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Original article

# Effects of Protein-Energy Wasting (PEW) and hyperphosphatemia on the prognosis in Japanese maintenance hemodialysis patients: A five-year follow-up observational study

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SUMMARY

*Background & aims:* In dialysis patients, malnutrition is a poor prognostic factor. In patients with chronic kidney disease (CKD), malnutrition is qualitatively different from general malnutrition, which is defined as "Protein-Energy Wasting (PEW)." Dietary therapy for the enhancement of PEW requires the aggressive intake of protein. Conversely, as protein intake and phosphorus intake correlate positively, increasing the protein intake increases the phosphorus intake, which is a poor prognostic factor in dialysis patients. One of the treatments for hyperphosphatemia in dialysis patients is the intake restriction of phosphorus by dietary counseling. However, protein uptake to maintain and augment the nutritional status and the protein intake restriction to correct hyperphosphatemia are contradictory treatments. Hence, this study aims to investigate the effects of PEW and hyperphosphatemia on the prognosis in hemodialysis patients.
*Methods:* We enrolled 60 outpatients who underwent maintenance hemodialysis for 6 months (May −November 2012) at Iga City General Hospital (Mie, Japan). In November 2012, we assessed the presence or absence of PEW and hyperphosphatemia in patients and evaluated the survival rate over the next 5 years.
*Results:* Overall, 10 patients (17%) were diagnosed as PEW. While 17 patients (28%) exhibited average phosphorus level >6.0 mg/dL (hyperphosphatemia). The 5-year survival rate was 30% in the PEW group, 66% in the non-PEW group, 57% in the hyperphosphatemia group, and 61% in the non-hyperphosphatemia group. A statistically significant difference existed between the PEW and non-PEW groups ($P = 0.021$). However, we observed no significant difference between the hyperphosphatemia and non-hyperphosphatemia groups.
*Conclusions:* This study suggests that PEW affects the prognosis more than hyperphosphatemia in maintenance hemodialysis patients. The normalization of the serum phosphorus level by the protein intake restriction could prevent secondary hyperparathyroidism and vascular calcification. Conversely, restricting the protein intake poses a risk of malnutrition. In fact, early death occurred in patients with PEW in this study. Perhaps, patients with PEW should prioritize improving their nutritional status rather than controlling the serum phosphorus level.


*Abbreviations:* CKD, chronic kidney disease; PEW, Protein-Energy Wasting; ISRNM, the International Society of Renal Nutrition and Metabolism; BMI, body mass index; BIA, bioelectrical impedance analysis; CI, confidence interval; KDOQI, Kidney Disease Outcomes Quality Initiative.

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## 1. Introduction

The nutritional disorder of dialysis patients is complicated by uremia, inflammation, loss of nutrients into the dialysate, and various metabolic changes. In patients with renal disease, several terms have been used for representing nutritional disorders such as uremic malnutrition [1], protein-energy malnutrition [2], malnutrition–inflammation complex syndrome [3], and malnutrition-inflammation-atherosclerosis syndrome [4]. In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) proposed "Protein-Energy Wasting (PEW)" [5], which is now prevalent and incorporates all causes of nutritional disorders in patients with CKD.

PEW is characterized by the loss of body protein and muscle/fat mass. As PEW correlates with increased mortality and decreased the quality of life in dialysis patients [6], avoiding PEW is imperative for a good prognosis. Dietary therapy to not cause PEW performs aggressive protein intake. However, as protein intake and phosphorus intake correlate positively [7], increasing the protein intake increases the phosphorus intake.

The serum phosphorus concentration is regulated by absorption from gastrointestinal, isolation from bone, take-in bone, and urinary excretion from the kidneys. Patients with CKD often develop hyperphosphatemia to decrease the excretion of phosphorus from the kidneys. Hyperphosphatemia causes secondary hyperparathyroidism and increases the risk of coronary artery disease morbidity and mortality in dialysis patients [8,9]. Treatment of hyperphosphatemia in dialysis patients involves the phosphorus intake restriction by dietary counseling, effective removal of phosphorus by dialysis, and medication therapy because of phosphorus adsorption drugs. As mentioned earlier, the protein intake restriction is sometimes executed as dietary therapy because both protein and phosphorus intake correlate positively [7].

