



# Association of serum IL-18 with protein-energy wasting in end-stage renal disease patients on haemodialysis

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## Abstract

**Purpose** Protein-energy wasting (PEW) is highly prevalent in end-stage renal disease (ESRD) patients with inflammation who are on haemodialysis treatment. Interleukin-18 (IL-18) is an important pro-inflammatory cytokine that is significantly elevated in ESRD patients. However, the relationship between PEW and IL-18 is unclear. We therefore performed a cross-sectional study on 100 ESRD patients undergoing haemodialysis to clarify this.

**Methods** PEW was defined according to the diagnostic criteria of the International Society of Renal Nutrition and Metabolism. Inflammation was assessed based on the serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-18. We analysed the association between PEW and IL-18 by using logistic analysis and linear regression after adjustment for basic characteristics, comorbidities and laboratory findings.

**Results** Among the 100 haemodialysis patients who were recruited, 56 had PEW. Even though there was no difference between the PEW group and non-PEW group with regard to disease causes, age, gender, cholesterol, ferritin, and haemoglobin, the levels of inflammation indicators such as CRP, IL-6, TNF- $\alpha$  and IL-1 $\beta$  were significantly higher in the PEW group. Moreover, IL-18 was found to contribute to PEW, but was negatively correlated with pre-albumin after adjustment for possible confounding factors.

**Conclusions** Thus, the findings indicate that IL-18 is associated with PEW in ESRD patients on haemodialysis, which suggests that IL-18 may be involved in the pathogenesis of PEW in this setting.

**Keywords** IL-18 · Protein-energy wasting · Pre-albumin

## Introduction

Protein-energy wasting (PEW) is common in patients with chronic kidney disease (CKD), and is associated with adverse clinical outcomes, especially in patients who are on maintenance dialysis treatment. It is characterized by decrease in the body stores of protein and energy fuels, including low serum albumin and pre-albumin concentrations, reduced body mass index (BMI), and insufficient

dietary protein intake [1]. There has been an increase in the prevalence of PEW, which has been associated with decline in renal function [2]. Thus, there is a need for investigations on the prevention and treatment of PEW in CKD patients, especially end-stage renal disease (ESRD) patients.

Inflammation is a common feature of uraemic conditions. In fact, serum levels of pro-inflammatory cytokines are often several times higher in ESRD patients than in healthy controls [3, 4]. Persistent inflammation has also been proved to be strongly associated with PEW; moreover, the presence of chronic inflammation may contribute not only to anorexia, but also to an increase in nutritional needs [5, 6]. Interleukin 18 (IL-18), an important pro-inflammatory cytokine, is believed to play a vital role in a variety of conditions and diseases including CKD [7, 8]. Its mature secreted form is generated from pro-IL-18, which is cleaved after activation of the nucleotide-binding domain and leucine-rich repeat containing PYD-3 (NLRP3) inflammasome and subsequent recruitment of caspase-1 [9, 10].

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According to recent studies, mice with elevated IL-18 levels induced by an activating gene mutation are prone to loss of adipose tissue and fatal cachexia even when they are fed a high-fat diet [11]. Further, there is some indication that IL-18 may also contribute to muscle wasting in chronic obstructive pulmonary disease patients [12]. Hence, IL-18 seems to play a pathogenetic role in inflammatory and degenerative conditions [13]. However, up to now, the pro-inflammatory cytokine IL-18 has not been studied in PEW patients who are on maintenance haemodialysis. Therefore, in the present study, we aimed to determine the association between PEW and IL-18 in ESRD patients undergoing haemodialysis.

