THERE ARE GENDER-RELATED DISTINCTIVE FEATURES OF THE RISK PROFILE FOR EARLY MORTALITY IN END STAGE RENAL DISEASE DIABETIC PATIENTS STARTING DIALYSIS

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Received May, 8, 2008

Early mortality (EM) of dialyzed patients is defined as all cause mortality registered in the first three months after starting dialysis; risk factors for EM are not related to dialysis procedures but to the status of the patient at the initiation moment. The aim of the present study is to evaluate the relationship between the gender of the diabetic end stage renal disease (ESRD) patients and the relative risk for EM. The comparative study of the two groups (female-F vs male – M gender) of patients displayed important influences of the diabetic patients' gender over the risk profile for EM: the F gender is associated with a higher relative risk (RR) for EM and the difference is even greater for type 2 diabetes mellitus (T2DM) F patients and for the F patients initiated on peritoneal dialysis (PD). The inflammatory malnutrition is correlated with EM in M patients and low intake malnutrition in F patients only. The severity of renal anemia is a risk factor for EM in F s but not in M patients. Hypocalcemia is a risk factor for EM in F patients and hyperphosphatemia in M patients only. Though the underlying mechanisms of these differences are not completely understandable yet, they might be considered as robust work hypotheses for further researches.

Key words: EM early mortality; ESRD end stage renal disease; Gender differences.

INTRODUCTION

Early mortality (EM) of the patients on RRT is defined by most authors as all-cause mortality registered in the first three months after starting renal replacement therapy (RRT) and is accounting for about 10–20% of the dialyzed patients. This type of mortality is generally considered to be not directly related to dialysis procedures.

The most frequently reported causes of EM are late initiation of RRT (mainly due to late referral to a nephrology service) and the severity of the co-morbidities (especially of cardio-vascular origin) at the time of dialysis initiation [1]. Long-term diabetes mellitus (DM), advanced age and previous cardiovascular events, as well as known ischemic heart disease or peripheral arterial disease, are the most important co-morbidities associated with EM [2, 3]; from this point of view, all diabetic patients starting dialysis should be considered as "high-risk" patients [4, 5].

In Romania, the RRT program for diabetic patients with renal involvement has been started in January 1995, and about 18% of the dialyzed patients countrywide are diabetics in the present (2006). The majority of these patients (about 75%) were initiated on dialysis in the Dialysis Centre of the National Institute of Diabetes, Nutrition and Metabolic Diseases "N. Paulescu", in Bucharest,

which makes this group of patients a representative sample for Romanian diabetic end stage renal disease (ESRD) population.

MATERIALS AND METHODS

The study group consists of 788 diabetic patients initiated on RRT (hemodialysis – HD or peritoneal dialysis – PD) in the Dialysis Centre of the National Institute of Diabetes, Nutrition and Metabolic Diseases "N. Paulescu" in Bucharest, between January 01, 1996 and December 31, 2005 and followed-up in the same unit for at least 12 weeks or till their death. This group comprises almost the totality of diabetic ESRD patients in RRT programs from Bucharest and other seven southern counties of Romania (accounting for about half of Romanian population).

Late initiation (LI) of dialysis was defined [6] either as late referral (LR), when the patient was initiated on dialysis in a four weeks interval after his first presentation in a nephrology unit or the RRT was initiated by central venous catheter in the intensive care unit [7]. Demographic, clinic and biologic parameters values were collected at the initiation of dialysis from all the patients.

The study group was first divided into two groups, regarding their 12 weeks survival status: the group D (deceased), of 237 patients registered as EM and the group S (survivors) of 551 patients. The study group was also divided according to the gender of patients, because we have considered the gender as the most certain (or "natural") classification parameter; we have defined the F (female gender) and the M (male gender) groups. The F and M groups were further divided, regarding their 12 weeks survival status into FD, FS, MD and MS groups respectively, in order to perform the EM analysis.

RESULTS

Gender

The study group was first divided into the F group (female gender), comprising of 335 (42.5%) and the M group (male gender) of 453 (57.5%) patients. 116 patients in the F group and 121 patients in the M group have met the criteria for the EM and were included in the DF and DM groups respectively. The relative risk for EM was significantly greater for F group patients (RR=1.45, p= 0.02) compared with the M group patients.