However, protein uptake to maintain and augment the nutritional status and the protein intake restriction to correct hyperphosphatemia are contradictory treatments. In addition, it remains unclear which of PEW treatment and hyperphosphatemia treatment should be given priority. Hence, this study aims to investigate the effects of PEW and hyperphosphatemia on the prognosis in hemodialysis patients.

## 2. Materials and methods

### 2.1. Patients

We enrolled 60 outpatients who underwent maintenance hemodialysis for 6 months (May–November 2012) at Iga City General Hospital (Mie, Japan), and without edema, ascites, inflammatory diseases, known malignancies, or history of physical deformities, after obtaining their informed consent. We conducted dialysis therapy using bicarbonate buffer, one time 3.5–4.5 h three times per week, blood flow rate 150–250 mL/min, and dialysate flow rate of 500 mL/min, which is a standard method in Japan. In addition, a collaborating doctor thoroughly reviewed the clinical records of each patient. The study period was from May 2012 to November 2017. This study was approved by the Ethics Committee of Iga City General Hospital.

### 2.2. Physical measurement

We obtained height data from patients' medical records. The body weight was used as dry weight defined as weight without edema after dialysis. The body mass index (BMI) was evaluated as dry weight in kilograms (kg) divided by the square of height in meters ($m^2$) and expressed in $kg/m^2$.

### 2.3. Serum chemistry

We collected blood samples at the first dialysis session of the week from May 2012 to November 2012. The complete blood counts were measured immediately after blood collection. Biochemical parameters were measured immediately after centrifugation. Of note, all inspections were performed in the hospital laboratory using routine methods. We measured the complete blood counts using the ADVIA2120 hematology analyzer (Siemens, Munich, Germany). Furthermore, biochemical parameters were measured using the Hitachi 7600–020 automatic biochemical analyzer (Hitachi Ltd., Tokyo, Japan).

### 2.4. Bioelectrical impedance analysis

We measured the body composition using Inbody S20 (Inbody Japan Inc., Tokyo, Japan) after dialysis; Inbody S20 is a method to measure using bioelectrical impedance analysis (BIA). BIA is a noninvasive and extensively used method to measure the body composition. For Inbody S20, 8-point contact type electrode system was used. All measurements were performed according to the manual.

### 2.5. Survey of dietary intake

The dietary intake survey asked patients to record the meal content of 3 consecutive days every month for 6 months from May 2012. The meal content standardization was performed by a skilled administrative dietician. There was no dietary restriction on patients, and they retained their everyday meal practice. The intake of energy and nutrients was calculated using Excel-Eiyokun software (Kenpakusha Co., Ltd., Tokyo, Japan).

### 2.6. Diagnosis of PEW

PEW was diagnosed per the ISRNM criteria. The diagnostic criteria of PEW, defined by ISRNM, is broadly categorized into four categories as follows: (1) serum chemistry: serum albumin <3.8 g/dL, serum transthyretin <30 mg/dL, serum total cholesterol <100 mg/dL; (2) body mass: BMI <23 $kg/m^2$, unintended weight loss, 5% over 3 months or 10% over 6 months, body fat percentage <10%; (3) muscle mass: reduced muscle mass, 5% over 3 months or 10% over 6 months, mid-arm muscle circumference, reduction >10% compared with healthy people; (4) dietary intake: unintentional low dietary protein intake <0.8 g/kg/day for 2 months for dietary patients, unintentional low dietary energy intake <25 kcal/kg/day for 2 months. If $\geq$ 3 categories were applicable, it was diagnosed as PEW.

### 2.7. Diagnosis of hyperphosphatemia

We diagnosed hyperphosphatemia with reference to "Clinical Practice Guideline for CKD-MBD" published by The Japanese Society for Dialysis Therapy [10]. A patient with hyperphosphatemia was a person whose 6-month average serum phosphorus level exceeded 6 mg/dL.

