochemical measurements, body mass index (BMI) and urea kinetic studies were obtained.

**Nutritional assessment**

The nutritional status of the patients was assessed by subjective global assessment (SGA) [6] and calculation of normalized protein equivalent of total nitrogen appearance (nPNA) [7]. Biochemical measurements, body mass index (BMI) and urea kinetic studies were obtained.

**SGA.** We used a seven-point Likert-type scale of four items [6]: weight loss, anorexia, subcutaneous fat and muscle mass. Each item was given scores to produce a global assessment. Scores of 1–2 represented severe PEW; 3–5, moderate to mild PEW; and 6–7, normal nutrition.

**Biochemical measurements.** A fasting venous blood sample was taken before the morning exercise. Blood chemistries were analysed by standard techniques. Concentrations of creatinine in dialysate and blood samples were measured by the Jaffe method and corrected for interference by bromo-cresol green method.

BMI. BMI was calculated as weight (in kilograms) / [height (in metres)]².

**Estimated protein intake.** Dietary protein intake was estimated from the protein equivalent of total nitrogen appearance (PNA) using the Bergström equation PNA = 15.1 + 6.95 UNA (g/24 h) + protein loss (g/24 h) [7]. Urea nitrogen appearance (UNA) and protein losses were determined from the measured urea and protein excretion in dialysate and urine. PNA was normalized to desirable body weight (nPNA).

**Adequacy of dialysis**

Weekly total urea mass removed (Kt) divided by urea distribution volume (V) (Kt/Vurea) was calculated from a 24-h collection of dialysate and urine. The distribution volume of urea (V) which is generally assumed to be equal to total body water, was calculated from the Watson equation [8].

**RFF**

RFF was estimated as the mean of renal urea and creatinine clearances [9].

**Peritoneal equilibration test**

A simplified peritoneal equilibration test was performed using 4.25% glucose-based solution to obtain the dialysate to plasma creatinine concentration ratio at 4 h of dwell (D/P Cr) as described previously [10].

**CMD**

The following categories of CMD were recognized: CVD was defined as a past history of or current myocardial infarction, angina, peripheral vascular disease or cerebrovascular disease. Respiratory disease included recent active tuberculosis, chronic lung disease or recurrent asthmatic attacks. Liver disease was defined as chronic liver disease proved on biopsy or by persistently elevated serum glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase. DM included both types I and II.

The comorbidity was graded by Davies index [11]. The comorboid score for each patient is simply the number of CMD. Low risk (none) is a zero score, intermediate risk is a score of 1–2 and high risk (severe) is a cumulative score of ≥3, respectively.

**Statistical analysis**

Analysis of variance and post hoc tests were used to compare the difference among the four study groups. Chi-square test was used to compare the nominal variables among the different subgroups. Actuarial survival rates were determined by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazards model constructed from all variables which were significant on univariate analysis was used to identify factors predicting patient mortality, following testing and confirmation of the assumption that the variables were proportional in the multivariate Cox model. Data are presented as mean SD, hazard ratios and 95% confidence intervals, unless otherwise noted. The difference was considered significant when the P-value was <0.05. All analyses were performed by using the software JMP version 8.0 (SAS, Cary, NC, USA).

**Results**

**Clinical characteristics at the start of PD**

Clinical characteristics of the patients at the start of PD are shown in Table 1. One hundred and nineteen (55.9%) patients were male, 16 (7.5%) were treated with automated peritoneal dialysis and 7 (3.3%) used icodextrin. Eighty-six (40.4%) had PEW and 138 (64.8%) had one or more CMD. One hundred and eighty (55.4%) patients had DM, 48 (22.5%) had CVD and 14 (6.6%) had other diseases. Based on Davies comorbidity index, 135 (63.4%) patients were classified as intermediate comorbidity group and 3 (1.4%) patients as severe.