## Methods

### Study design and materials

This cross-sectional study population comprised 126 ESRD patients who were undergoing haemodialysis at the Shanghai 9th Hospital Hemodialysis Center. Patients with a history of autoimmune and inflammatory diseases, heart failure, cancer, chronic liver disease, acute infection and thyroid, parathyroid, adrenal insufficiencies were excluded. Further, only patients who had been under haemodialysis treatment for more than 1 year and were clinically stable and free of obvious oedema were included. After these exclusion and inclusion criteria were applied, the final number of patients was 100 (59 men and 41 women). Data on the basic characteristics, primary diagnosis, comorbidities and laboratory findings of the patients were obtained from their latest medical records. The dietary intake of each patient over three consecutive days, including 2 weekdays and 1 weekend, was recorded to determine the dietary protein intake (DPI) of each patient. Blood samples were drawn before haemodialysis and sent to a central laboratory for measurement. IL-18 was measured using human IL-18 ELISA kits according to the manufacturer's instructions (Raybio, Norcross, GA). The sensitivity level of the kit was 1 pg/ml. IL-6 and TNF- $\alpha$  were measured using the human IL-6 ELISA kit (sensitivity, <0.8 pg/ml) and the human TNF- $\alpha$  ELISA kit (sensitivity, 14 pg/ml), respectively, purchased from Abcam (Cambridge, MA). All patients in this study provided their written informed consent, and had the right to withdraw at any stage. The study was approved by the ethics committee of Ninth Peoples Hospital at Shanghai Jiaotong University.

### Indicators for diagnosis of PEW

The indicators for diagnosis of PEW in this study were in accordance with the criteria of the International Society of Renal Nutrition and Metabolism [14]. The indicators were as follows: serum albumin level <38 g/L or pre-albumin level <0.3 g/L,

BMI <23, >10% reduction in mid-arm muscle circumference in relation to the 50th percentile of the reference population, and unintentional DPI of <0.8 g/kg per day. Patients who had three or more of these indicators were diagnosed with PEW.

### Estimation of body composition

Body composition was estimated using bioelectrical impedance analysis with a medical body composition analyzer (mBCA; Seca GmbH, Hamburg, Germany). The measurements were performed according to the manufacturer's directions. The mBCA takes measurements at 19 different frequencies ranging from 1 to 1000 kHz, and provides a measure of the fat tissue index (FTI), skeletal muscle mass (SMM), total body water (TBW), extracellular water (ECW) and phase angle. Further, skeletal muscle mass was normalized to the square of height and defined as skeletal muscle mass index (SMMI).

### Statistical analysis

The data are shown as the mean  $\pm$  standard deviation values or median and interquartile ranges, depending on their distribution. The Student's *t* test or Mann–Whitney *U* test was used as appropriate to analyse differences between groups, and the Fisher exact test was used for comparison of categorical data. The Spearman correlation coefficient was applied for correlation analysis of nonparametric data.

In logistic analysis of PEW, odds ratio (OR) and 95% confidence interval (CI) for every 1 pg/ml increase in IL-18 were determined; the higher IL-18 group was categorized based on the median IL-18 value, and the value of the lower IL-18 group was used as the reference. Model 1 was adjusted for age and gender. Model 2 was adjusted for model 1 variables, hypertension, diabetes and cardiovascular disease. Model 3 was adjusted for model 2 variables and laboratory findings (haemoglobin, ferritin, C-reactive protein and PTH levels). In linear regression analysis of pre-albumin, the data obtained were adjusted for the variables identified as significant in logistic regression analysis, and the correlation between IL-18 (per 1 pg/ml increase) and pre-albumin level was determined. The correlation coefficient  $\beta$  and 95% CI were calculated.

All statistical analyses were performed using SPSS Version 20.0 (IBM, New York, USA). Statistical significance was defined by *p* values <0.05.

## Results

### Patient characteristics

After the diagnostic criteria for PEW were applied, two groups emerged: PEW patients (*n* = 56, 30 males and 26

females; age,  $60.59 \pm 12.42$  years) and non-PEW patients ( $n=44$ , 29 males and 15 females; age,  $55.75 \pm 13.99$  years).