### 2.8. Survival rate

We observed the survival rate for 5 years from 2012. All-cause deaths were regarded as events, and patients who could not be traced because of changing the hospital were considered to be dropped out.

### 2.9. Statistical analysis

In this study, continuous variables are expressed as mean ± standard deviation. We evaluated the between-group difference by the Student's *t*-test. In addition, categorical variables were compared among groups using the chi-square test. The survival curve was drawn by the Kaplan–Meier and log-rank tests. We considered $P < 0.05$ as statistically significant. All statistical analyses were performed using JMP version 11 (SAS Institute, Cary, NC).

## 3. Results

### 3.1. Patients' characteristics

Table 1 summarizes the patients' characteristics. Patients' mean age was 66.2 ± 9.5 years, and 73% ($n = 44$) were males. The average hemodialysis period was 12.3 ± 8.5 years. Of all, 24 patients (40%) had diabetic nephropathy. The mean BMI was 20.7 ± 3.0 kg/m$^2$, serum albumin was 3.8 ± 0.4 g/dL, and serum phosphorus level was 5.5 ± 0.8 mg/dL.

### 3.2. Survival rate between PEW and non-PEW groups

Based on the ISRNM diagnostic criteria, 10 patients (17%) were diagnosed with PEW. Table 2 presents the characteristics of patients with or without PEW. Between PEW and non-PEW groups, age, gender ratio, hemodialysis duration, and diabetes morbidity rates were comparable. Likewise, no significant differences were noted in the BMI, skeletal muscle index, body fat ratio, energy intake, protein intake, and serum cholesterol level, and phosphorus between both groups. Conversely, the PEW group was significantly lower in the serum levels of albumin and transthyretin, and significantly higher C-reactive protein (CRP) than the non-PEW group.

Fig. 1 shows the survival curves. The 5-year survival rate was 30% [95% confidence interval (CI): 10%–62%] in the PEW group and 66% (95% CI: 52%–78%) in the non-PEW group. Furthermore, the survival rate of the PEW group was markedly lower than that of the non-PEW group ($P < 0.01$).

### 3.3. Survival rate between hyperphosphatemia and non-hyperphosphatemia

Table 3 summarizes the characteristics of patients with or without hyperphosphatemia. The hyperphosphatemia group comprised 17 patients (28%) with the mean age of 65.6 ± 9.2 years (13 males). Between hyperphosphatemia and non-hyperphosphatemia groups age, gender ratio, and diabetes morbidity rates were comparable. Conversely, the hyperphosphatemia group was significantly shorter in the hemodialysis period ($P = 0.028$) and higher in the serum phosphate level ($P < 0.001$) and CRP than that in the non-hyperphosphatemia group.

Fig. 2 shows the survival curves. The 5-year survival rate was 57% (95% CI: 33%–78%) in the hyperphosphatemia group and 61% (95% CI: 45%–75%) in the non-hyperphosphatemia group, with no significant difference in the 5-year survival rate with or without hyperphosphatemia ($P = 0.88$).

## 4. Discussion

This study investigated the impact of PEW and hyperphosphatemia on the prognosis in maintenance hemodialysis patients and established that PEW affects the 5-year survival rate, while hyperphosphatemia exerts no effect.

**Table 1**
Characteristics of the study sample.

| | Mean |
|---|---|
| Age (years) | 66.2 ± 9.5 |
| Sex (Men/Women) | 44/16 |
| Hemodialysis duration (years) | 12.3 ± 8.5 |
| Diabetes (diabetes/non-diabetes) | 24/36 |
| Body mass index (kg/m$^2$) | 20.7 ± 3.0 |
| Skeletal muscle index (%) | 40.3 ± 5.4 |
| Body fat ratio (%) | 24.0 ± 9.5 |
| Energy intake (kcal/kg/day) | 32.9 ± 6.9 |
| Protein intake (g/kg/day) | 1.2 ± 0.3 |
| Serum albumin level (g/dL) | 3.8 ± 0.4 |
| TTR (mg/dL) | 24.9 ± 6.9 |
| Serum total cholesterol (mg/dL) | 143.4 ± 32.3 |
| mean phosphorus (mg/dL) | 5.5 ± 0.8 |
| CRP (mg/dL) | 0.47 ± 0.98 |

Abbreviations: TTR, transthyretin; CRP, C-reactive protein.
Data are presented as mean ± SD.