**Final status of study patients**

At the end of follow-up, 50 (23.5%) patients were still on PD, 61 (28.7%) had died, 72 (33.8%) transferred to HD, 20 (9.3%) transferred to other units and 10 (4.7%) received kidney transplantation. Of 61 deceased patients, 42 (68.9%) were DM and 19 (31.1%) were non-DM. The causes of death were CVD (50%), infection (43%), other (5%) and unknown (2%) for DM patients and CVD (47%), infection (32%), other (16%) and unknown (5%) for non-DM patients. CVD was the cause of death in 71% of DM female, 57% of non-DM female, 42% of non-DM male and in 36% of DM male.

**Initial variables in patients by primary diagnosis**

The initial variables in DM and non-DM patients are shown in Table 2. At the start of PD, DM patients were...
older and had higher prevalence of CVD and PEW and higher blood glucose but had lower serum albumin concentrations, lower blood urea nitrogen (BUN) and lower serum creatinine compared to non-DM patients. Female DM patients had higher prevalence of PEW but lower BUN and creatinine concentrations and lower RRF compared to male DM patients.

Prevalence of CVD and PEW

Figure 1 shows the prevalence of CVD and PEW. Of 118 DM patients, 25 (21%) had both CVD and PEW and 48 (41%) had none of these comorbidities (A). Of 95 non-DM patients, 5 (5%) had both CVD and PEW and 60 (63%) had none (B).

Findings at reassessment

The variables at reassessment in DM and non-DM patients are shown in Table 3 and changes in serum albumin and BMI over the 11-month period are shown in Figure 2. After 11 months on PD, DM patients showed a significant trend towards higher prevalence of PEW (P < 0.05) and lower serum albumin concentration (P < 0.005) compared to non-DM patients. Female DM patients had the highest prevalence of PEW but lower BUN and creatinine concentrations and lower RRF compared to male DM patients.

Patient survival

Patient survival rates are shown in Figure 3. On Kaplan–Meier analysis, patient survival was significantly lower in
female DM patients than in the other groups. The 3-year patient survival rate was 46, 70, 82 and 83% for female DM, male DM, male non-DM and female non-DM, respectively (P=0.003).

Patient survival rates according to presence of CVD or PEW alone or in combination in DM patients are shown in Figure 4. In DM patients, patient survival was significantly lower in the patients with both CVD and PEW compared to the patients without CVD and PEW. The 3-year patient survival rate was 22% in patients with both CVD and PEW, 51% in patients with CVD or PEW alone and 96% in patients without CVD and PEW (Figure 4A). However, patient survival in DM patients without CVD and PEW was not different from that of non-DM without CVD and PEW, and DM patients without CVD and PEW had significantly better patient survival rate than non-DM patients with CVD and PEW (Figure 4B). The 3-year patient survival was 96% in DM patients without CVD and PEW, 92% in non-DM patients without CVD and PEW and 30% in non-DM with CVD and PEW <0.0001.

**Predictors of mortality and risk ratio for mortality**

Predictors of mortality and risk ratio for mortality are shown in Tables 4, 5 and 6, respectively. On Cox proportional hazards multivariate analysis including all patients, old age, presence of CVD or PEW, low serum albumin concentrations and low RRF were independent predictors of mortality but not DM per se or female gender (Table 4). However, in DM patients, old age, female gender, presence of CVD or PEW and low RRF were independent predictors of mortality while old age was the only risk factor in non-DM patients (Table 5). After adjustment for age, gender and RRF, DM patients with both CVD and PEW had a risk of mortality that was 3.26 times than that of DM patients without CVD and PEW (Table 6).

**Discussion and Conclusions**

It is well established that the survival rate of diabetic ESRD patients remains the lowest among all primary diagnoses probably because of higher prevalence of CVD associated with diabetes. This study was designed to evaluate the impact of CVD and other risk factors includ-
ing PEW and gender on mortality in diabetic PD patients. Our study shows that in addition to CVD and old age, PEW, female gender and low RRF are independent predictors of mortality in DM patients whereas DM per se was not found to be an independent risk factor in this group of PD patients. Moreover, our data show that female DM patients are more susceptible to develop CVD, PEW and overweight.

After adjustment for age, gender and RRF, DM patients with both CVD and PEW had a risk of mortality that was 3.26 times that of DM patients without CVD and PEW. Patient survival in patients without CVD and PEW was not different between DM and non-DM. Female DM patients had a risk of mortality that was 1.42 times that of male DM patients.

