

Prevalence of Protein-Energy Wasting and Its Association With Cardiovascular Disease Risk Factors in Iranian Peritoneal Dialysis Patients

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Introduction. Protein-energy wasting (PEW) is prevalent in dialysis patients, and cardiovascular disease (CVD) is the leading cause of mortality in these patients. This study aimed to determine the prevalence of PEW and its relationship with CVD risk factors in peritoneal dialysis (PD) patients in Tehran, Iran.

Materials and Methods. All eligible PD patients in Tehran peritoneal dialysis centers were included in this cross-sectional study. The diagnosis of PEW was done based on the criteria of the International Society of Renal Nutrition and Metabolism. Serum high-sensitivity C-reactive protein, soluble intercellular adhesion molecule type 1, malondialdehyde, and lipid profile were measured.

Results. The prevalence of PEW was 29% in the PD patients. Significant associations were found between the prevalence of PEW in PD patients and sex ($P = .01$), age ($P = .03$), type of PD dialysis solution ($P = .04$), and microinflammation ($P = .03$). Serum C-reactive protein ($P = .02$), soluble intercellular adhesion molecule type 1 ($P = .001$), and triglyceride ($P = .03$) were significantly higher in the PD patients without PEW as compared to those with PEW, whereas high-density lipoprotein cholesterol level was significantly lower in the PD patients without PEW as compared to those with PEW ($P = .003$).

Conclusions. Our study shows that PEW is prevalent in Iranian PD patients. In addition, serum concentrations of CVD risk factors are dependent on the amount of glucose absorbed from PD solutions and are more impaired in PD patients without PEW as compared to those with PEW.

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INTRODUCTION

Protein-energy wasting (PEW) is the state of reduced body store of protein and energy fuel (ie, body protein and fat mass).¹ Protein-energy wasting is a prevalent complication in chronic kidney disease patients including dialysis patients,^{2,3} and it is related to low quality of life, higher hospitalization rate, and increased morbidity and mortality.²⁻⁵

The determination of PEW in dialysis patients can be performed according to several methods.^{6,7} The

subjective global assessment is a common method for the diagnosis of PEW in these patients⁷⁻¹⁰; however, this subjective method is a potential clinical indicator of PEW but not a definitive diagnostic method for PEW.¹ For this reason, the International Society of Renal Nutrition and Metabolism (ISRNM) developed a set of objective criteria for the clinical diagnosis of PEW in patients with kidney diseases.^{1,7} In peritoneal dialysis (PD) patients, only few studies have reported prevalence

of PEW based on the ISRNM criteria.¹¹⁻¹⁴ These investigations showed that the prevalence of PEW ranged between 14.1% and 83.0% in PD patients.¹¹⁻¹⁴ To our knowledge, although most Iranian PD patients are in Tehran (the capital of Iran), no study has yet been performed on the prevalence of PEW and its determinants in Iranian PD patients based on the ISRNM criteria.

Cardiovascular disease (CVD) is the leading cause of mortality in dialysis patients.¹⁵⁻¹⁷ Protein-energy wasting increases cardiovascular mortality in patients with kidney diseases, especially hemodialysis patients.^{18,19} It has been shown that systemic and vascular inflammation markers are two CVD risk factors in hemodialysis patients with PEW.^{20,21} According to the literature, no study has compared various risk factors of CVD between PD patients with and without PEW. Therefore, this study was designed to assess prevalence of PEW based on the ISRNM criteria and its relationship with CVD risk factors in Iranian PD patients

MATERIALS AND METHODS

Study Design

For this cross-sectional study, we included all eligible PD patients (n = 79) in Tehran peritoneal dialysis centers. Inclusion criteria were age of 18 years and greater and being on continuous ambulatory peritoneal dialysis for at least 6 months, while exclusion criteria were the presence of edema, based on physical examination, and peritonitis in PD patients. After the treatment of edema and peritonitis, these PD patients were enrolled in our study. The study protocol was approved by the Ethics Committee of the National Nutrition and Food Technology Research Institute of Iran. Written informed consent was obtained from all patients.