**Table 2**
Difference of characteristics between PEW and non-PEW group.

| | Non-PEW group (n = 50) | PEWgroup (n = 10) | P value |
|---|---|---|---|
| Age (years) | 65.7 ± 9.8 | 69.1 ± 7.4 | NS |
| Sex (Men/Women) | 38/12 | 6/4 | NS |
| Hemodialysis duration (years) | 12.4 ± 8.2 | 11.9 ± 10.1 | NS |
| Diabetes (diabetes/non-diabetes) | 18/32 | 6/4 | NS |
| Body mass index (kg/m$^2$) | 20.8 ± 3.1 | 20.5 ± 2.4 | NS |
| Skeletal muscle index (%) | 40.4 ± 5.3 | 39.8 ± 5.8 | NS |
| Body fat ratio (%) | 24.0 ± 9.3 | 23.9 ± 10.8 | NS |
| Energy intake (kcal/kg/day) | 33.3 ± 7.2 | 30.9 ± 5.3 | NS |
| Protein intake (g/kg/day) | 1.1 ± 0.3 | 1.2 ± 0.2 | NS |
| Serum albumin level (g/dL) | 3.8 ± 0.3 | 3.5 ± 0.4 | <0.05 |
| TTR (mg/dL) | 25.7 ± 6.4 | 20.7 ± 8.0 | <0.05 |
| Serum total cholesterol (mg/dL) | 145.8 ± 30.0 | 131.0 ± 42.8 | NS |
| mean phosphorus (mg/dL) | 5.4 ± 0.9 | 5.7 ± 0.7 | NS |
| CRP (mg/dL) | 0.34 ± 0.73 | 1.14 ± 1.68 | <0.05 |

Abbreviations: PEW, Protein-Energy Wasting; TTR, transthyretin; CRP, C-reactive protein.
Data are presented as mean ± SD.
Normal range: Serum albumin level (4.1–5.1 g/dL); TTR (22.0–40.0 mg/dL); Serum total cholesterol (142–248 mg/dL); mean phosphorus (2.7–4.6 mg/dL); CRP (0.00–0.14 mg/dL).

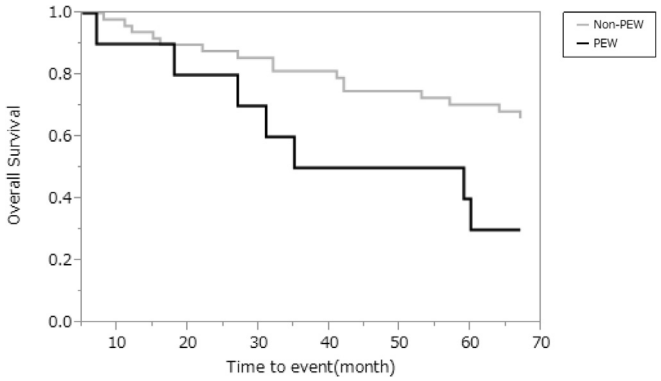


**Fig. 1. Difference of survival curve between PEW and non-PEW group**. The 5-year survival rate was 30% (95%CI (confidence interval) = 10%–62%) in PEW group and 66% (95%CI = 52%–78%) in non-PEW group, and those with maintenance hemodialysis patients with PEW had a significantly lower than non-PEW had ($p < 0.05$).

