The importance of hypoalbuminemia in peritoneal dialysis patients: Impact of gender

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Abstract

Background. High mortality in peritoneal dialysis (PD) patients is associated with the presence of non-traditional cardiovascular risk factors, such as malnutrition. However, hypoalbuminemia in patients undergoing PD may have gender-dependent consequences.

Objectives. The aim of the study was to evaluate the relationship between hypoalbuminemia, overhydration (OH), inflammation, and cardiovascular risk, depending on gender.

Material and methods. The group studied consisted of 54 PD patients: 26 male (mean age: 59 ± 19 years) and 28 female (mean age: 52 ± 15 years). Serum albumin levels were measured routinely by the hospital central laboratory. The degree of OH was assessed by bioelectrical impedance analysis (BIA). Serum concentrations of C-reactive protein (CRP) and interleukin (IL)-6 were measured as inflammatory markers. Levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin T (TnT) were used to assess cardiovascular risk.

Results. Median serum albumin concentration was 3.9 g/dL (3.6–4.2 g/dL). Both genders were comparable regarding most parameters except body weight (79 ± 16 kg vs 67 ± 16 kg; $p = 0.009$), but no differences were observed in body mass index (BMI) (26.3 ± 5.0 kg/m² vs 26.2 ± 5.9 kg/m²; non significant (NS)). There was also no difference in the prevalence of hypoalbuminemia between female and male PD patients (23% vs 21%; NS). In females, low serum albumin concentrations were associated with OH, inflammation and cardiovascular risk, while in males serum albumin levels correlated with the parameters of dialysis and cardiovascular risk.

Conclusions. The impact of hypoalbuminemia may be gender-dependent. It seems that hypoalbuminemia is more important for female patients. It is also possible that different mechanisms regulate serum albumin concentration in female and male PD patients.

Key words: inflammation, cardiovascular risk, peritoneal dialysis, overhydration, hypoalbuminemia

Introduction

High mortality in peritoneal dialysis (PD) patients is associated with the presence of non-traditional cardiovascular risk factors, such as malnutrition, chronic inflammation and fluid overload.^{1,2} It appears that malnutrition plays a key role in the development of complications in PD patients.³ Hypoalbuminemia in PD patients may result from the combined effects of high protein loss, malnutrition, inflammation, overhydration (OH), and comorbidity.²

It appears that hypoalbuminemia is an important determinant of the hydration status in PD patients.⁴ Large cross-sectional studies have revealed that malnutrition is common in PD patients and is associated with OH.⁵ Protein-energy wasting associated with OH predicts both all-cause and cardiovascular mortality in PD patients.⁶

Many authors suggest an association between the nutritional status and inflammation, which may have an impact on the development of many complications. The coexistence of protein-calorie malnutrition, chronic non-specific inflammation and accelerated development of atherosclerosis is known as the malnutrition-inflammation-atherosclerosis (MIA) syndrome.⁷

Moreover, it seems that in PD patients malnutrition occurs even more often, because body mass index (BMI) is not a reliable indicator of malnutrition in that group of patients.⁸ In PD patients, muscle may account for a smaller percentage of body weight because of wasting or edema. Peritoneal dialysis patients often have normal (or even elevated) BMI and, at the same time, hypoalbuminemia, with all its complications.⁶ The poor diagnostic performance of BMI may potentially explain the paradoxical association between higher BMI and lower mortality in that group of patients.⁶

There are apparent anthropometric and physiological differences between male and female patients. On the other hand, there is not a lot of data regarding the effect of gender on nutritional parameters in PD patients.⁹

The main aim of the study was to evaluate the relationship between hypoalbuminemia, OH, inflammation, and cardiovascular risk, depending on gender. This study also investigated the frequency of malnutrition in PD patients.