As shown in Table 1, the causes of ESRD in the patients included hypertensive nephropathy, chronic

glomerulonephritis, diabetic nephropathy, chronic pyelonephritis, obstructive nephropathy, polycystic renal disease, and IgA nephropathy. In some patients, the aetiology was unclear. There was no statistically significant difference between the PEW group and non-PEW group with regard to causes of ESRD ( $p > 0.05$ ). The demographic and clinical characteristics of the PEW and non-PEW group are shown in Table 2. In our study population, 84% of the patients had hypertension; 25%, diabetes; and 15%, cardiovascular disease. The prevalence of PEW was 56%. Although no significant difference was found between the PEW group and non-PEW group with regard to age, gender, LDL, HDL, cholesterol, ferritin and uric acid, the level of inflammatory indicators, such as CRP, IL-6, TNF- $\alpha$  and IL-18, was significantly higher in the PEW group than in the non-PEW group. The distribution of serum IL-18 levels is shown in Fig. 1. Moreover, the total body water and extracellular water were obviously higher in the PEW group than in the non-PEW group. Phase angle, which reflected the nutritional

**Table 1** Primary diseases of the patients

Primary diseases	PEW group	Non-PEW group
Hypertensive nephropathy	15	12
Chronic glomerulonephritis	17	16
Diabetic nephropathy	7	4
Chronic pyelonephritis	5	3
Obstructive nephropathy	1	1
Polycystic renal disease	3	2
IgA nephropathy	1	2
Aetiology unknown	7	4

PEW protein-energy wasting

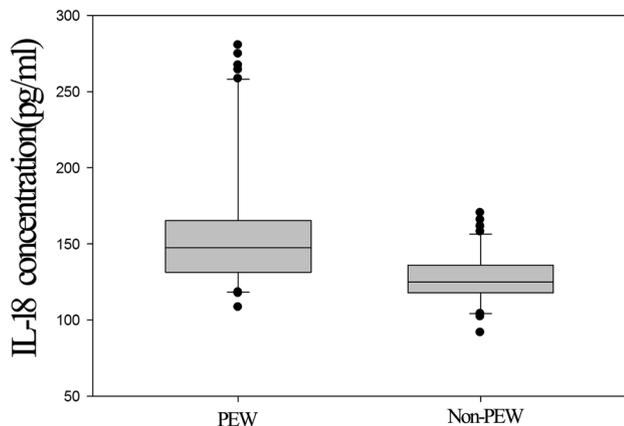
**Table 2** Characteristics of participants, divided by PEW or non-PEW

Clinical and biochemical values	PEW group	Non-PEW group	<i>p</i> value
Age (years)	$60.59 \pm 12.42$	$55.75 \pm 13.99$	NS
Gender (male)	53.57% (30/56)	65.91% (29/44)	NS
BMI ( $\text{kg}/\text{m}^2$ )	$22.43 \pm 2.69$	$24.25 \pm 3.38$	0.003
Hypertension	83.93% (47/56)	86.05% (37/43)	NS
Diabetes	26.79% (15/56)	22.72% (10/44)	NS
CVD	16.07% (9/56)	13.64% (6/44)	NS
Triglyceride (mmol/L)	1.99 (0.55, 2.83)	2.18 (1.51, 3.57)	0.011
Cholesterol (mmol/L)	3.52 (3.12, 4.24)	3.53 (3.01, 4.17)	NS
LDL (mmol/L)	$2.03 \pm 0.44$	$1.97 \pm 0.48$	NS
HDL (mmol/L)	$0.95 \pm 0.069$	$0.86 \pm 0.061$	NS
Albumin (g/L)	$36.69 \pm 1.84$	$38.84 \pm 1.18$	<0.001
Pre-albumin	$0.27 \pm 0.061$	$0.34 \pm 0.091$	<0.001
Ferritin (ng/ml)	201.59 (45.67, 393.22)	230.31 (47.01, 437.84)	NS
Haemoglobin (g/L)	$98.82 \pm 19.49$	$104.45 \pm 14.35$	NS
PTH	301.75 (154.23, 657.5)	226.05 (79.97, 488.0)	0.04
CRP (mg/L)	2.60 (1.44, 4.50)	1.71 (0.53, 3.08)	0.005
IL-6 (pg/ml)	4.00 (2.51, 6.52)	3.01 (2.00, 4.34)	0.015
TNF- $\alpha$ (pg/ml)	18.95 (16.80, 22.90)	18.30 (15.20, 20.00)	0.05
IL-18 (pg/ml)	147.56(131.34, 165.1)	123.82 (117.75, 136.1)	<0.001
DPI (g/kg/day)	$0.68 \pm 0.15$	$1.14 \pm 0.23$	<0.001
FTI ( $\text{kg}/\text{m}^2$ )	$6.24 \pm 3.39$	$6.64 \pm 2.42$	NS
SMMI ( $\text{kg}/\text{m}^2$ )	$6.89 \pm 1.34$	$7.31 \pm 1.67$	NS
Extracellular water (%)	$56.32 \pm 6.43$	$51.92 \pm 5.74$	0.004
Total body water (%)	$26.20 \pm 2.71$	$24.11 \pm 2.18$	0.001
Phase angle ( $^\circ$ )	$4.01 \pm 0.65$	$4.38 \pm 0.64$	0.015