Although many factors contribute to the development of CVD and PEW in ESRD patients, DM is a well-known risk factor for CVD [12,13] and PEW [14], and these factors are interrelated. In the present study, 21% of DM patients had both CVD and PEW while 5% of 95 non-DM patients had both CVD and PEW (P=0.001).

CVD and PEW may influence DM patient survival. However, there is little available information about the predictive power of the impact of combinations of both CVD and PEW in DM PD patients. In the present study, although DM was indeed a predictor of mortality on univariate analysis, DM lost its predictive power for mortality when the multivariate analysis included CVD and PEW. Moreover, DM patients with both CVD and PEW had a risk of mortality that was 3.26 times that of DM patients without CVD and PEW. The 3-year patient survival rate was 22% in patients with both CVD and PEW, 51% in patients with CVD or PEW alone and 96% in patients without CVD and PEW. Furthermore, the present study shows that patient survival in patients without CVD and PEW was not different between DM and non-DM patients, and DM patients without CVD and PEW had a higher patient survival rate compared to non-DM patients with CVD and PEW. This agrees with previous results from us [15] and others [16], reporting that CVD and PEW when combined synergistically increase mortality in PD patients. The prognosis of diabetic patients has in general improved during the last couple of years. Interestingly, a recent Finish study [17] showed that patient survival of type 2 diabetic patients on renal replacement therapy improved probably as a consequence of more active therapeutic interventions resulting in modification of risk factors for CVD with lowering of total cholesterol, LDL cholesterol, total triglycerides and diastolic blood pressure and increasing HDL cholesterol, serum albumin.

### Table 4. Risk factors for mortality in all patients (n=213) as assessed by multivariate Cox proportional hazards analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.07 (1.04–1.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.21 (0.91–1.59)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.08 (0.80–1.49)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.71 (1.25–2.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protein-energy wasting</td>
<td>1.53 (1.14–2.09)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Serum albumin (per 1 g/L)</td>
<td>0.94 (0.88–0.99)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RRF (per 1 mL/min)</td>
<td>0.84 (0.71–0.99)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D/P Cr</td>
<td>0.98 (0.80–1.20)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RRF, residual renal function; D/P Cr, dialysate to plasma creatinine concentration ratio at 4 h of dwell.

![Fig. 3. Probability of patient survival by gender and primary diagnosis. Female DM patients had significantly lower patient survival compared to other groups (P=0.003).](image)

![Fig. 4. Probability of patient survival in DM patients. In DM, patient survival was significantly lower in the patients with both CVD and PEW compared to the patients without CVD and PEW (A). However, patient survival in patients without CVD and PEW was not different between DM and non-DM patients (B), and DM patients without CVD and PEW had higher patient survival rate than non-DM patients with CVD and PEW.](image)
and haematocrit levels. One may speculate that similar changes may have contributed also to the elimination of DM as such as a risk factor in this group of Korean diabetic PD patients.

In line with previous studies in ESRD patients [2,3], the present study shows a significant impact of female gender on mortality in DM patients. Interestingly, the negative impact of female gender on mortality seems to be confined to diabetic patients. Thus, in the present study, female gender was an independent risk factor for mortality in DM patients while it did not influence survival in non-DM patients. A similar finding was observed in a study from the Australia and New Zealand Dialysis and Transplant Registry [3], reporting that while the risk ratio for death was 1.19-fold higher in women than in men, this effect was due to increased mortality in type 2 DM patients aged ≥60 years. In a prospective study of French ESRD patients [2], Villar et al. demonstrated that standardized mortality ratios were 1.5-fold higher in women than in men in the first 4 years after onset of dialysis. In contrast, the Dialysis Outcomes in Colombia study [4] showed no association between gender and mortality in both HD and PD patients.