Body Composition and Anthropometric Measurements

Dry weight was assessed to the nearest 0.1 kg, and height, to the nearest 0.5 cm. Fat mass was measured using bioelectrical impedance analysis by Body Composition Analyzer X-Contact 356 (Jawon Medical Co, Seoul, South Korea). All anthropometric and body composition measurements were done in the fasting state, with an empty urinary bladder and gastrointestinal tract, and without dialysate in the peritoneal cavity. Midarm circumference was assessed to the nearest 0.1 cm with a nonstretch

measuring tape. The triceps skinfolds (TSF) was measured by using a skinfold caliper (Harpender, British Indicators Ltd, UK). Midarm muscle circumference (MAMC) was determined using the following equation²²:

Midarm circumference in centimeters – [3.14 × (triceps skinfolds in millimeters / 10)]

Dietary Measurements

The dietary intakes were determined based on a 3-day diet diary-assisted recall, for 3 consecutive days,²³ and dietary recalls were analyzed by Nutritionist IV software (N Squared Computing, San Bruno, CA, USA) modified for some Iranian foods, to determine daily energy and protein intakes. Dry weight was applied for determining intake of energy or protein per kg of body weight in PD patients with body mass index (BMI) of 25 kg/m² and lower, while adjusted dry weight was used for patients with BMI greater than 25 kg/m².²⁴

Laboratory Measurements and Dialysis Adequacy

A 5-mL blood sample was taken from each patient after a 12- to 14-hour fast, and the sera were obtained by centrifugation of blood samples at 2500 rpm for 15 minutes.

The serum concentrations of high sensitive C-reactive protein (HSCRP), soluble intercellular adhesion molecule type 1 (soluble ICAM-1), lipoprotein(a), and prealbumin were measured using enzyme-linked immunosorbent assay kits (Zellbio GmbH, Ulm, Germany). The intra-assay coefficients of variations for serum HSCRP, soluble ICAM-1, lipoprotein(a), and prealbumin were 4%, 3.3%, 5.5%, and 5.5%, respectively. Serum malondialdehyde concentration was measured using colorimetry method by commercial kits (Zellbio GmbH, Ulm, Germany), with an intra-assay coefficients of variations of 5.8%. Serum creatinine, urea, albumin, triglyceride, total cholesterol and high-density lipoprotein cholesterol (HDLc) were determined using various colorimetry methods by commercial kits (Pars-Azmoon, Tehran, Iran) with the aid of a Selectra 2 Autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Intra-assay coefficients of variations for these biochemical parameters were less than 3%. As serum triglyceride in all PD patients was < 400 mg/dL, serum low-density lipoprotein cholesterol (LDLc) was

determined by the Friedwald equation.²⁵

Total dialysis adequacy (as total Kt/V per week) was assessed by a Kt/V calculator, using information recorded in patient files, including 24-hour dialysate drain volume, dialysate urea concentration, blood urea concentration, urine urea concentration, 24-hour urine volume, age, height, and weight.⁽²⁶⁾ In this study, from among 79 PD patients, information regarding Kt/V index was available only for 65 PD patients. The peritoneal equilibration test for glucose was done based on a 2-L 4.25% dextrose dwell with dialysate samples at zero and 4 hours during the dwell period. The ratio of dialysate glucose level at time 4 to dialysate glucose concentration at time zero (D4/D0) was determined and then the percent of glucose absorbed from the dialysate was calculated by the $1 - D4/D0$ formula.²⁷⁻²⁹ The total amount of glucose absorbed daily from PD solutions was equal to the total infused anhydrous glucose multiplied by the percent of glucose absorbed.²⁷ In addition, the ratio of dialysate to serum creatinine and urea was determined.²⁹

Diagnosis of Protein-Energy Wasting

The expert panel of ISRNM has recommended that 4 main categories should be recognized for diagnosis of PEW: (1) serum chemistry: low serum concentrations of albumin, prealbumin, or total cholesterol; (2) body mass: unintentional weight loss over time, reduced BMI or total body fat percentage; (3) muscle mass: reduced muscle mass over time, midarm muscle circumference, or creatinine appearance; and (4) dietary intake: unintentional reduced protein or energy intake.¹ The presence of PEW was defined

as the patient meeting at least 1 criterion in 3 of the 4 listed categories (Table 1). In our study, of the 79 eligible PD patients, 3 patients did not give a blood sample; therefore, the prevalence of PEW was assessed in 76 PD patients.

Statistical Analysis

Data are shown as the mean \pm standard error. Statistical analysis of the data was done by Statistical Package for the Social Sciences (SPSS, Inc, Chicago, IL, USA) for windows version 21.0. The chi-square test was applied to assess associations between qualitative variables. All quantitative parameters had normal distribution based on the Kolmogorov-Smirnov test. We used t-test to compare quantitative parameters between the two groups. The adjustment of the effects of confounding factors on serum concentration of cardiovascular risk factors was performed by analysis of covariance. A *P* value less than .05 was considered significant.

RESULTS

The prevalence of PEW and its criteria are summarized in Table 2. The prevalence of PEW based on the ISRNM definition was 29% in PD patients. Low serum prealbumin, low dietary protein intake, and low serum albumin had the highest prevalence among PEW criteria in these patients, respectively (Table 2).

