Original Article

Prevalence of protein-energy wasting (PEW) and evaluation of diagnostic criteria in Japanese maintenance hemodialysis patients

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Background and Objectives: The International Society of Renal Nutrition and Metabolism (ISRNM) has recently recommended the use of the term “protein-energy wasting” (PEW). PEW is a state of malnutrition with decreased body stores of protein and energy fuel in hemodialysis patients and is known as a risk factor for morbidity and mortality. We examined the prevalence of PEW and the characteristics of PEW patients in a hemodialysis center in Japan. **Methods and Study Design:** Fifty-nine outpatients undergoing maintenance hemodialysis at Iga City General Hospital were evaluated. We observed their biochemical data, body composition, dietary intake, and the number of steps prospectively. PEW was defined according to ISRNM criteria. **Results:** Nine patients (15% of total) were diagnosed as having PEW. Among indicators of PEW criteria, the relevance ratios of “reduced muscle mass” and “unintentional low dietary energy intake” were significantly higher in PEW than in non-PEW. The number of steps was lower, and serum levels of glucose and C-reactive protein were higher in PEW. **Conclusion:** About 15% of Japanese hemodialysis patients are estimated to have PEW. Our results suggested that major contributing factors to PEW were reduced muscle mass, unintentional low dietary energy intake, lower amount of exercise, insulin resistance, and chronic inflammation.

Key Words: protein-energy wasting, hemodialysis, malnutrition, skeletal muscle, dietary intake

INTRODUCTION

Chronic kidney disease (CKD) has recently become a public health problem worldwide due to its frequency and high morbidity and mortality.[1,2] Although cardiovascular disease is the primary cause of death in CKD patients on hemodialysis,[3] it has been described that malnutrition is also one of the major risk factors for morbidity and mortality.[4] Moreover, wasting and malnutrition are identified as common problems in patients on maintenance hemodialysis. In advanced CKD patients who require dialysis therapy to survive, 20%-75% patients show evidence of uremic malnutrition, muscle wasting, and body fat loss.[5] Many nutritional abnormalities found in CKD patients are not always caused by inadequate diet but by inflammatory conditions causing the loss of protein stores or inducing anorexia and reduced nutrient intake. In addition, many other conditions may contribute to the loss of lean body mass not related to reduced nutrient intake such as hypercatabolism, metabolic acidosis, hyperparathyroidism, endocrine disorders related to insulin resistance, growth hormone, insulin growth factor 1, and glucocorticoids, oxidative stress, loss of nutrients into the dialysate, and dialysis-related blood loss.[5]

The syndrome of wasting includes the loss of muscle and fat tissue, malnutrition, and inflammation. Several designations have been previously used for this syndrome such as uremic malnutrition,[6] protein-energy malnutrition,[7] or malnutrition–inflammation complex.[8] To avoid nomenclatural confusion, an expert panel of the Interna-

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tional Society of Renal Nutrition and Metabolism (ISRNM) has recently recommended the use of the term "protein-energy wasting" (PEW) to incorporate all the different aspects of malnutrition and other metabolic or nutritional derangements, such as inflammation, in patients with CKD.[5] PEW can be diagnosed if at least three of the four categories are present [serum chemistry: low serum levels of albumin, transthyretin, or total cholesterol; body mass: unintentional weight loss over time, decreased BMI, or total body fat percentage; muscle mass: decreased muscle mass over time, midarm muscle circumference, or creatinine appearance; and dietary intake: unintentional decreased protein or energy intake].[5]

The presence of PEW is clearly associated with increased mortality and decreased quality of life in dialysis patients.[9] However, the prevalence of PEW in Japan and the appropriateness of diagnostic criteria for Japanese maintenance hemodialysis patients has not yet been described using ISRNM criteria. Moreover, the parameters proposed for defining PEW have been established for the American population, so there is a question as to whether these findings can be utilized in other countries. In the present study, we examined the prevalence of PEW and the characteristics of PEW patients in a hemodialysis center in Japan.

