

## Low Prevalence of Protein Energy Wasting in Advanced Chronic Kidney Disease Patients Managed with a Nutritional Monitoring Program

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### Abstract

**Objectives:** To analyze the prevalence of Protein Energy Wasting (PEW) in Advanced Chronic Kidney Patients (ACKD) using monitoring tools normally used in the multidisciplinary CKD Unit. To assess the differences in nutritional parameters, body composition and muscle strength between patients with and without PEW.

**Design and Method:** Retrospective cross sectional study of patients from the ACKD Unit. The study included outpatient consultations offering specialized care for ACKD in the multidisciplinary hospital unit. We performed an initial nutritional assessment with screening and a complete baseline assessment followed by screening at each consultation (minimum every 3 months) and complete assessment every 6 months or if malnutrition appeared in the screening of risk. We performed screening and complete evaluation with biochemical parameters, body composition assessed by vectorial-bioimpedance and anthropometry, and hand grip strength measurement. PEW was diagnosed according to international society of renal nutrition and metabolism (ISRNM) criteria.

**Results:** We found a PEW prevalence of 9.1% (29/320 patients) without significant differences between men and women. The mean age of the patients with PEW was higher than that of non-PEW patients ( $74.58 \pm 12.84$  vs  $70.54 \pm 12.37$ ), although the difference was not statistically significant.

We observed significant differences in biochemical parameters, vectorial bioimpedance and anthropometric values, and hand grip strength between patients with and without PEW. A multivariate regression analysis showed that age, transferrin, % fat-free-mass, % total body water and phase-angle were predictive factors for PEW. Of them, phase angle was the best predictive factor.

**Conclusions:** The use of nutritional status monitoring protocols results in low prevalence of PEW and allows its early detection, thereby favoring the reversion of this condition with the appropriate intervention. An adequate nutritional status monitoring is a priority for the integral care of patients at ACKD Units.

**Keywords:** Advanced Chronic Kidney Disease Unit (ACKD); Protein Energy Wasting (PEW); Malnutrition; Inflammation

### Introduction

Chronic kidney disease (CKD) has been recognized as a global health problem that associates with cardiovascular risk. The prevalence of malnutrition in patients with chronic kidney disease

(CKD) is high. This condition is related to modifiable factors such as caloric-protein intake, reversible comorbidities associated or not with CKD, inflammatory status, and socioeconomic level, as well as to non-modifiable factors such as retention of uremic toxins due to CKD, age, and gender [1,2].

In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) described a syndrome in hemodialysis (HD) patients called Protein Energy Wasting (PEW). Criteria defining this syndrome encompass alterations that appear in renal patients due to a combination of toxin retention, endocrine metabolic disorders and low intakes, which are interrelated with inflammatory processes causing a syndrome characterized by wasting losses of the lean body mass and fat body mass compartments that increase mortality [3-6].

Diagnosis criteria are divided into four categories (biochemical parameters, body composition, muscle mass, and protein and energy intake). The ISRNM proposed that PEW could be diagnosed when the following criteria are met in three out of the four proposed categories: low levels of biochemical indicators (i.e., albumin, transthyretin or cholesterol), decreased body mass (i.e., body mass index, unintentional weight loss and body fat percentage), reduced muscle mass (i.e., muscle wasting or sarcopenia and reduced mid-arm muscle circumference), and unintentional low dietary intake (i.e., energy and protein intake). These criteria must be sustained for a minimum time to be considered for PEW diagnosis [3].

Preventing PEW is one of the most pressing objectives in the management of advanced CKD patients. Accordingly, an adequate caloric intake is important in CKD because it contributes to limit excess protein intake, thereby avoiding PEW development [7].

A PEW prevalence of 28-80% has been reported in HD patients [8-13].

Although initially described in HD patients, PEW has been later reported in non-dialysis advanced CKD (ACKD) patients. In these patients PEW prevalence increases with CKD progression, showing the highest values in stage 5 [11]. Several studies have reported that the prevalence is less than 2% in stages 1-2 [9,10], 11-46% in stages 3-5 [10-13]; the last meta-analysis described 28-54% prevalence in 16434 HD patients and 11-54% in stages 3-5 [11-19].

PEW diagnosis is dependent of a wide variety of parameters assessed by different tools. Cut-off points to establish normality ranges for these parameters may vary with ethnicity, sex and environmental factors of the study population, thereby determining the great variability of PEW prevalence values across different studies, especially in HD patients (where more studies have been published), but also in peritoneal dialysis or ACKD [18,19].