Characteristics of PD patients with and without PEW are shown in Table 3. No significant differences were found between PD patients with and without PEW with regards to age, dialysis vintage, total dialysis adequacy, the ratio of dialysate to serum creatinine and urea, the percent of absorbed glucose from PD dialysis solution, serum concentrations

Table 1. Criteria Proposed by the International Society of Renal Nutrition and Metabolism for Diagnosis of Protein-Energy Wasting¹

Categories	Criteria Within Categories
Serum chemistry	Serum albumin < 3.8 g/dL Serum prealbumin < 30 mg/dL Serum cholesterol < 100 mg/dL
Body mass	Body mass index < 23 kg/m ² Unintentional weight loss over time: 5% over 3 months or 10% over 6 months* Body fat percentage < 10%
Muscle mass	Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months* Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population) Creatinine appearance*
Dietary intake*	Unintentional dietary protein intake < 0.8 g/kg/d for at least 2 months for dialysis patients Dietary energy intake < 25 kcal/kg/d for at least 2 months

*These criteria were not used for the diagnosis of PEW in this study.

Table 2. Prevalence of Protein-Energy Wasting and Its Criteria in the Peritoneal Dialysis Patients

Features	All Patients (%) (n = 79)
Prevalence of protein-energy wasting	22 (29)
Serum albumin < 3.8 g/dL	31 (41)
Serum prealbumin < 30 mg/dL	49 (64.5)
Serum total cholesterol < 100 mg/dL	1 (1.3)
Body mass index < 23 kg/m ²	22 (28)
Total body fat percentage < 10%	12 (15)
Reduction of mid-arm muscle circumference area > 10% in relation to 50th percentile of reference population	26 (33)
Unintentional low dietary protein intake < 0.8 g/kg/d	38 (48)
Unintentional low dietary energy intake < 25 kcal/kg/d	26 (33)

of creatinine, urea and glucose, and intakes of statins, gemfibrozil, levothyroxine, and L-carnitine. However, the total amount of glucose absorbed daily from PD dialysis solutions ($P = .007$) and BMI ($P = .001$) were significantly higher in non-PEW patients in comparison with PEW patients (Table 3).

Significant associations were found between the prevalence of PEW in PD patients with gender ($P = .01$), the age of patients ($P = .03$), type of PD dialysis solution ($P = .04$), and microinflammation ($P = .03$; Table 4). However, there were no significant associations between the prevalence of PEW with dialysis vintage, and total dialysis adequacy, and the presence of diabetes (Table 4).

Serum concentrations of HSCRIP ($P = .02$), soluble ICAM-1 ($P = .001$), and triglyceride ($P = .03$) were

Table 4. Prevalence of Protein-Energy Wasting (PEW) in Peritoneal Dialysis Patients Based on Different Factors

Variable	PEW		P
	Yes	No	
Sex			
Male	15 (44)	19 (56)	
Female	7 (17)	35 (83)	.01
Age, y			
< 60	18 (38)	29 (62)	
≥ 60	4 (14)	25 (86)	.03
Dialysis vintage, y			
≤ 5	17 (27)	47 (73)	
> 5	5 (42)	7 (58)	> .05
Total dialysis adequacy (Kt/V)			
< 1.7	6 (25)	18 (75)	
≥ 1.7	11 (27.5)	29 (72.5)	> .05
Dialysis solutions			
With a dextrose concentration of 1.5%	16 (40)	24 (60)	
With a dextrose concentration > 1.5% or a combined regimen	6 (17)	30 (83)	.04
Diabetes mellitus			
Yes	7 (24)	22 (76)	
No	15 (32)	32 (68)	> .05
Microinflammation			
Yes (C-reactive protein > 3 mg/L)	10 (20)	40 (80)	
No (C-reactive protein ≤ 3 mg/L)	12 (46)	14 (54)	.03

significantly higher in PD patients without PEW as compared to those with PEW, whereas serum HDLC was significantly lower in PD patients without PEW as compared to those with PEW ($P = .003$; Table 5). No significant differences were found in serum concentrations of malondialdehyde,

Table 3. Characteristics of Peritoneal Dialysis Patients With and Without Protein-Energy Wasting (PEW)