MATERIALS AND METHODS

Subjects

Fifty-nine outpatients (44 men, 15 women) who had been undergoing maintenance hemodialysis at Iga City General Hospital (Mie, Japan) for more than 6 months were evaluated from May 2012 to November 2012. Patients found to have the following during assessment were excluded: edema or ascites, inflammatory diseases, known malignancies, or any physical deformities. The medical records of each subject were thoroughly reviewed by a collaborating physician in this study. Dialysis treatment consisted of 3.5-4.5-h sessions three times a week and the blood flow rate ranged from 150 to 250 mL/min, with a dialysate flow rate of 500 mL/min and the use of a bicarbonate buffer; these values are standard in Japan.

The physical activity of each patient was evaluated using a Lifecorder (Suzuken Co., Ltd., Nagoya, Japan), which is a commercially available activity monitor based on a uniaxial accelerometry sensor. Food surveys involved individual interviews of subjects by dieticians using self-administered 3-day dietary records. Subjects did not have any food restrictions during the study and were requested to maintain their usual dietary habits and normal physical activity. Energy and nutrient content of each diet was calculated using Excel-Eiyokun software (Kenpakusha Co., Ltd., Tokyo, Japan). The study protocol was approved by the Ethics Committee of Iga City General Hospital and complied with the Declaration of Helsinki. All participants were included in the study after obtaining their informed consent.

Serum chemistry

Blood samples were collected at the start of the first dialysis session of the week. Plasma and serum were separated and kept frozen at -80°C if not analyzed immediately. Complete blood counts were determined immediately after collection. Biochemical parameters were measured immediately after centrifugation. Hematological parameters and biochemical assessments were determined in the hospital laboratory using commercially available test kits. In brief, complete blood counts were measured using the ADVIA2120 hematology analyzer (Siemens, Munich, Germany). Biochemical parameters were measured using the Hitachi 7600-020 automatic biochemical analyzer (Hitachi Ltd., Tokyo, Japan). Normalized protein catabolic rate (nPCR), estimated dietary protein intake, was determined by urea kinetic model. Urea clearance (Kt/V) was used to represent the adequacy of dialysis.

Bioelectrical impedance analysis (BIA)

Body composition of each patient was assessed using the InBody S20 multifrequency analyzer (Biospace, Tokyo, Japan), because bioelectrical impedance analysis (BIA) is a noninvasive and commonly used method for estimating body composition. The analyzer uses an 8-point tactile electrode system that measures the total and segmental impedance and phase angle of alternating electric current at four different frequencies. It was used according to the manufacturer's instructions.

Diagnosis of PEW

The expert panel of ISRNM has recommended that four main and established categories be recognized for the diagnosis of PEW: (1) serum chemistry: low serum levels of albumin, transthyretin, or total cholesterol; (2) body mass: unintentional weight loss over time, decreased BMI, or total body fat percentage; (3) muscle mass: decreased muscle mass over time, midarm muscle circumference, or creatinine appearance; and (4) dietary intake: unintentional decreased protein or energy intake.[5] The presence of PEW was defined as the patient meeting at least three of the four listed categories (and at least one test result in each of the selected categories) for malnutrition markers. Height was obtained from the patient's chart. Weight was used as dry weight, defined as the postdialysis weight in which the patient was normotensive and showed no signs of overhydration. BMI was calculated as dry weight in kilograms divided by the square of height in meters and expressed in kg/m^2.

Statistical analysis

Data are expressed as mean±SD. All statistical analyses were conducted using JMP version 10 software (SAS Institute, Cary, NC, USA). p values <0.05 were considered to be statistically significant. Student's t-tests were used to examine the difference between means, and the Mann–Whitney test was used for nonparametric data. The chi-square test was used for categorical variables.