An adequate monitoring of the nutritional status in patients with CKD, mainly in non-dialysis patients in stages 3b, 4 and 5, has been reported to reduce PEW rates and its associated cardiovascular mortality [11].

The aim of this study was to analyze the prevalence of PEW in ACKD patients undergoing nutritional assessment with the monitoring program normally used in our multidisciplinary CKD Unit. The secondary aim was to establish the relationship of PEW with the nutritional parameters, body composition, and muscle strength used for nutritional assessment.

## Materials and Methods

### Study design and population

This was a retrospective cross-sectional study carried out with anonymous data collected from outpatients of the Advanced Chronic Kidney Disease Unit in Madrid who underwent a nutritional monitoring program. The study included outpatient consultations offering specialized care for ACKD in the multidisciplinary hospital unit. The inclusion criteria were: patients older than 18 years, CKD stages 3b, 4 and 5 without dialysis, without cognitive impairment, who had at least two outpatient consultations with a complete nutritional assessment (6 months) and had all the parameters collected. Exclusion criteria: patients who refused the full assessment or those who could not make any of the routine determinations included in the study.

### Nutritional monitoring program

- The ACKD multidisciplinary Unit performs a nutritional monitoring program with initial screening and a complete baseline assessment, screening at each consultation (minimum every 3 months), and a complete assessment every 6 months or if malnutrition appears in the screening of risk (Figure 1).
- The assessment frequency may increase if the Malnutrition Screening Tool (MST) (screening test) detects malnutrition and/or if the patient requires hospital admission.
- According to the assessment, dietary advice was provided as well as nutritional intervention if required.

PEW was diagnosed in ACKD patients using ISRNM criteria. To analyze difference in nutritional parameters, body composition

**Figure 1:** Algorithm of nutritional assessment in the ACKD Unit.

Malnutrition Screening Tool (MST), C-reactive protein (CRP), Subjective global assessment of nutritional status (SGA), Malnutrition-Inflammation Score (MIS), Protein Energy Wasting (PEW), Bioelectrical impedance analysis (BIA).

and muscle strength associated with PEW, patients were classified in two groups: Group 1 (G1), PEW patients, and group 2 (G2), non-PEW patients.

The following parameters were collected:

- **General parameters:** Age, gender, time in the ACKD Unit, diabetes, weight, height and comorbidities
- **Laboratory parameters:** Proteins (albumin, transferrin, prealbumin), C-reactive protein (CRP) as an inflammation parameter, total lymphocytes, hemoglobin (Hb), cholesterol, creatinine.
- Body composition assessed by using Akhern BIA 101 mono-frequency vector bioimpedance: phase angle, exchangeable Na/K, cell mass, total body water, intracellular water, extracellular water, lean mass, fat mass, muscle mass, cell mass index and body mass index (BMI).
- **Anthropometric measurements:** Waist circumference and brachial circumference (brachial circumference) measured with inextensible measuring tape “Cescorf”; tricipital skin fold (tricipital fold) measured with a “Holtain” Caliper, and muscle mass circumference (arm muscle circumference) determined with the formula  $MAC = \text{brachial circumference} - (3,1416 \times \text{tricipital skin fold cm})$
- Muscle strength measured with hand grip strength (dynamometer) (baseline model 12-0240).

Parameters were collected at each nutritional assessment. PEW diagnosis and variables used for statistical analysis were those collected at the second assessment.

### Statistical analysis

Data were collected in an Excel database specifically created for this study.

Quantitative variables of are represented as mean and standard deviation, Quantitative variables were compared with the Student’s test or non-parametric tests as appropriate. Categorical variables were compared using the chi-square test or Fisher’s exact test. We performed also the univariate regression analysis to establish the association of multiple biochemical nutritional and anthropometric parameters and multivariate analysis to choice the best model adjusted.

All statistical analyses were carried out with the SPSS 23 statistical program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

### Results

A total of 320 patients of the multidisciplinary ACKD Unit were included in the study. Mean age was  $70.90 \pm 12.45$  years, 214 (66.9%) patients were men and 106 (33.1%) were women. Twenty-seven (8.4%) patients were in stage G3b, 181 (56.6%) in G4, and 112 (35%) in G5. The mean CKD-EPI was  $18.58 \pm 7.64$  ml/min/1.73m<sup>2</sup>.

Prevalence of PEW was 9.1% (29/320 patients), without significant difference between men and women. Data on demographic and biochemical parameters of patients with and without PEW are shown in table 1.

Mean age was higher in patients with PEW compared with non-PEW patients ( $74.58 \pm 12.84$  years vs  $70.54 \pm 12.37$ ), although this difference was not statistically significant. While difference of mean age was not observed between these groups in men, women showed statistically significant differences ( $p = 0.041$ ).