Parameters	PEW Patients (n = 22)	Non-PEW Patients (n = 54)	P
Age, y	49.0 ± 3.0	55.0 ± 2.0	> .05
Dialysis vintage, mo	3.8 ± 0.7	2.8 ± 0.3	> .05
Total dialysis adequacy (Kt/V)	2.2 ± 0.2	2.0 ± 0.1	> .05
Dialysate-serum creatinine ratio	70 ± 3	74 ± 2	> .05
Dialysate-serum urea ratio	86 ± 2	88 ± 1	> .05
Percent of absorbed glucose from dialysis solution, %	66 ± 0.02	69 ± 0.01	> .05
Amount of absorbed glucose from dialysis solutions, g/d	66 ± 7	94 ± 6	.007
Serum glucose, mg/dL	88 ± 4	98 ± 6	> .05
Serum creatinine, mg/dL	4.9 ± 0.4	5.8 ± 0.3	> .05
Serum urea, mg/dL	97 ± 5	93 ± 3	> .05
Body mass index, kg/m ²	22 ± 0.6	27 ± 0.6	.001
Intake of statins, %	59	59.5	> .05
Intake of gemfibrozil, %	0	0	> .05
Intake of levothyroxine, %	9	9.5	> .05
Intake of L-carnitine, %	18	11	> .05

Table 5. Serum Concentrations of Cardiovascular Disease Risk Factors in Peritoneal Dialysis Patients With and Without Protein-Energy Wasting (PEW)

Parameters	PEW Patients (n = 22)	Non-PEW Patients (n = 54)	P
High-sensitivity C-reactive protein, mg/L	3.8 ± 0.7	5.7 ± 0.4	.02
soluble intercellular adhesion molecule type 1, ng/mL	75 ± 20	253 ± 18	.001
Malondialdehyde, μmol/L	7 ± 0.9	6.8 ± 0.6	> .05
Lipoprotein(a), mg/dL	54 ± 9	59 ± 5	> .05
Triglyceride, mg/dL	138 ± 11	178 ± 11	.03
Total cholesterol, mg/dL	158 ± 8	176 ± 9	> .05
Low-density lipoprotein cholesterol, mg/dL	80 ± 7	100 ± 9	> .05
High-density lipoprotein cholesterol, mg/dL	50 ± 3	41 ± 1	.003

lipoprotein(a), total cholesterol, and LDL-C between the two groups (Table 5).

After adjusting the effect of residual dialysis adequacy, as a confounding factor, on serum concentrations of cardiovascular risk factors, no changes were observed in our results, except that serum triglyceride concentration was marginally significantly higher in PD patients without PEW as compared to those with PEW ($P = .09$).

DISCUSSION

This study showed that the prevalence of PEW based on the ISRNM criteria was 29% in adult PD patients of Tehran peritoneal dialysis centers in Iran. According to the available literature, few studies have assessed prevalence of PEW in PD patients based on the ISRNM criteria. In agreement with our study, Liu et al. in a study from China, indicated that the prevalence of PEW was 14.1% in PD patients with low peritoneal transport and 37.0% in PD patients with high peritoneal transport.¹¹ Markaki and colleagues, in a study conducted in Greece, showed that the prevalence of PEW was 22.2% in PD patients.¹² In the Harvinder and coworkers' study from Malaysia, 83% of PD patients had PEW.¹³ Zhou and colleagues, in another study from China, reported that 51.8% of PD patients had PEW.¹⁴

Protein-energy wasting leads to low quality of life, high hospitalization rate, and increased morbidity and mortality in dialysis patients.²⁻⁵ In dialysis patients, PEW may be caused by inadequate intakes of energy and protein, metabolic acidosis, inflammation, decreased secretion of testosterone, growth hormone resistance, comorbidities, and nutrient losses during dialysis.³ In our study, insufficient energy and protein intakes based on the ISRNM criteria were observed in 33% and 48%

of PD patients, respectively. Insufficient intakes of energy and protein often are caused by anorexia. Available literature indicates that anorexia may be caused by changes in secretion of hormones and neurotransmitters affecting the appetite, nitrogen-based uremic toxins, inflammatory cytokines, altered serum amino acid patterns, infections and emotional disorders, particularly depression.³⁰

In our study, there was a significant association between PEW and sex. The prevalence of PEW in male PD patients was significantly higher in comparison with their female counterparts, which may be due to decreased secretion of testosterone,³¹ resulting in reduced muscle protein synthesis and increased muscle protein catabolism.³¹ The frequency of PEW was significantly higher in PD patients below the age of 60 years in comparison with those aged of 60 years and greater, which may be due to a higher energy requirement for PD patients below the age of 60 years.²⁷ In addition, the prevalence of PEW was significantly higher in PD patients using 1.5% dextrose PD solutions compared to those using PD solutions with a dextrose concentration higher than 1.5% or receiving a combined regimen of various types of PD solutions. This could be because of the fact that PD solutions with a dextrose concentration of 1.5% provide less energy for PD patients than other PD solutions.²⁷ In this study, no significant associations were found between the frequency of PEW with dialysis vintage, total dialysis adequacy, and the presence of diabetes mellitus.