RESULTS

Patient characteristics and the prevalence of PEW

Table 1 summarizes the characteristics of subjects. Subjects in the present study were 59 dialysis patients with a mean age of 66±9 years; 75% (n=44) were men. Causes of end-stage renal failure were primary renal disease in 34 patients (58%) and diabetes in 25 patients (42%). As shown in Figure 1, nine patients (15%) had PEW according to the ISRNM definition, as they met three criteria in

Table 1. Patient characteristics

	Patients (n=59)
Age (years)	66±9
Gender (men/women)	44/15
Hemodialysis duration (years)	12±9
Diabetic nephropathy (%)	42
Body mass index (kg/m^2)	20.7±3.2
Skeletal muscle ratio (%)	39.9±5.1 (men), 35.6±5.1 (women)
Body fat ratio (%)	25.3±9.5 (men), 29.9±9.6 (women)
Serum albumin (g/dL)	3.7±0.3
Serum transthyretin (mg/dL)	26.4±6.1
Serum total cholesterol (mg/dL)	143±1.0
Dietary energy intake (kcal/kg/day)	29.8±6.1
Dietary protein intake (g/kg/day)	1.0±0.3
Dietary salt intake (g/day)	6.7±1.7

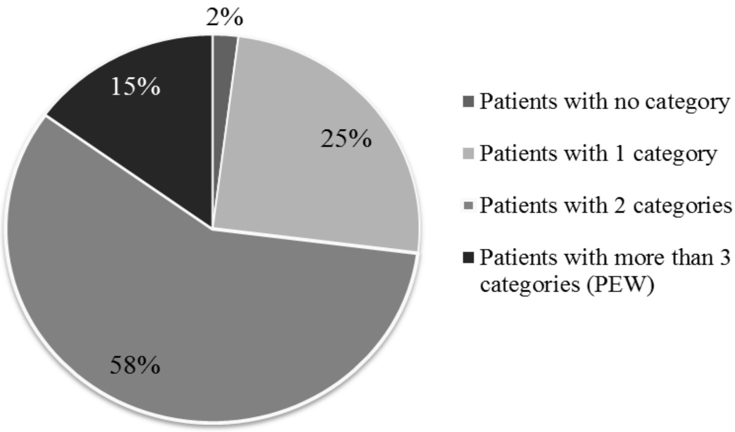

Figure 1. Prevalence of protein-energy wasting. Fifteen percent of our dialysis population had PEW according to the ISRNM definition. Fifty-eight percent of patients met two categories, and 25% of patients met one category.

the four different categories. Fifty-eight percent of patients met two categories, and 25% of patients met one category. There were only 2% of patients who had no indicators of PEW criteria. Table 2 shows the distribution of the various malnutrition indicators according to PEW criteria. Seventy-eight percent of our dialysis population met the criterion of BMI <23 kg/m^2.

Difference of PEW criteria between PEW and non-PEW

Table 3 shows the distribution of the various malnutrition indicators according to PEW criteria in PEW and non-PEW patients. Among indicators of PEW criteria, the relevance ratios of reduced muscle mass and unintentional low dietary energy intake were significantly higher in PEW than in non-PEW. In contrast, serum albumin, serum transthyretin, serum total cholesterol, BMI, unintentional weight loss, and unintentional low dietary protein intake were not significantly different between PEW and non-PEW patients.

Clinical factors associated with PEW

The clinical and biochemical characteristics of patients on maintenance hemodialysis according to PEW are presented in Table 4. Mean age, duration of hemodialysis (HD) therapy, height, dry weight, BMI, normalized protein catabolic rate (nPCR), and Kt/V were comparable between PEW and non-PEW patients. On the other hand, the number of steps and serum levels of creatinine phosphokinase, creatinine, and iron were significantly higher in non-PEW than in PEW. The serum levels of glucose and C-reactive protein were significantly lower in PEW than in non-PEW.

DISCUSSION

The present study analyzed, for the first time, the prevalence of PEW defined according to ISRNM criteria in hemodialysis patients in Japan. Fifteen percent of our hemodialysis patients had PEW. On the other hand, it has been reported that 20%-75% of patients with dialysis showed evidence of uremic malnutrition, muscle wasting, and body fat loss.[5] Seventy-four percent of European patients on hemodialysis in the CONTRAST study,[9] 38% of 331 patients on hemodialysis in the United States,[10] and 39% of 221 patients on hemodialysis in Northern Europe[11] have been defined as having malnutrition. Moreover, Spanish literature shows that 40% of their dialysis population met PEW criteria.[12] Thus, the prevalence in Japan is lower than that has been seen in European or American studies. The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that the crude 1-year mortality rates were 6.6% in Japan, 15.6% in Europe, and 21.7% in the United States. After adjusting for age, gender, race, and 25 comorbid conditions, the relative risk of mortality was 2.84 (p<0.0001) for Europe in comparison with Japan and was 3.78 (p<0.0001) for the US in comparison with Japan.[13] Because PEW is closely connected