The values of biochemical parameters and body composition in patients with PEW were striking, as some of them were close to the low limit of normality. These results suggested that the altered parameters could be reversed if they were diagnosed and intervened on time.

Parameter	With PEW (G1) (n = 29)	Without PEW (G2) (n = 296)	P
Age (years)	74.58 ± 12,84	70.52 ± 12.37	ns
Male	71.27 ± 14,23	70.44 ± 11.22	ns
Female	80.00 ± 8.08	70.74 ± 14.52	0.041
Gender			
Male	18 (62%)	196 (67.3%)	ns
Female	11 (38%)	95 (32.7%)	
nPNA (gr/kg/day)	0.73 ± 0.21	0.93 ± 0.26	0.003
Albumin (gr/dl)	3.77 ± 0.67	4.20 ± 0.41	0.002
CRP	1.17 ± 2.05	0.68 ± 1.21	0.06
Transferrin (mg/dl)	201,6 ± 48.61	224.76 ± 40.10	0.017
Hemoglobin (gr/l)	11.30 ± 1.53	11.96 ± 1.48	0.023

**Table 1:** Sociodemographic and biochemical parameters in ACKD patients according to PEW.

Categorical variables are expressed as number (%) and quantitative variables as mean ± standard deviation. Differences were analyzed by student t-test for quantitative variables and by Chi square test for categorical variables, p ≤ 0.05 was considered statistically significant.

Abbreviations. CRP: C-reactive Protein; nPNA: Normalized Nitrogen Protein Appearance; ns: Not Significant; PEW: Protein Energy Wasting.

Table 2 shows mean values of body composition parameters of patients with PEW and non-PEW patients. These data showed significant differences in phase angle, exchangeable Na/K, % cell mass, % total body water and, as expected, intracellular water as an indirect indicator of muscle mass. Likewise, patients with PEW presented lower mean triceps fold, as a measure of subcutaneous body fat, body surface area and waist circumference.

Parameter	With PEW (G1)	Without PEW (G2)	P
Phase Angle	3.43 ± 1.23	4.21 ± 1.15	0.001
Exchangeable Na/K	1.85 ± 0.67	1.39 ± 0.46	0.001
%Body cell mass	33.27 ± 10.33	39.07 ± 9.23	0.002

% Total Body Water	57.68 ± 7.86	53.23 ± 6.88	0.001	
%Intracellular Body Water	38.42 ± 10.38	43.82 ± 8.12	0.001	
%Fat Mass	25.63 ± 11.24	32.21 ± 9.17	0.005	
%Fat Free Mass	74.36 ± 11.24	67.75 ± 9.31	0.001	
BMI	24.80 ± 4.89	27.64 ± 4.99	0.004	
Body Cell Mass Index	5.91 ± 2.77	7.02 ± 2.11	0.009	
Brachial Circumference	26.24 ± 4.79	27.64 ± 4.40	0.001	
Tricipital Skin Fold	15.12 ± 0.86	18.52 ± 9.41	0.072	
Muscle Mass Circumference	25.97 ± 4.39	28.38 ± 4.04	0.004	
Waist Circumference	90.05 ± 22.16	99.68 ± 14.93	0.020	
Body Surface Area	1.74 ± 0.21	1.83 ± 0.22	0.038	
HGS Right (kg)	Overall	20.96 ± 11.24	25.22 ± 10.46	0.039
	Male	23.72 ± 12.21	29.21 ± 9.82	ns
	Female	16.45 ± 8.01	16.98 ± 5.99	
HGS Left (kg)	Overall	20.13 ± 8.70	23.14 ± 10.17	ns
	Male	21.83 ± 9.70	26.89 ± 9.90	ns
	Female	17.36 ± 6.20	15.53 ± 5.28	

**Table 2:** Body composition and muscle strength parameters in ACKD patients according to PEW.

All variables are expressed as mean ± standard deviation. Differences were analyzed by student t test, p ≤ 0.05 was considered statistically significant.

Abbreviations. BMI: Body Mass Index; HGS: Hand Grip Strength; ns: Not Significant; PEW: Protein Energy Wasting.

Phase angle values were further grouped into quartiles with upper limits of Q1:3.30, Q2: 4.1, Q3:4.9, Q4:5.7. Percentages of patients with PEW (G1) compared to those without PEW (G2) in the different quartiles were: 55.2% (16 patients) vs 23.7% (67 patients) in Q1, 17.2% (5) vs 26.8% (7) in Q2, 17.2% (5) vs 23% (67) in Q3, and 10% (3) vs 26.5% (77) in Q4, p = 0.003. These results showed that phase angle values in PEW patients were mainly found in Q1.