Mean  $\pm$  SD presented for variables according with normal distribution while median (IQR) presented for variables with abnormal distribution. Values were missing for ferritin ( $n=1$ ), PTH ( $n=4$ ), CRP ( $n=4$ ), IL-6 ( $n=3$ ) and TNF- $\alpha$  ( $n=3$ )

BMI body mass index, CVD cardiovascular disease, LDL low density lipoprotein, HDL high density lipoprotein, CRP C-reactive protein, DPI dietary protein intake, FTI fat tissue index, SMMI skeletal muscle mass index

status in the patients, was significantly lower in the PEW patients than in the non-PEW patients, as shown in Table 2.



**Fig. 1** Distribution of IL-18 in PEW group and non-PEW group. *PEW* protein-energy wasting

## IL-18 and PEW

The characteristics of the patients according to their IL-18 levels are shown in Table 3. Patients with higher serum levels of IL-18 tended to have lower BMI. Further, patients with higher IL-18 levels had lower levels of triglyceride, higher levels of inflammatory indicators, and a higher prevalence of PEW than patients with lower IL-18 levels. Phase angle seems to decrease slightly in patients with higher levels of IL-18 as compared to patients with lower levels of IL-18, but no significant difference was found between the two groups of patients. Multivariate logistic regression analysis showed that PEW was associated with higher IL-18 by each 1 pg/ml increase in the IL-18 level in model 3 (OR, 1.047; 95% CI 1.020–1.074;  $p = 0.001$ ; Table 4). This association was strengthened by the results of IL-18 group analysis: the higher IL-18 group contributes to PEW compared with the lower group (model 1: OR = 5.63, 95% CI = 2.36–13.42; model 2:

**Table 3** Characteristics of participants, divided by serum IL-18 concentration

Clinical and biochemical values	IL-18 higher	IL-18 lower	$p$ value
Age (years)	59.76 ± 14.25	57.16 ± 12.26	NS
Gender (male)	62.0% (31/50)	56.0% (28/50)	NS
BMI (kg/m <sup>2</sup> )	22.15 ± 2.47	23.94 ± 2.89	0.001
Hypertension	86.0% (43/50)	82.0% (41/50)	NS
Diabetes	28.0% (14/50)	22.0% (11/50)	NS
CVD	18.0% (9/50)	12.0% (6/50)	NS
Triglyceride (mmol/L)	1.54 (1.13, 2.47)	2.24 (1.43, 3.58)	0.021
Cholesterol (mmol/L)	3.41 (3.07, 3.96)	3.91 (3.06, 4.49)	NS
LDL (mmol/L)	1.97 ± 0.34	2.04 ± 0.58	NS
HDL (mmol/L)	0.91 ± 0.053	0.91 ± 0.082	NS
Albumin (g/L)	37.43 ± 1.85	38.35 ± 1.96	0.015
Pre-albumin	0.28 ± 0.061	0.32 ± 0.069	0.003
Ferritin (ng/ml)	158.76 (47.32, 452.08)	334.38 (55.19, 437.59)	NS
Haemoglobin (g/L)	102.42 ± 17.52	100.18 ± 17.71	NS
PTH	278.2 (137.2638.35)	254.4 (84.18, 557.85)	NS
CRP (mg/L)	3.10 (1.29, 4.50)	2.09 (0.65, 2.77)	0.011
IL-6 (pg/ml)	4.00 (2.84, 5.14)	3.04 (2.00, 5.24)	0.048
TNF-α (pg/ml)	18.75 (15.48, 23.30)	18.70 (16.10, 20.00)	NS
IL-18 (pg/ml)	157.79 (147.01, 182.9)	121.08 (117.56, 128.5)	<0.001
DPI (g/kg/day)	0.72 (0.58, 0.86)	0.89 (0.77, 1.25)	0.02
FTI (kg/m <sup>2</sup> )	6.79 ± 3.71	6.07 ± 2.58	NS
SMMI (kg/m <sup>2</sup> )	7.13 ± 1.35	7.02 ± 1.64	NS
Extracellular water (%)	25.33 ± 2.61	25.24 ± 2.80	NS
Total body water (%)	54.67 ± 6.44	54.14 ± 6.61	NS
Phase angle (°)	4.11 ± 0.65	4.23 ± 0.70	NS
PEW	0.76	0.36	<0.001