Inflammation is another cause of PEW in PD patients,³² which is caused by low clearance of inflammatory cytokines due to kidney failure, high synthesis of inflammatory cytokines because of the accumulation of various compounds, and the bioincompatibility of PD solutions.^{33,34} Inflammation

may induce PEW by increasing skeletal muscle protein breakdown and suppressing appetite.^{32,35} In our study, mean serum HSCRPs in PD patients with and without PEW was higher than 3 mg/L that indicates the presence of microinflammation in both groups. However, mean serum HSCRPs was significantly higher in PD patients without PEW compared to those with PEW. This could be due to the fact that most non-PEW patients used PD solutions with a dextrose concentration higher than 1.5% or receiving a combined regimen of various types of PD solutions; for this reason, amount of absorbed glucose from dialysis solution was significantly higher in PD patients without PEW compared to those with PEW. Evidence shows that continuous exposure to hyperosmotic and hyperglycemic dialysis solutions may cause chronic inflammation.³⁶ In addition, mean BMI was significantly higher in PD patients without PEW compared to those with PEW, and overweight itself results in an inflammatory state.³⁷

Cardiovascular disease is the main cause of death in patients with kidney disease, including dialysis patients, and approximately 50% of mortality in these patients are due to CVD.^{1,2} Protein-energy wasting may increase cardiovascular mortality among chronic kidney disease patients especially hemodialysis patients.^{18,19} Some studies have shown that serum HSCRPs, a marker of systemic inflammation, and soluble ICAM-1, a marker of vascular inflammation, are two CVD risk factors in hemodialysis patients with PEW.^{20,21} To our knowledge, only one study in this field has been performed in PD patients³⁸; therefore, the present study was designed to compare CVD risk factors between PD patients with and without PEW. In our study, contrary to investigations performed in hemodialysis patients,^{20,21} serum HSCRPs, and soluble ICAM-1 were significantly higher in PD patients without PEW compared to those with PEW. The reasons for the higher concentrations of inflammatory markers in PD patients without PEW were explained previously. In addition, contrary to our findings, Choi et al. showed that the malnourished PD patients had significantly higher serum HSCRPs and soluble ICAM-1 than the well-nourished PD patients.³⁸ The disagreement may be due to the fact that in Choi and colleagues' study, mean BMI was within the normal range in the well-nourished PD patients, whereas in our

study, mean BMI was within the overweight range in PD patients without PEW, and overweight itself results in an inflammatory state.³⁷

In the present study, serum triglyceride was significantly higher in PD patients without PEW compared to those with PEW. This may be due to the fact that amount of absorbed glucose from dialysis solution was significantly higher in PD patients without PEW as compared to those with PEW. The absorbed glucose from PD solutions results in increased hepatic synthesis of triglycerides.^{38,39} In addition, inflammatory cytokines decrease the activity of lipoprotein lipase and cause an increase in serum concentration of triglyceride-rich lipoproteins such as VLDL.⁴⁰ No research in this field was found in available literature to compare with the findings of our study. In this study, serum HDLC was significantly lower in PD patients without PEW compared to those with PEW. This is attributable to high serum triglyceride in PD patients without PEW. In hypertriglyceridemic states, the exchange of triglycerides with cholesterol esters between triglyceride-rich lipoproteins (such as VLDL and IDL) and HDLC increases by cholesteryl ester transfer proteins. These triglyceride-rich, cholesterol-poor HDLCs are better substrates for hepatic lipase. This enzyme, by lipolysis of triglycerides, transforms these HDLCs into small dense HDLCs, which are catabolized more rapidly than their larger counterparts and consequently leads to low concentration of serum HDLC.⁴¹ Also, inflammatory cytokines decrease the activity of lecithin-cholesterol acyl transferase, and synthesis of apoprotein AI,^{35,42} and consequently cause a reduction in serum HDLC. No studies in this field were found in available literature to compare with the findings of our study.

In the present study, we did not measure 24-hour urine protein, and three ISRNM criteria according to table 1, and we did not use food frequency questionnaire for the assessment of dietary intakes. These were limitations of our study.

CONCLUSIONS

Our study indicates that PEW is prevalent in Iranian PD patients. In addition, serum concentrations of CVD risk factors are dependent on the amount of glucose absorbed from PD solutions and are in a more inappropriate status in PD patients without PEW as compared to those with PEW.

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CONFLICT OF INTEREST

None declared.

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