Table 2. Distribution of malnutrition indicators according to PEW criteria

Features	Patients (n=59), %
Prevalence of PEW	15
Serum albumin <3.8 g/dL	49
Serum transthyretin <30 mg/dL	63
Serum total cholesterol <100 mg/dL	2
Body mass index <23 kg/m^2	78
Unintentional weight loss over time: 5%/3 months or 10%/6 months	0
Total body fat percentage <10%	2
Muscle wasting: reduced muscle mass: 5%/3 months or 10%/6 months	14
Unintentional low dietary protein intake <0.8 g/kg/day for at least 2 months	0
Unintentional low dietary energy intake <25 kcal/kg/day for at least 2 months	15

PEW: protein-energy wasting.

Table 3. Difference of PEW criteria between PEW and non-PEW patients

Features	Non-PEW, % (n=50)	PEW, % (n=9)	*p* value
Serum albumin <3.8 g/dL	44	67	NS
Serum transthyretin <30 mg/dL	60	89	NS
Serum total cholesterol <100 mg/dL	0	11	NS
Body mass index <23 kg/m^2	78	89	NS
Unintentional weight loss over time: 5%/3 months or 10%/6 months	0	0	NS
Total body fat percentage <10%	2	0	NS
Muscle wasting: reduced muscle mass: 5%/3 months or 10%/6 months	4	67	<0.01
Unintentional low dietary protein intake < 0.8 g/kg/day for at least 2 months	0	11	NS
Unintentional low dietary energy intake <25 kcal/kg/day for at least 2 months	10	44	<0.05

PEW: protein-energy wasting; NS: not significant.

with morbidity and mortality, one of the causes of the lower mortality rate in Japan may be this lower prevalence of PEW. Although the dialysis center in the present study is one of the most popular Japanese hemodialysis facilities, further studies are needed to clarify the real prevalence of PEW in hemodialysis patients in Japan.

PEW can be diagnosed if at least three of the four categories are present. Serum albumin levels and BMI have been traditionally known as nutritional markers. However, these markers were not significantly different between PEW and non-PEW in our study. Hypoalbuminemia has been the strongest predictor of cardiovascular disease and mortality in dialysis patients.[14] A drop of 1 g/dL in serum albumin has been associated with an increased mortality risk of 47% in HD patients.[15] On the other hand, it has been reported that serum albumin levels may not be a reliable marker of nutritional status; rather, these levels may be more a marker of inflammation.[16] Although ISRNM suggests a specific cutoff point for BMI (23 kg/m^2) in CKD, the average BMI of Japanese dialysis patients is approximately 20-21 kg/m^2, and the average BMI of the general Japanese populations is approximately 22-23 kg/m^2.[17] Because the criterion of BMI <23 kg/m^2 was described based on an American population, ISRNM has recognized that the threshold for BMI criteria (<23 kg/m^2) may need further adjustment; especially in some populations, such as those from southeast Asia, a low BMI may not indicate pathology.[5] In addition, BMI paradox in hemodialysis patients has been reported. While mortality decreased with BMI increases in whites, the relationship between BMI and survival was U-shaped in Asians.[18] In another study in Brazilian showed that HD patients with BMI <23 kg/m^2 did not present signs of energy wasting, whereas those with BMI >23 kg/m^2 had more inflammation, probably because of a greater adiposity.[19] They said in their report, it might be interesting to determine three cutoff points for BMI to classify patients on HD into three categories: those with PEW, eutrophic patients, and those with overweight/obesity. Thus, the cutoff point established by ISRNM does not seem to be a reliable marker of PEW in Japanese hemodialysis patients, further studies are required. In contrast, according to our data, the relevance ratios of reduced muscle mass and unintentional low dietary energy intake among indicators of PEW criteria were significantly higher in PEW than in non-PEW. These seem to be reliable markers of PEW in Japanese hemodialysis patients.