Mean ± SD presented for variables according with normal distribution while median (IQR) presented for variables with abnormal distribution. Values were missing for ferritin ( $n = 1$ ), PTH ( $n = 4$ ), CRP ( $n = 4$ ), IL-6 ( $n = 3$ ) and TNF-α ( $n = 3$ )

*BMI* body mass index, *CVD* cardiovascular disease, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *CRP* C-reactive protein, *DPI* dietary protein intake

**Table 4** Adjusted odds ratio for PEW according to the IL-18 values in 100 hemodialysis patients

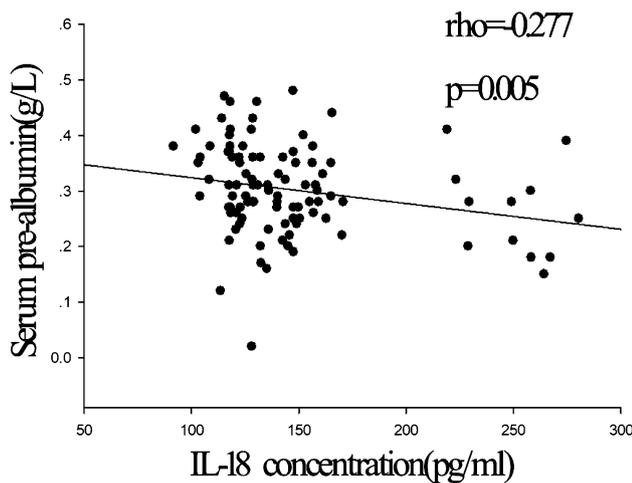
Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>		
OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	
Continuous: each 1 pg/ml increase in IL-18	1.048 (1.021–1.076)	<0.001	1.048 (1.021–1.076)	<0.001	1.047 (1.020–1.074)	0.001
Categorical: lower IL-8 group (reference), higher IL-18 group	5.63 (2.36–13.42)	<0.001	5.95 (2.45–14.45)	<0.001	6.50 (2.54–16.67)	<0.001

CI confidence interval, OR odds ratio

<sup>a</sup>Model 1 adjusted for age and gender

<sup>b</sup>Model 2 adjusted for model 1 variables, hypertension, diabetes and cardiovascular disease

<sup>c</sup>Model 3 adjusted for model 2 variables, haemoglobin, C-reactive protein, ferritin and PTH



**Fig. 2** Negative correlation between serum pre-albumin and IL-18

OR = 5.95, 95% CI = 2.45–14.45; model 3: OR = 6.50, 95% CI = 2.54–16.67; Table 4).