In the present study, female DM patients had a higher prevalence of PEW and lower RRF at initial evaluation and higher prevalence of PEW, higher BMI and lower RRF after 1-year of PD. CVD was the most common cause of death in female DM patients (71%) compared to female non-DM (57%), male non-DM (42%) and male DM patients (36%). Although BMI is not a very precise parameter of nutritional status, especially in patients in whom gross imbalances in fluid homeostasis are commonly observed such as in patients with ESRD, these results are consistent with the findings of Stenvinkel et al. [18], showing that it is not seldom that patients with high BMI (>25 kg/m²) show signs of PEW and that PEW had an independent predictive impact on cardiovascular mortality in chronic kidney disease patients. Furthermore, after 1 year of PD, body fat mass increased markedly, especially in DM patients, and patients who lost lean body mass had higher initial C-reactive protein (CRP) levels [19]. Moreover, menopause is accompanied by several cardiovascular risk factors in the general population [20,21], and the impact of cardiovascular factors such as DM on CVD was greater in elderly women on PD [22]. Thus, our results suggest that high mortality in female DM patients may be due to higher prevalence of CVD and PEW and lower RRF in females.

Low RRF is associated with high mortality in PD patients. In the present study, initial RRF was an independent predictor of mortality in DM patients but not in non-DM patients. This finding is in agreement with the results of Hocher et al. [23], which indicated that oliguria of <200 mL/d was the most important risk factor for mortality among ESRD patients with DM but not among non-DM patients. Low RRF has been reported to be associated with inflammation [23–25] and to have a strong effect on the risk of death resulting from infection especially in DM patients [23]. Moreover, decline in RRF has been reported to correlate with hs-CRP in DM PD patients [22]. Thus, it is likely that the decreased patient survival in DM patients could be due to interaction between DM, low RRF and inflammation.

In the present study, at the start of PD, serum albumin concentrations were higher in female DM patients than in male DM patients. Serum albumin levels in ESRD patients are influenced by several factors. A low serum albumin level mainly represents the acute phase response and albumin losses in dialysate and urine, and only to a lesser extent reflects a poor nutritional status [26]. In the present study, protein losses in dialysate and urine were lower in female DM patients than in male DM patients (10.8 ± 0.8 vs 12.8 ± 0.6 g/day; P = 0.05). Thus, our results suggest that the higher initial serum albumin level in female DM patients, at least in part, may be due to lower protein losses in dialysate and urine at start of PD in female DM patients compared to male DM patients.

However, several shortcomings of the present study should be considered. First of all, the study included relatively limited number of patients and therefore a low number.

### Table 5. Risk factors for mortality in patients by primary diagnosis as assessed by Cox proportional hazards multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetes n=118</th>
<th>Non-diabetes n=95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.04 (1.01–1.08)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.42 (1.01–2.00)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.75 (1.19–2.56)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Protein-energy wasting</td>
<td>2.10 (1.41–3.34)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Serum albumin (per 1 g/L)</td>
<td>0.94 (0.87–1.00)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RRF (per 1mL/min)</td>
<td>0.83 (0.68–0.99)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RRF, residual renal function.

### Table 6. Adjusted* risk ratios for mortality in diabetic patients with CVD and protein-energy wasting

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM with CVD and protein-energy wasting</td>
<td>3.26</td>
<td>1.89–6.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DM with CVD or protein-energy wasting</td>
<td>1.75</td>
<td>1.05–3.12</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>DM without CVD and protein-energy wasting</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, gender and residual renal function. Abbreviations: CI, confidence interval; DM, diabetes; CVD, cardiovascular disease.
mer of events were retrospectively analysed and we can therefore not exclude a type two statistical error. Second, this study is a single-centre study with retrospective analysis and the results may therefore not necessarily be generalized to other populations. Finally, there may be a selection bias at reassessment since sicker patients could have been excluded from reassessment. However, this effect seems to be small as the death rate of 154 patients who were reassessed was 28.6% while it was almost identical, 28.8%, in the 59 patients who were excluded from reassessment.

In conclusion, this study shows that high mortality in diabetic PD patients is due to a combination of old age, CVD, PEW, female gender and low RRF whereas DM per se was not an independent risk factor in this group of PD patients. Among all the patients, female DM patients had the highest mortality which was associated with high prevalence of CVD and PEW and low RRF.

Conflict of interest statement. We have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated. The results presented in this paper have not been published previously in whole or part, except in abstract format.

References


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