Material and methods

Patients

In this cross-sectional study, patients were recruited consecutively from 3 regional dialysis centers between 2011 and 2014. The studied group consisted of 54 patients undergoing PD. Inclusion criteria for the study were: 1. age >18 years; 2. time on PD ≥3 months; and 3. informed consent for participation in the study. Exclusion criteria were: 1. the presence of acute inflammatory disease within 3 months prior to enrolment; 2. after amputation; or

3. the presence of a cardioverter-defibrillator or pacemaker. Only 1 patient was excluded from the study because of amputation. No patients were excluded from the analysis. The patients were fully informed and each of them provided a written consent for participation in the study. The study was approved by the Poznan University of Medical Sciences Bioethics Committee (decisions No. 85/09 and 424/13) and was conducted in accordance with the Declaration of Helsinki.

Nutritional status

Serum albumin levels were measured routinely by the hospital central laboratory, with the reference value >3.5 g/dL. To assess the nutritional status in more detail, the following parameters and techniques were also used: weight and BMI, subjective global assessment (SGA) questionnaire, and fat and lean tissue mass (LTM) in bioelectric impedance analysis (BIA), using Body Composition Monitor (BCM) (Fresenius Medical Care, Bad Homburg vor der Höhe, Germany).^{10,11}

Inflammatory markers

Serum C-reactive protein (CRP) was measured routinely by the hospital central laboratory. Serum concentrations of interleukin (IL)-6 were measured using the Quantikine High-Sensitivity IL-6 Immunoassay (R&D Systems, Minneapolis, USA). The immunoassays were performed according to the manufacturer's instructions. The sensitivity of the assays were 0.1 pg/mL and 33 pg/mL, respectively.

Hydration status

The hydration status was assessed by clinical symptoms and BIA, using BCM. The study used whole-body BIA. The measurements were performed under the standardized conditions recommended by the manufacturer, in the supine position after 2 min of rest. Reference values for the bioelectrical impedance measurements considered the hydration status to be from -1.1 L to 1.1 L.¹² Clinical assessment of OH was based on the presence of peripheral edema, dyspnea, jugular vein distension, and blood pressure measurements.

Cardiovascular risk

The N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin T (TnT) were used as biomarkers for cardiovascular diseases.

Assessment of peritoneal membrane function and laboratory measurements

Peritoneal membrane function was measured with the peritoneal equilibration test (PET) during a 4-hour dwell,

using 2.27% glucose dialysate.¹³ All laboratory tests were made by standard methods, using automated biochemical analyzers in the hospital central laboratory.

Statistical analysis

The analyzed data is presented as medians and interquartile ranges (IQRs) or percentage, as appropriate. Comparisons between the groups were tested for significance using the Mann-Whitney U test. Categorical data was analyzed with the χ^2 test or the Fisher-Freeman-Halton test. The relationship between variables was analyzed with Spearman's rank correlation coefficient. All results were considered significant at $p < 0.05$. Statistical analyses were

performed with STATISTICA v. 10.0 PL (StatSoft Polska, Kraków, Poland).

Results

Patient characteristics according to serum albumin levels

Serum albumin concentration in the group of 54 patients ranged from 2.6 g/dL to 4.9 g/dL. Median serum albumin concentration was 3.9 g/dL (3.6–4.2 g/dL). Patients were divided into 2 subgroups, depending on median serum albumin levels:

Table 1. Patients' characteristics according to serum albumin

Parameters	Albumin <3.9 g/dL (n = 29)	Albumin ≥3.9 g/dL (n = 25)	Mann-Whitney or χ^2 p-value
Demographic and PD-related parameters			
Men, n [%]	14 (48)	12 (48)	NS
Age [years]	60 (51–70)	51 (34–66)	NS
Diabetic nephropathy, n [%]	12 (41)	2 (8)	0.005
DM, n [%]	14 (48)	5 (20)	0.030
Time on PD [months]	28 (17–56)	28 (17–38)	NS
APD mode, n [%]	7 (24)	8 (32)	NS
Ultrafiltration [mL/day]	1,400 (600–2,000)	1,000 (900–1,200)	NS
Residual diuresis [mL/day]	1,500 (500–2,200)	1,600 (1,300–2,400)	NS
4-hour D/P creatinine in PET	0.68 (0.59–0.77)	0.61 (0.54–0.67)	0.034
Parameters of nutritional status			
Weight [kg]	71 (63–81)	71 (63–82)	NS
BMI [kg/m ²]	25.2 (22.3–30.3)	25.9 (21.1–28.6)	NS
Lean tissue [%] in BIA	45 (36–60)	49 (44–56)	NS
Fat tissue [%] in BIA	36 (27–45)	36 (30–40)	NS
Lean tissue [kg] in BIA	31 (27–42)	34 (28–41)	NS
Fat tissue [kg] in BIA	27 (18–34)	25 (19–34)	NS
SGA	9.0 (8.0–9.0)	8.0 (7.0–9.0)	0.026
Inflammatory markers			
CRP [mg/L]	5.9 (2.6–9.7)	2.1 (1.1–5.7)	0.038
hs IL-6 [pg/mL]	1.2 (0.8–1.8)	1.0 (0.5–1.3)	0.046
Hydration status in BIA and clinical examination			
Hydration status [L]	2.0 (0.7–2.7)	0.6 (0.2–1.0)	0.003
Hydration status/weight [%]	2.6 (1.1–3.9)	0.9 (0.2–1.3)	0.002
Patients with edema, n [%]	9 (31)	1 (4)	0.011
Cardiovascular parameters			
SBP [mm Hg]	140 (130–150)	130 (120–130)	0.001
DBP [mm Hg]	80 (70–94)	80 (70–80)	NS
TnT [pg/mL]	54 (26–109)	28 (16–37)	0.005
NT-proBNP [pg/mL]	3,024 (1,172–9,404)	1,240 (619–3,201)	0.020

Data presented as median (interquartile range (IQR)) or as n [%]. NS – non significant; PD – peritoneal dialysis; DM – diabetes mellitus; APD – automated peritoneal dialysis; D/P – dialysate and plasma ratio; PET – peritoneal equilibration test; BMI – body mass index; BIA – bioimpedance analysis; SGA – subjective global assessment; CRP – C-reactive protein; hs IL-6 – high-sensitivity interleukin-6; SBP – systolic blood pressure; DBP – diastolic blood pressure; TnT – troponin T; NT-proBNP – N-terminal prohormone of brain natriuretic peptide.

- group A: albumin <3.9 g/dL (n = 29);
- group B: albumin ≥3.9 g/dL (n = 25).

Patient characteristics according to serum albumin are shown in Table 1. There were no differences in body weight, BMI or body composition in BIA between the subgroups. In contrast, there were significant differences in the SGA.

The data showed significantly higher levels of serum IL-6 and a tendency for higher levels of CRP in patients with lower serum albumin. As expected, serum albumin correlated negatively with IL-6 levels ($r = -0.35$; $p = 0.009$).

Clinical signs of OH were found in 18% (10/54) of all patients, and OH as measured by BIA was found in 41% (22/54) of patients. There was a significant difference in the distribution of those patients (Table 1). In the group with higher albumin level, only 20% (5/25) of patients were overhydrated (as measured by BIA), while OH occurred in 62% (18/29) of patients in the group with lower albumin level. Indeed, there was an inverse correlation between the hydration status and serum albumin ($r = -0.55$; $p < 0.001$).

There was also a tendency to higher blood pressure and increased serum concentrations of TnT and NT-proBNP in patients with hypoalbuminemia.

Patient characteristics according to gender

The study group consisted of 26 (48%) male and 28 (52%) female patients. Both gender subgroups were comparable regarding most of the investigated parameters. Differences between genders occurred only in body weight in kg, but there was no differences in BMI and LTM in BIA.