**IL-18 and PEW markers**

PEW markers mainly include albumin, prealbumin, BMI and dietary protein intake (DPI). As shown in Fig. 2, the pre-albumin level was negatively associated with the IL-18 level ( $\rho = -0.277$ ,  $p = 0.005$ ). Further, multiple linear regression analysis showed that after adjusting for confounding factors, IL-18 was negatively correlated with the pre-albumin level

(model 1: adjusted  $\beta = -0.24$ , 95% CI = -0.44 to -0.046; model 2: adjusted  $\beta = -0.24$ , 95% CI = -0.44 to -0.046; model 3: adjusted  $\beta = -0.22$ , 95% CI = -0.42 to -0.023; Table 5). With regard to the other PEW markers, the levels of albumin, BMI and DPI were lower in the patients with higher levels of IL-18 than in the patients with lower levels of IL-18 (Table 3). However, no significant linear relationship was found between IL-18 and these PEW markers.

**Discussion**

This is the first study that evaluates the association between PEW and serum IL-18 levels. We show that among ESRD patients undergoing haemodialysis, those who present with PEW have higher serum levels of the pro-inflammatory cytokine IL-18 than those who do not have PEW. Moreover, pre-albumin, a PEW indicator, is negatively correlated with the serum IL-18 levels. These findings indicate that elevated serum levels of IL-18 may contribute to the development of PEW in ESRD patients.

PEW is highly prevalent in ESRD patients, with an incidence of 30%–75% among patients on hemodialysis [15, 16]. The survival rate of PEW patients is significantly lower than that of non-PEW patients [17]. Several factors contribute to the development of PEW, including decreased daily nutrient intake, inadequate dialysis, metabolic derangements, inflammation and comorbid conditions. Inadequate dialysis may play a central role in the development of PEW and interact

**Table 5** Linear regression analysis of the association of IL-18 with pre-albumin

	Crude $\beta$ (95% CI)	<i>p</i> value	Adjusted $\beta$ (95% CI)	<i>p</i> value
Model 1 <sup>a</sup>	-0.47 (-0.84, -0.089)	0.016	-0.24 (-0.44, -0.046)	0.016
Model 2 <sup>b</sup>	-0.47 (-0.84, -0.089)	0.016	-0.24(-0.44, -0.046)	0.016
Model 3 <sup>c</sup>	-0.42 (-0.80, -0.045)	0.029	-0.22 (-0.42, -0.023)	0.029

CI confidence interval

<sup>a</sup>Model 1 adjusted for age and gender

<sup>b</sup>Model 2 adjusted for model 1 variables, hypertension, diabetes and cardiovascular disease

<sup>c</sup>Model 3 adjusted for model 2 variables, haemoglobin, C-reactive protein, ferritin and PTH

with other factors. Inadequate dialysis leads to metabolic acidosis, accumulation of uraemic toxins and persistent inflammation, which increase resting energy expenditure and cause hypermetabolism. Moreover, uraemic toxins and pro-inflammatory cytokines also act on the central nervous system to reduce appetite, and this results in a decrease in protein and energy intake as well as a decrease in anabolic activity. On the other hand, fluid overload due to inadequate dialysis also promotes release of pro-inflammatory cytokines. In our study, extracellular water and total body water contents were higher in PEW patients than in non-PEW patients; this also implies the importance of the adequacy of dialysis in PEW pathogenesis [6, 18].

Inflammation is normally a protective and physiological response to harmful stimuli, but typically, it tends to develop into an uncontrolled, maladaptive, and persistent process in ESRD patients receiving haemodialysis. Besides the complications and immune dysfunction associated with CKD, there are several factors related to haemodialysis procedures that promote inflammation, including membrane composition, dialysis adequacy, the purity of the dialysis solution and the type of vascular access [19, 20]. Different types of dialysis membranes lead to different degrees of inflammation, not only because of bio-incompatibility issues, but also due to the capacities of the membrane to filter medium- and large-sized molecules that may be key factors in the inflammatory process. According to previous reports, the dialysis membrane plays a significant role in T-lymphocyte apoptosis and monocyte preactivation via both complement-dependent and complement-independent pathways. The purity of dialysis solutions is another factor that influences preactivation of monocytes. Pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  are often overproduced by preactivated monocytes in haemodialysis patients. Studies have shown that the inflammation markers IL-6 and CRP are strongly associated with PEW [1, 21]. In agreement with these studies, our study demonstrates that higher serum levels of IL-6, TNF- $\alpha$  and CRP are found in patients with PEW. However, it remains unclear whether other pro-inflammatory cytokines are also involved in the pathophysiology of PEW. Activation of inflammasomes and subsequent release of pro-inflammatory cytokines such as IL-18 in response to tissue damage, which may lead to secondary tissue damage and organ dysfunction, have been demonstrated to be involved in many disease conditions. Elevated levels of IL-18 in plasma and skeletal muscle were reported in COPD patients, who were prone to develop muscle wasting [12]. Previous reports have also shown that elevated expression of IL-18 was detected in both the serum and skeletal muscle of CKD mice [22]. A recent report further showed that NLRP3 deficiency along with decreased expression of IL-18 in skeletal muscle ameliorated muscle wasting in old mice [23]. Therefore, in this study, we aimed to explore the relationship between