No significant differences were found in the EM relative risk between F and M type 1 diabetes mellitus (T1DM) patients. The relative risk for EM was significantly higher for the female type 2 diabetes mellitus (F T2DM) patients comparing with M T2DM patients (RR=1.59; p= 0.013).

No significant differences in the risk for EM were found between F and M diabetic patients initiated on HD (p= 0.44). The relative risk for EM was significantly higher for the F compared with M diabetic patients initiated on PD (OR= 3.38; p = 0.001). The relative risk for EM was significantly higher for the HD compared with the PD initiated diabetic patients (RR= 4.11; p< 0.0001); similar results have been found for F (RR=2.51; p< 0.001) group patients and for M patients (RR= 6.7; p< 0.0001) group also.

Nutritional status

No significant differences between S and D groups were detected for the weight (70.3 ± 14.5 kg *vs* 70.9 ± 14.5 kg) and for the BMI (26.17 ± 4.6 kg/m^2 *vs* 25.5 ± 4.9 kg/m^2) values, also.

The T test (Student) revealed a significant inverse relationship between the values of plasma albumin (PA) and the risk for EM in the diabetic patients initiated on dialysis (t = – 3.88; p < 0.001). No significant difference was detected between the PA values of the F and M groups (p = 0.68). The T test (Student) showed a significant inverse relationship between the values of PA and the risk for EM in the M group (t = – 2.93; p = 0.004), but no such relationship was found for F group (p=0.014).

The mean value of total plasma proteins (TP) for the whole study group was inside the normal range: 6.35 ± 0.8 g/dl; the mean values for the D and S groups were 6.2 ± 0.74 g/dl and 6.4 ± 0.8 g/dl, respectively. The T test (Student) showed a significant inverse relationship between the TP values and the risk for EM in diabetic patients initiated on dialysis (t = – 2.62; p = 0.009). There was a significant inverse relationship between the TP values and the risk of EM in the F group (t = –2.7; p = 0.007), but no relationship in the M group patients (p = 0.31).

Late initiation of dialysis (LI)

509 (64.6%) patients from the total of 788 patients were included in the late initiated (LI) group, 413 (52.4%) of them being included in the late referred (LR) group. The relative risk for EM for the LI compared with non-LI patients was 2.2 (p<0.001) in our study.

In the F group (335 pts) 202 (60.3%) patients have been included in the LI group and the rest of 133 (39.7%) patients formed the non-LI group. The relative risk (RR) for EM in the LI compared with non-LI female patients was 1.8 (p=0.01).

In the M group (453 pts), 307 (67.7 %) of them have been included in the LI group and the rest of 146 (32.3 %) have formed the non-LI group. The OR for EM in the LI compared with non-LI male patients was 2.9 (p< 0.001).

Anemia

The mean value of Ht for the study group patients was 25.3 ± 5.9 %; after dividing the study group into D and S groups the mean values of Ht for these two groups patients were 23.95 ± 5.1 % and 25.75 ± 6 %, respectively. The T test (Student) have shown a significant inverse relationship between the values of Ht and the risk for EM (t = 3.07; p = 0.002).

After dividing the group F into FD and FS groups, the mean values of Ht for these two groups patients were 23.2 ± 4.9 % and 25.4 ± 5.8 %. There is a significant inverse relationship between the values of Ht and the risk for EM in the F group patients (t = –2.71; p = 0.007); no such relationship was detected for the M group patients (p = 0.13).

Calcium and phosphate metabolism (CPM) disorders

The mean value of serum calcium (sCa) for the study group patients (788 patients) was 8.1 ± 1.1 mg/dl; after dividing the study group into D and S groups, the mean values of sCa for these two groups were 7.8 ± 1.2 mg/dl and 8.2 ± 1.1 mg/dl, respectively. The T test has shown a significant inverse relationship between the sCa values and the risk for EM in the diabetic patients initiated on dialysis (t = – 2.96; p = 0.003).

After dividing the group F into the FD and FS groups, the mean values for these two groups were 7.7 ± 1.2 mg/dl and 8.2 ± 1.1 mg/dl, respectively. There was a significant inverse relationship between the sCa values and the risk for EM in female diabetic patients initiated on dialysis (t = –2.22; p = 0.01). No relationship between the sCa values and EM was detected for the M group patients.