In the present study, we evaluated the prevalence of PEW and its relationship with various clinical markers in a comprehensive way. According to our data, among the clinical markers, number of steps and serum levels of creatinine phosphokinase and creatinine were significantly lower in PEW than in non-PEW. It has been reported that abnormalities in muscle function, exercise performance, and physical activity abnormalities begin in the early stages of CKD and decline dramatically as end-stage renal disease (ESRD) develops.[20,21] In addition, several metabolic studies have suggested the beneficial effects of combining exercise with nutritional supplementation.[22] Although a number of studies have examined the effects of fitness training in ESRD patients,[23] few studies have examined the role of exercise training on stimulating muscle growth. The number of steps, namely daily exercise, may have beneficial effects on the maintenance of muscle mass despite the unclear mechanisms. Moreover, the present study showed that the serum levels of glucose

Table 4. Difference of clinical and biochemical factors between PEW and non-PEW patients

	Non-PEW (n=50)	PEW (n=9)	*p* value
Age (years)	66±9.8	69±7.4	NS
Gender (men/women)	38/12	6/3	NS
Hemodialysis duration (years)	12.4±8.2	11.9±10.1	NS
Diabetic nephropathy (%)	36	60	NS
Height (cm)	161±1	157±3	NS
Dry weight (kg)	53.9±11.5	50.4±7.8	NS
Body mass index (kg/m^2)	20.8±3.1	20.5±2.3	NS
Body fat ratio (%)	24.0±9.3	23.9±10.8	NS
Dietary energy intake/body weight (kcal/kg)	33.3±7.2	30.8±5.3	NS
Dietary protein intake/body weight (g/kg)	1.15±0.29	1.18±0.23	NS
Dietary salt intake (g)	6.7±1.5	7.1±2.1	NS
Total protein (g/dL)	6.5±0.5	6.7±0.5	NS
Albumin (g/dL)	3.8±0.3	3.5±0.4	<0.05
Transthyretin (mg/dL)	25.7±6.4	20.7±8.0	<0.05
Total cholesterol (mg/dL)	146±30	131±43	NS
Aspartate aminotransferase (IU/L)	15±6	13±5	NS
Alanine aminotransferase (IU/L)	12±6	8±3	NS
Alkaline phosphatase (IU/L)	239±110	279±120	NS
Lactate dehydrogenase (IU/L)	202±46	191±25	NS
Creatine phosphokinase (IU/L)	120±85	70±29	<0.05
Blood urea nitrogen (mg/dL)	63±15	56±15	NS
Creatinine (mg/dL)	11.7±2.9	9.8±2.4	<0.05
Sodium (mEq/L)	140±3	140±3	NS
Potassium (mEq/L)	4.8±0.6	4.7±1.0	NS
Chloride (mEq/L)	104±3	104±4	NS
Calcium (mEq/L)	9.2±0.5	9.3±0.6	NS
Phosphate (mEq/L)	5.7±1.2	6.0±1.4	NS
Magnesium (mg/dL)	2.3±0.3	2.2±0.3	NS
Glucose (mg/dL)	130±33	172±61	<0.01
C-reactive protein (mg/dL)	0.3±0.7	1.1±1.7	<0.01
Iron (μg/dL)	57±21	42±21	<0.05
Total iron binding capacity (μg/dL)	271±55	261±52	NS
Ferritin (ng/mL)	102±192	106±92	NS
Intact parathyroid hormone (pg/mL)	149±90	177±121	NS
nPCR (g/kg/day)	0.81±0.14	0.74±0.15	NS
%CGR	112±25	96±19	NS
Kt/V	1.43±0.24	1.45±0.19	NS
Number of steps on the days of hemodialysis session (steps/day)	4190±3100	1720±1420	<0.05
Number of steps on the other days of hemodialysis session (steps/day)	6630±5280	1880±1530	<0.05

PEW: protein-energy wasting; nPCR: normalized protein catabolic rate; %CGR: % creatinine generation rate; Kt/V: urea clearance; NS: not significant.