Albumin in male patients

Serum albumin concentration ranged from 2.6 g/dL to 4.9 g/dL. Median serum albumin concentration was 3.9 (3.6–4.1). Six out of 26 (23%) investigated males had hypoalbuminemia. In male patients, serum albumin levels correlated with PD parameters: diuresis ($r = 0.59$; $p = 0.001$), ultrafiltration ($r = -0.33$; $p = 0.098$), peritoneal

Table 2. Male (n = 26) patients' characteristics according to serum albumin

Parameters	Albumin <3.9 g/dL (n = 14)	Albumin ≥3.9 g/dL (n = 12)	Mann-Whitney or χ^2 p-value
Demographic and PD-related parameters			
Age [years]	64 (52–70)	63 (51–70)	NS
Diabetic nephropathy, n [%]	6 (43)	1 (8)	0.048
DM, n [%]	7 (50)	3 (25)	NS
Time on PD [months]	48 (19–66)	26 (14–35)	NS
Ultrafiltration [mL/day]	1,450 (900–1,800)	950 (550–1,200)	0.047
Residual diuresis [mL/day]	1,400 (200–2,000)	2,350 (1,600–2,800)	0.022
4-hour D/P creatinine in PET	0.69 (0.61–0.75)	0.61 (0.53–0.65)	NS
Parameters of nutritional status			
Weight [kg]	72.8 (65.0–85.0)	78.4 (65.0–85.0)	NS
BMI [kg/m ²]	24.7 (21.4–29.1)	26.6 (22.3–28.7)	NS
Lean tissue [%] in BIA	48.7 (36.1–64.5)	51.5 (44.4–62.6)	NS
Fat tissue [%] in BIA	33.8 (25.7–44.0)	33.6 (26.9–38.9)	NS
Lean tissue [kg] in BIA	41.4 (28.2–44.5)	39.8 (34.8–46.4)	NS
Fat tissue [kg] in BIA	24.4 (17.2–33.0)	26.2 (18.9–34.4)	NS
SGA	9.0 (8.0–9.0)	8.5 (7.5–9.0)	NS
Inflammatory markers			
CRP [mg/L]	2.7 (2.1–8.4)	3.4 (1.0–6.7)	NS
hs IL-6 [pg/mL]	1.10 (0.80–1.70)	0.91 (0.70–1.41)	NS
Hydration status in BIA			
Hydration status [%]	1.2 (0.3–4.4)	0.8 (0.6–1.8)	NS
Hydration status/weight [%]	1.6 (0.5–5.9)	1.2 (0.8–2.3)	NS
Cardiovascular parameters			
TnT [pg/mL]	80 (33–127)	31 (22–40)	0.020
NT-proBNP [pg/mL]	2,498 (1,159–6,714)	868 (689–4,637)	NS

Data presented as median (interquartile range (IQR)) or as n [%]. NS – non significant; PD – peritoneal dialysis; DM – diabetes mellitus; D/P – dialysate and plasma ratio; PET – peritoneal equilibration test; BMI – body mass index; BIA – bioimpedance analysis; SGA – subjective global assessment; CRP – C-reactive protein; hs IL-6 – high-sensitivity interleukin-6; TnT – troponin T; NT-proBNP – N-terminal prohormone of brain natriuretic peptide.

equilibration test (PET) dialysate and plasma ratio (D/P) creatinine ($r = -0.59$; $p = 0.002$) and PD vintage ($r = -0.43$; $p = 0.028$). The study also showed a relationship between albumin levels and biomarkers for cardiovascular diseases: TnT ($r = -0.60$; $p = 0.001$) and NT-proBNP ($r = -0.43$; $p = 0.028$). The differences after the division into 2 subgroups according to the median serum level of albumin (A <3.9 g/dL; B ≥ 3.9 g/dL) are shown in Table 2.

Albumin in female patients

Median serum albumin concentration in female patients was 3.9 (3.6–4.2) and ranged from 2.7 g/dL to 4.6 g/dL. Six out of 28 (21%) female patients presented hypoalbuminemia. In female patients, the study showed statistically significant correlations of albumin levels with OH ($r = -0.74$, $p < 0.001$) and hs IL-6 ($r = -0.45$; $p = 0.015$). There was also a clear tendency to a significant correlation regarding albumin concentration and CRP ($r = -0.45$; $p = 0.052$). Serum albumin levels also correlated with TnT

($r = -0.44$; $p = 0.026$) and NT-proBNP ($r = -0.46$; $p = 0.014$). The differences after the division into 2 subgroups according to the median albumin level (A <3.9 g/dL; B ≥ 3.9 g/dL) are shown in Table 3.