IL-18 and PEW in ESRD patients receiving maintenance haemodialysis.

IL-18, which is different from IL-6, is generated from an inactive 24-kDa precursor protein (pro-IL-18) that is processed by caspase-1 into its mature and biologically active form IL-18 [24]. IL-18 has central anorexigenic effects in certain diseases, in which high IL-18 levels are associated with loss of appetite. Several studies have shown that endogenous IL-18 suppresses appetite and feed efficiency via its effects on the IL-18 receptor. Further, mice that were partially or totally deficient in IL-18 were found to be hyperphagic in young adulthood and then become overweight [25–27]. A recent study further pointed out that IL-18 regulates feeding by acting on the bed nucleus of the stria terminalis [28]. Therefore, elevated levels of IL-18 probably result in downregulation of food intake and lead to insufficient nutrition intake. Phase angle has been used to assess nutritional status in ESRD patients undergoing haemodialysis. In our study, we found that phase angle was significantly lower in PEW patients than in non-PEW patients, which was consistent with a previous report [29]. The patients in the present study with higher levels of IL-18 showed a slight, but non-significant, decrease in phase angle. This may imply a potential relationship between IL-18 and nutritional status, which needs further investigation. Furthermore, IL-18 is believed to be involved in tissue destruction, and according to a previous report, IL-18 may have important regulatory roles in muscle physiology [12]. In this study, we found that PEW patients tend to have higher serum levels of IL-18 than non-PEW patients among ESRD patients undergoing haemodialysis. Patients with relatively high serum IL-18 had lower protein intake, but no linear relationship was found between serum IL-18 levels and DPI. Moreover, IL-18 was found to be negatively correlated with pre-albumin, which is an indicator of PEW. Pre-albumin is regarded as a better nutritional marker than albumin, with higher sensitivity due to its short half-life [30]. Its decrease is associated with the risk of death even in normoalbuminaemic patients [31]. Patients with higher levels of IL-18 also showed lower levels of serum albumin, but no linear relationship was found between them, possibly owing to its relatively longer half-life. On the other hand, IL-18 is involved in the development of metabolic syndrome, especially insulin resistance [32], which is likely to play a critical role in the pathogenesis of PEW through the insulin/IGF-1 intracellular signalling pathway [33]. Therefore, it is reasonable to deduce that IL-18 makes a greater contribution to PEW than pre-albumin. Thus, we demonstrate for the first time that IL-18 is associated with PEW in haemodialysis patients, which implies that IL-18 may be a potential inflammation marker in predicting PEW in ESRD patients.

Some limitations of our study should be considered. First, some important causes of PEW in haemodialysis patients,

such as vitamin D deficiency and metabolic acidosis, were not included in the current study. Second, the patient population was small. Third, the interaction between IL-18 and other pro-inflammation cytokines in PEW patients remains unclear.

## Conclusions

Our study shows that IL-18 is associated with PEW in ESRD patients undergoing haemodialysis. This finding sheds new light on the pathogenesis of PEW and presents a new target for evaluation in the treatment of PEW patients. A larger population-based research is necessary to further determine the reliability of IL-18 and its cut-off in haemodialysis patients.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individuals who participated in the study.

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