and C-reactive protein were significantly higher in PEW than in non-PEW. This glucose difference may be partly dependent on the percentage of diabetic patients. Although not statistically significant, the ratio of diabetic nephropathy in PEW (60%) tended to higher than in non-PEW (36%). Although an improper diet by itself may contribute to PEW, endocrine disorders and systemic inflammation may cause malnutrition in hemodialysis patients. HD patients often have other comorbidities that can adversely affect their nutritional status. For instance, patients with CKD secondary to diabetes mellitus have a higher incidence of PEW in comparison with nondiabetes mellitus patients.[24] The degree of insulin resistance and/or insulin deprivation seems to play the most critical role in this process.[25] In addition, insulin resistance exists in hemodialysis patients even in the absence of severe obesity and is strongly associated with increased muscle protein breakdown, even after controlling for inflammation.[26] Accordingly, appropriate management of diabetes and insulin resistance may be important for preventing further muscle loss and PEW in maintenance dialysis patients. Chronic inflammation is also an important factor affecting PEW in HD patients. Previous studies have reported that higher levels of proinflammatory cytokines contribute to increased lipolysis, muscle protein breakdown, and nitrogen loss, leading to sarcopenia and increased mortality in these patients.[27] In addition, chronic inflammation may be associated with inadequate dietary protein and energy intake because it can cause anorexia.[10] Inadequate nutrient intake may also occur in comorbid diseases that can affect gastrointestinal function, depression, poor socioeconomic situation, or early feeling of satiety. However, little knowledge is available with regard to treatment for chronic inflammation in hemodialysis patients.

The present study had several limitations. First, our study was limited by its observational nature, which allowed us to establish associations but not causality. Further intervention studies are needed to elucidate the mechanisms of PEW. Second, only 59 dialysis patients in a single center were evaluated, although the dialysis center in the present study is one of the most popular Japanese hemodialysis facilities. Thirdly, not only the cutoff point for BMI is inappropriate, but also the sensitivity and specificity of serum albumin, transthyretin, total cholesterol and weight loss seems insufficient for the diagnosis of PEW. However, we could not find the reliable diagnostic methods suitable for Japanese in this study. In conclusion, about 15% of Japanese hemodialysis patients may have PEW, which was a lower prevalence of PEW than that in other countries; this suggests that it may be necessary to rethink the definition of the diagnostic criteria of PEW for Asian patients in the future. In addition, our results suggested that major contributing factors to PEW in maintenance hemodialysis patients were reduced muscle mass, unintentional low dietary energy intake, lower amount of exercise, insulin resistance, and chronic inflammation. An integrated approach will be needed to prevent and treat PEW in hemodialysis patients.

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Original Article

Prevalence of protein-energy wasting (PEW) and evaluation of diagnostic criteria in Japanese maintenance hemodialysis patients

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日本维持性血液透析患者蛋白质能量消耗的患病率和诊断标准评估

背景与目的：国际肾营养与代谢协会（ISRNM）最近推荐使用术语“蛋白质能量消耗（PEW）”。PEW 是血液透析患者体内蛋白质和能量储存减少的一种营养不良状态，并且被认为是患病率和死亡率的危险因素。我们在日本的一个血液透析中心研究了 PEW 的患病率和 PEW 患者的特征。**方法与研究设计**：我们评估了 58 名在伊贺市综合医院做维持性血液透析的门诊患者，并观察了他们的生化数据、体成分、膳食摄入量和行走的步数。根据 ISRNM 标准诊断 PEW。**结果**：9 名（占总数的 15%）患者被诊断为 PEW。在 PEW 诊断标准指标中，PEW 患者“肌肉量减少”和“无意识的低膳食能量摄入”的比例高于非 PEW 患者。PEW 患者中行走的步数较低，而血清葡萄糖和 C-反应蛋白水平较高。**结论**：约有 15%的日本血液透析患者患有 PEW。我们的研究结果表明：引起 PEW 的主要因素是肌肉量减少、无意识的低膳食能量摄入、运动量低、胰岛素抵抗和慢性炎症。

关键词：蛋白质能量消耗、血液透析、营养不良、骨骼肌、膳食摄入量