The mean value of serum phosphorus (sP) for the study group patients was 6 ±2 mg/dl; after dividing the study group into the D and S groups the mean values of sP for the two groups were 6.4 ± 2 mg/dl and 5.9 ± 2 mg/dl, respectively. The T test has shown a significant direct relationship between the sP values and the risk for EM in the diabetic patients initiated on dialysis (t = 2.56; p = 0.01).

After dividing the M group into MD and MS groups the mean sP values for these groups were 6.7 ± 2.2 mg/dl and 5.9 ± 1.9 mg/dl, respectively. The T test have shown a significant direct relationship between the sP values and the risk for EM in the M group patients (t = 2.90; p = 0.004); no such relationship was detected for the F patients group (p=0.44).

CONCLUSIONS

The present study examined the risk factors for EM in a large sample of diabetic ESRD patients starting dialysis; 788 diabetic patients with ESRD have been initiated on RRT in the Institute of Diabetes, Nutrition and Metabolic Diseases "N. Paulescu" Dialysis Center in Bucharest and followed-up in the same unit for at least 12 weeks or till their death.

Our results have shown significant differences in the magnitude of relative risk and in the risk profiles also, related to the gender of the studied patients. The relative risk for EM was significantly greater for female gender patients (RR=1.45, p= 0.02) compared with male patients. This tendency was more distinct for female patients with T2DM and for those initiated on PD (OR= 3.38; p = 0.001). Our data are in concordance with those in the literature [8], indicating that female gender is associated with a significantly greater risk for EM, but the cited authors consider the more frequent LI for female gender patients as an explanation of this difference, which is not true in our study group. Because the number of the patients in the present study is greater than in above mentioned studies, we can presume that the underlying mechanisms might be more complex, including social and economic issues, like difficulties in attending medical care. Other possible explanation of this finding should be metabolic disadvantageous particularities [9, 10] or the influence of long-term diabetes mellitus on the cardiovascular risk in female renal failure patients. Alternatively, the EM risk was greater for the male patients initiated on HD(OR = 6.7; p< 0.0001) compared with female patients initiated on the same dialysis method (OR=2.5; p = 0.002). A possible explanation for this difference is the more severe cardiovascular comorbidity present in male, compared with female patients starting HD in emergency (the majority of them).

The analysis of the nutritional status parameters have shown that the EM risk is inversely correlated with the PA levels in male patients (MPC II, inflammation)and with TP levels in female patients (MPC I, intake). The protein-calorie malnutrition type II (MPC II) which is associated with inflammatory status [5] and is characterized by hypoalbuminemia is recognized by the majority of authors as an important risk factor for mortality in

dialyzed patients [12, 13]. In the present study this finding was confirmed only for male gender patients; the underlying mechanism for this difference is not clear and might be considered as a working hypothesis for further researches.

Late initiation of dialysis, which is a widely recognized EM etiology, is associated with a greater risk for EM in male (OR=2.9; p<0.001), compared with female patients (OR = 1.8; p = 0.01). The difference might be explained by the more severe cardiovascular complications in male than in female patients with LI on dialysis [14].

The severity of anemia, evaluated through the Ht values is associated with an increased EM risk in female patients but not in males. A possible explanation for the difference is related to the finding that for the same plasma levels of erythropoietin the anemia is more severe in female than in male ESRD patients [15]; this phenomenon seems to be determined by particularities in iron metabolism and dialysis adequacy [16].

Hypocalcemia is associated also with an increased EM risk only in female patients; alternatively, hyperphosphatemia is associated with increased EM risk in male patients but not in females. Hypocalcemia is relatively specific to diabetic patients [17], because of their skeletal resistance to PTH action and the female diabetic patients are more prone to it. Hyperphosphatemia is an expression of cardiovascular complications (arterial wall calcifications) which are more severe in male diabetic ESRD patients [18].

In our opinion, these findings should represent an important hypothesis for further researches looking for the underlying gender related mechanisms and for the predictive value of the various risk factors present at the moment of dialysis initiation.

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