**Table 3**
Difference of characteristics between Hyperphosphatemia and non-Hyperphosphatemia group.

| Mean phosphorus* *Average phosphorus value for 6 months | ≦6 mg/dL (n = 43) | >6 mg/dL (n = 17) | P value |
|---|---|---|---|
| Age (years) | 66.5 ± 9.7 | 65.6 ± 9.2 | NS |
| Sex (Men/Women) | 31/12 | 13/4 | NS |
| Hemodialysis duration (years) | 13.7 ± 8.4 | 8.8 ± 7.9 | <0.05 |
| Diabetes (diabetes/non-diabetes) | 14/29 | 10/7 | NS |
| Body mass index (kg/m$^2$) | 20.4 ± 3.1 | 21.4 ± 2.7 | NS |
| Skeletal muscle index (%) | 40.7 ± 5.6 | 39.4 ± 4.7 | NS |
| Body fat ratio (%) | 23.2 ± 9.9 | 26.0 ± 8.3 | NS |
| Energy intake (kcal/kg/day) | 33.9 ± 7.3 | 30.3 ± 5.3 | NS |
| Protein intake (g/kg/day) | 1.2 ± 0.3 | 1.1 ± 0.2 | NS |
| Serum albumin level (g/dL) | 3.8 ± 0.4 | 3.7 ± 0.3 | NS |
| TTR (mg/dL) | 25.7 ± 7.2 | 22.8 ± 5.7 | NS |
| Serum total cholesterol (mg/dL) | 143.3 ± 27.8 | 143.7 ± 42.8 | NS |
| mean phosphorus (mg/dL) | 5.1 ± 0.6 | 6.4 ± 0.4 | <0.001 |
| CRP (mg/dL) | 0.31 ± 0.11 | 0.87 ± 1.43 | <0.05 |

Abbreviations: TTR, transthyretin; CRP, C-reactive protein.
Data are presented as mean ± SD.
Normal range: Serum albumin level (4.1–5.1 g/dL); TTR (22.0–40.0 mg/dL); Serum total cholesterol (142–248 mg/dL); mean phosphorus (2.7–4.6 mg/dL); CRP (0.00–0.14 mg/dL).

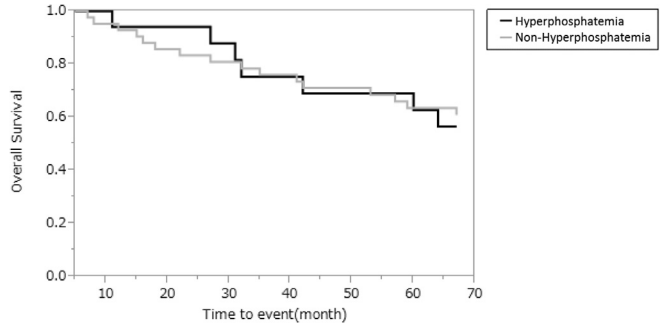


**Fig. 2. Difference of survival curve between Hyperphosphatemia and non-Hyperphosphatemia group**. The 5-year survival rate was 57% (95%CI = 33%–78%) in hyperphosphatemia group and 61% (95%CI = 45%–75%) in non-hyperphosphatemia group, and those there was no significant difference in 5-year survival rate with or without hyperphosphatemia (p = 0.88).

In this study, hyperphosphatemia did not affect the prognosis. Reportedly, hyperphosphatemia, which is a common condition in patients with CKD, causes hyperparathyroidism, renal osteopathy, progression of vascular calcification, increase in cardiovascular events, and elevated mortality rate [8,9]. In addition, as serum phosphorus levels elevate in people with high protein intake [11], the protein intake restriction is sometimes executed in dietary therapy. Conventionally, the idea of protein intake restriction was common as limiting the phosphorus intake [12]. However, per 2003 the National Kidney Foundation KDOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines, dialysis patients' protein intake should be set at 1.2 g/kg body weight/day [8], which is higher than Japanese guidelines of 0.9–1.2 g/kg ideal body weight/day [13]. In recent years, several studies have highlighted the significance of protein intake rather than serum phosphorus control. Shinaberger et al. [14] reported that the hazard ratio for death was significantly higher in the groups with the protein intake of ≥1.4 g/kg body weight/day and <0.8 g/kg body weight/day. In the subsequent study [15], the survival rate was low in the group in which the serum phosphorus level was elevated despite protein intake reduction, whereas the survival rate was high in the group in which the protein intake elevated and the serum phosphorus concentration declined. Perhaps, controlling the serum phosphorus level without the protein intake restriction is effective in hemodialysis patients from these results.