Discussion

Hypoalbuminemia in patients undergoing PD is known to be an important prognostic factor of their clinical outcome.¹⁴ In this study we investigated hypoalbuminemia and its gender differences in a group of PD patients in relation to OH, inflammation, nutritional status, and cardiovascular risk.

First, we found that the prevalence of fluid overload by BIA in PD patients was 41%. The prevalence of hypoalbuminemia was 21% in females and 23% in males. Fluid overload in PD patients was associated with low albumin levels. The finding was not a surprise, as fluid overload has been associated with hypoalbuminemia.¹⁵ Despite the fact

Table 3. Female ($n = 28$) patients' characteristics according to serum albumin

Parameters	Albumin <3.9 g/dL ($n = 14$)	Albumin ≥ 3.9 g/dL ($n = 14$)	Mann-Whitney or χ^2 p-value
Demographic and PD-related parameters			
Age [years]	58 (34–66)	46 (33–64)	NS
Diabetic nephropathy, n [%]	6 (43)	1 (7)	NS
DM, n [%]	7 (50)	2 (14)	NS
Time on PD [months]	26 (15–46)	32 (14–43)	NS
Ultrafiltration [mL/day]	1,200 (500–2,000)	1,000 (900–1,400)	NS
Residual diuresis [mL/day]	1,300 (500–2,200)	1,450 (1,000–2,100)	NS
4-hour D/P creatinine in PET	0.68 (0.58–0.80)	0.61 (0.55–0.69)	NS
Parameters of nutritional status			
Weight [kg]	69.5 (59.7–81.5)	62.8 (54.2–72.0)	NS
BMI [kg/m^2]	28.9 (22.3–31.0)	24.7 (20.4–27.2)	NS
Lean tissue [%] in BIA	42.5 (32.5–60.4)	47.9 (39.8–50.7)	NS
Fat tissue [%] in BIA	41.0 (27.7–48.5)	38.6 (35.2–43.2)	NS
Lean tissue [kg] in BIA	28.2 (24.0–33.5)	28.0 (26.8–32.1)	NS
Fat tissue [kg] in BIA	27.7 (18.2–36.0)	24.4 (19.4–31.4)	NS
SGA	9.0 (8.0–9.0)	8.0 (7.0–8.0)	0.028
Inflammatory markers			
CRP (mg/L)	6.5 (4.0–18.1)	2.6 (1.5–4.0)	0.049
hs IL-6 [pg/mL]	1.27 (0.82–2.08)	0.67 (0.51–1.04)	0.012
Hydration status in BIA			
Hydration status [L]	1.7 (0.8–2.6)	0.4 (–0.7–0.8)	0.003
Hydration status/weight [%]	2.4 (1.4–4.0)	0.6 (0.0–1.2)	0.003
Cardiovascular parameters			
TnT [pg/mL]	34 (23–90)	26 (13–33)	0.044
NT-proBNP [pg/mL]	5,592 (1,402–21,553)	1,421 (609–3,201)	0.011

Data presented as median (interquartile range (IQR)) or as n [%]. NS – non significant; PD – peritoneal dialysis; DM – diabetes mellitus; D/P – dialysate and plasma ratio; PET – peritoneal equilibration test; BMI – body mass index; BIA – bioimpedance analysis; SGA – subjective global assessment; CRP – C-reactive protein; hs IL-6 – high-sensitivity interleukin-6; TnT – troponin T; NT-proBNP – N-terminal prohormone of brain natriuretic peptide.