Muscle strength measured by right hand grip strength was lower in patients with PEW compared to non-PEW patients (20.96 ± 11.24 Kg vs 25.22 ± 10.46 Kg, p = 0.039). While this parameter was also lower in male patients, it did not show difference in females patients (table 2, cut-off point according to the European sarcopenia group EWGSOP 2019: 27 kg in men and 16 kg in women).

We carried out a univariate regression model to assess the effect of the different parameters on the appearance of PEW (Table 3). Most of the parameters analyzed were associated with PEW.

Variable	OR (95% CI)	p
Age	0.970(0.936 - 1.006)	0.097
Phase Angle	1.993 (1.329 - 2.988)	0.001
Exchangeable Na/K	0.291 (0.159 - 0.533)	0.001
%Body Cell Mass	1.071 (1.025 - 1.120)	0.002
%Total Body Water	0.913 (0.864 - 0.966)	0.002
%Intracellular Body Water	1.079 (1.030 - 1.131)	0.001
%Fat Mass	1.077 (1.033 - 1.124)	0.001
%Fat Free Mass	0.929 (0.891 - 0.969)	0.001
Body Cell Mass Index	1.302 (1.063 - 1.595)	0.011
Brachial Circumference	1.157 (1.056 - 1.268)	0.002
Muscle Mass Circumference	1.157 (1.042 - 1.284)	0.006
Waist Circumference	1.030 (1.008 - 1.052)	0.006
Body Surface Area	6.179 (1.061 - 35.972)	0.043
Hemoglobin	1.376 (1.055 - 1.796)	0.019
Transferrin	1.010 (1.002 - 1.018)	0.017
Right Hand Grip Strength	1.042 (1.002 - 1.084)	0.039

**Table 3:** Univariate regression analysis of the association between different nutrition and anthropometric parameters and PEW. Analysis was carried out by...test. p ≤ 0.05 was considered statistically significant.

Abbreviations. CI: Confidence Interval; OR: Odds Ratio.

The multivariate regression analysis showed that age, transferrin, % fat free mass, %total body water and phase angle were predictive factors for PEW; of these parameters, phase angle showed the highest predictive capacity (Figure 2).

**Figure 1:** Multivariate regression analysis of factors associated with PEW. Abbreviations. FFM: Fat Free Mass; CI: Confidence Interval; OR: Odds Ratio; TBW: Total Body Water; PA: Phase Angle.

### Discussion

The incidence of PEW in CKD patients described in the literature is high, although ranges reported vary considerably among different studies [8-11].

In 1983, the World Health Organization adopted the term “wasting” to refer to an involuntary loss of more than 10% of patient’s basal weight in the absence of opportunistic infection, cancer or chronic diarrhea [11,22].

Wasting is often present in CKD in response to anorexia-induced insufficient energy and protein intake in addition to other alterations in which inflammation commonly appears.

Cachexia is considered by the Society on Sarcopenia, Cachexia and Wasting Disorders as a complex syndrome associated with underlying illness and characterized by loss of muscle mass, with or without loss of fat mass [22].

In 2008, the IRSNM proposed a specific classification of uremia induced wasting disorders (Protein Energy Wasting) in which cachexia was the most severe stage [5,21,22].

PEW is considered as a state of nutritional and metabolic disorder in patients with CKD characterized by simultaneous loss of systemic body protein and energy stores, leading ultimately to loss of muscle and fat mass and cachexia [5,22].

The terms PEW and cachexia appeared in more than 300 and 200 CKD publications, respectively; cachexia is currently considered as a final stage of PEW in which reversibility is practically nil [11].

In CKD, factors such as malnutrition hypercatabolic stage, uremic toxins and increased release of serum inflammatory cytokines, caused in part by uremic toxin stimulation, may contribute to PEW pathogenesis [23-26].

The PEW syndrome was originally described in hemodialysis patients but has subsequently been characterized in CKD patients without dialysis; in addition, the prevalence of PEW has been shown to increase as CKD progresses [11].

The difference of PEW prevalence ranges among different studies, likely due to differences in the cut-off points used to establish normality values for the parameters within the PEW diagnosis criteria, which may vary according to factors such as ethnicity and geographical location, among others. Therefore, cut-off choice is crucial for PEW prevalence assessment. In this sense, muscle mass and strength may vary according to the normality cut-off points chosen. In the present study we chose for these parameters the 2019 criteria of the European Working Group on Sarcopenia [27].