In hemodialysis patients, as hyperphosphatemia affects the prognosis [8,9], correcting hyperphosphatemia has gained some attention to date. However, this study reveals that PEW exerted more impact on the prognosis than hyperphosphatemia; one of the reasons for this result is aging of dialysis patients. The Japanese Society for Dialysis Therapy Committee of Renal Data Registry reported that the average age of the Japanese dialysis population is increasing annually, and the average age of dialysis patients was 68.2 years at the end of 2016 [16]. Based the statistics of the cabinet office, the Japanese aging rate was 27.7% on October 1, 2017, and it is projected to continue increasing in the future [17]. Reportedly, the elderly tend to lower their dietary intake because of various factors, such as social factors or psychosomatic factors, as well as the loss of appetite or dysgeusia because of aging [18]. In 2016, the National Health and Nutrition Survey reported that the rate of elderly aged ≥65 years with malnutrition tended to be 17.8%, which applied to approximately one-sixth elderly [19]. Malnutrition of the elderly is the risk of the onset of sarcopenia and frailty, progression of arteriosclerosis, and bone mineral density. Reportedly, sarcopenia occurs commonly and correlates with the nutrition status, especially in the elderly with end-stage renal failure [20]. In addition, Levine et al. reported that the mortality rate was low in the low protein intake group aged <65 years; however, the mortality rate was high in the low protein intake group aged ≥66 years [21]. A study reported that an increase in Insulin-like growth factor-1 resulting in the increased protein intake could be beneficial in the elderly [22]. Hence, sufficient energy and protein intake are essential for the nutritional management of dialysis patients, especially older adults. Furthermore, if the cut-off for hyperphosphatemia is higher, there may be a difference in prognosis. The cut-off value for hyperphosphatemia may be better to reconsider in the view of Japanese aging population demographics.

This study has some limitations. First, the sample size could be small, as it was a single-center study. Although muscle mass is a very strong predictor of survival, in the present study there was no significant difference in muscle mass between PEW and non-PEW group. In addition, other studies have stated that the definition of PEW should be adjusted and considered based on BMI <18.5 kg/m2, especially in Japanese [23], but we didn't confirm in the present. These may be due to the small group size in the PEW group. Second, the effects of confounders cannot be excluded. Although age, gender, and diabetes status were not markedly different between the PEW and non-PEW groups or the hyperphosphatemia and non-hyperphosphatemia groups in this study, several studies have reported that these factors affect PEW or serum phosphorus levels [6,13,24]. Thus, multicenter studies with large sample size are warranted to support the validity of the present study and examine the significance of the contribution of the different parameters.

In conclusion, this study demonstrates that PEW affects prognosis more than hyperphosphatemia. The normalization of serum phosphorus level in the protein intake restriction could prevent secondary hyperparathyroidism and vascular calcification while restricting the protein intake poses a risk of malnutrition. In fact, early death occurred in patients with PEW in this study. Perhaps, patients with PEW should prioritize improving their nutritional status rather than controlling the serum phosphorus level.

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## Author's contributions

Conception and design of study: Eiji Ishikawa, Yasuhiro Hamada.

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Analysis and/or interpretation of data: Arisa Inoue, Eiji Ishikawa, and Yasuhiro Hamada.

Drafting the manuscript: Arisa Inoue, Yasuhiro Hamada.

Revising the manuscript critically for important intellectual content:

Approval of the version of the manuscript to be published: All authors.

## Declaration of Competing Interest

All authors declare no conflict of interest.

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