that patients on PD lose about 5 g of albumin per day, many of them can compensate for this loss by increased liver albumin synthesis.¹⁶ However, Yeun and Kaysen showed that low-grade chronic inflammation reduces this compensative ability.¹⁷ This is in agreement with our results, which showed a significant inverse correlation between albumin levels and IL-6 concentration, which typically reflects ongoing chronic inflammation. Unexpectedly, further analysis in regard to gender of the investigated patients showed that inflammatory parameters (IL-6 and CRP) were associated with hypoalbuminemia only in females. This finding is difficult to interpret, as there is a lack of literature investigating gender differences in PD patients. One possible reason for the observed gender differences is that females have stronger behavioral and somatic responses to stress and more potent immune and inflammatory reactions than males.¹⁸ Further, in patients with acute or chronic respiratory diseases, the inflammatory response was reported to be higher in females than in males.¹⁹ Moreover, in children with chronic inflammatory diseases, i.e., asthma, cystic fibrosis and sickle cell anemia, symptoms and the inflammatory status were more prominent in females.²⁰ The fact that hypoalbuminemia in PD patients is usually a consequence of low-grade chronic inflammation being a part of the MIA syndrome, and that the gender differences seem to be evident in chronic inflammatory diseases, may explain the association between the inflammation and hypoalbuminemia observed only in females in the presented study.²¹

All the above could also elucidate the association between OH and hypoalbuminemia observed in this study only in the female subgroup. In more detail, the results of large cross-sectional studies have revealed that BIA-determined OH is associated with loss of residual renal function, malnutrition and inflammation.^{5,22} The close association between inflammation, hypoalbuminemia and OH was also confirmed by other studies, which found inflammation and hypoalbuminemia being the strongest determinants of OH.^{23,24} On one hand, malnutrition and low albumin level contribute to systemic inflammation through tissue OH, while on the other hand, as a result of a kind of vicious circle, chronic inflammation leads to hypoalbuminemia, and ultimately to OH.^{4,25}

Furthermore, diabetes and diabetic nephropathy may be an additional risk factor for malnutrition in PD patients. It is possible that diabetes mellitus (DM) is consistently linked with chronic low-grade inflammation driven by oxidative stress and changed protein glycation.²⁶

Surprisingly, only in male patients was hypoalbuminemia positively associated with diuresis and negatively with PD parameters. It is well-known that patients with preserved residual renal function have better nutritional status, with all its beneficial consequences.²⁷ As mentioned above, women present more potent immune and inflammatory reactions than males, which could diminish the positive influence of residual diuresis in the presented

study.¹⁸ The negative correlation between low albumin levels and PD parameters can result from a changed rate of transperitoneal transport in favor of a faster rate, with subsequent decreased ultrafiltration, increased protein loss and malnutrition.²⁸ In what way gender affects this mechanism, remains to be explored. Of note, the results of Tang et al. showed that gender was an independent determinant of the edema status in PD patients.²⁹

In both gender groups, patients with hypoalbuminemia had significantly elevated levels of NT-proBNP and TnT. This finding points to albumin level as a useful additional marker in the assessment of cardiovascular risk in PD patients and is concordant with the results of a previous study, which showed a connection between hypoalbuminemia and poor cardiovascular outcome.³⁰ Moreover, Yamamoto et al. noted an inverse correlation between brain natriuretic peptide (BNP) change and albumin, and confirmed by multivariate analysis that both factors are independent predictors of major adverse cardiac events.³¹

Conclusions

There was no difference in malnutrition prevalence between female and male PD patients. However, hypoalbuminemia in patients undergoing PD may have gender-dependent consequences. It is also possible that different factors are responsible for hypoalbuminemia in female and male PD patients. It seems that hypoalbuminemia is more important for female patients (at comparable concentrations of serum albumin). In female patients, lower values of serum albumin were associated with OH, inflammation and cardiovascular risk, while in male patients the only relationship observed was between albumin levels and the parameters of dialysis and cardiovascular risk. Probably, malnutrition and low albumin contribute to systemic inflammation through tissue OH and it is known that all these factors have an impact on cardiovascular risk.

Limitations

Our study has some limitations, including a regional center design, a small sample size and lack of stepwise multivariate analysis. Additionally, some patients had comorbid medical illnesses.

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