Frailty and sarcopenia closely correlate with PEW, muscle wasting and cachexia. Prevention and treatment of PEW should offer individualized and full care approaches to early risk factor detection and target associated comorbidities.

It is worth remarking that the prevention and early treatment of PEW can contribute to reverse this condition. Therefore, using adequate PEW diagnosis criteria and nutritional status monitoring using different scoring tools is important for its management [11].

Our results showed that combining nutritional parameters, close assessment of body composition and muscular strength by hand grip strength can contribute to a complete evaluation of the status of these patients. In addition, Malnutrition Inflammation Score (MIS phase angle and hand grip strength have been consid-

ered as factors associated to increase in morbidity and mortality. Therefore, taken together, all these tools could help to better assess PEW beyond ISRN criteria [4].

PEW is closely associated with morbi-mortality in ACKD patients, especially in those in G3b, G4 and G5 CKD stages [7,11]. For this reason, we studied our patients in these advanced CKD stages. However, despite the mean CKD-EPI of our patients was  $18.58 \pm 7.64$  ml/min/1.73m<sup>2</sup> and more than 50% of them were in G4 stage, PEW prevalence was low.

Old age and advanced disease stages are factors that predispose to malnutrition. In our study population mean age was high and most patients were in G4 and G5 stages. Therefore, high prevalence could be expected. However, the PEW prevalence found in patients of our ACKD Unit was 9,1%, which was lower than the range (11-46%) previously reported for CKD 3-5 stages [7,11].

In this study we have demonstrated that adequate monitoring of nutritional status could help to prevent the appearance or decrease the prevalence of PEW, even in elderly patients with advanced CKD.

We observed significant differences in biochemical and body composition parameters between patients with PEW and non-PEW patients. Mean albumin, transferrin and Hb values were significantly lower in patients with PEW, although transferrin and Hb are not included as parameters within the PEW criteria. Although the patients studied did not have a high degree of inflammation in any group, CRP values were higher in the group with PEW, but the difference was at the limit of significance.

As expected, body composition parameters, assessed by vector bioimpedance and anthropometry, were better in patients without PEW. As previously described in the literature, these patients showed better phase angle and better intracellular water indicating better muscle mass as well as better muscle arm circumference. It is worth remarking that considering quartile distribution of phase angle in our patients, more than 50% of patients with PEW showed phase angles in Q1, in agreement with results reported in the literature [28,31].

Hand grip strength has proven to be a good tool to assess the risk of malnutrition and inflammation in HD and a good predictive factor for survival [32,33]. Our univariate analysis showed that this

parameter was associated with PEW. In addition, right hand dynamometry was significantly better in patients without PEW; while this parameter was also better in male patients without PEW, it did not show statistically significant differences in female patients.

The univariate regression analysis showed the association of multiple biochemical nutritional and anthropometric parameters with PEW, such as phase angle, exchangeable Na/K, % body cell mass, % total body water, % intracellular body water, % fat mass, % fat free mass, body cell mass index, brachial circumference, muscle arm muscle circumference, waist circumference, body surface area, hemoglobin, transferrin and right hand grip strength. In the multivariate analysis, age, total body water, lean mass and phase angle remained significantly associated with PEW. Of these variables, phase angle showed the highest predictive value.

## Conclusion

- The use of nutritional status monitoring protocols results in low prevalence of PEW and allows its early detection, thereby favoring the reversion of this condition with the appropriate intervention.
- An adequate nutritional status monitoring is a priority for the integral care of patients at ACKD Units.

## Practical Application

Implementation of a good Nutritional Monitoring Program for advanced chronic kidney disease patients can help in the adequate assessment of their nutritional status. This favors earlier diagnosis and prevention of malnutrition reducing the appearance of the PEW syndrome.

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## Authors' Contributions

Guillermina Barril, Angel Nogueira y Graciela Alvarez wrote the main manuscript. Almudena Nuñez, Carmen Sanchez y Paula Romasco help in the clinical practice. All authors have read and approved this information before submission.

## Funding

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## Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This research was approved by the Research Ethics Committee of Hospital Universitario de la Princesa (No. 4342) and was conducted according to the ethical principles contained within the Declaration of Helsinki.

Informed consent was not required because this is a retrospective study in which the data was retrieved from patients' medical histories from regular clinical practice.

## Consent for Publication

Not applicable.

## Competing Interests

Guillermina Barril has received honorarium for conference and course from: Abbott, Nutricia, Nestlé, Rubió. The other authors declare that they have no competing interests.

## Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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