

# Nutritional Status in Adults with Predialysis Chronic Kidney Disease: KNOW-CKD Study

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Received: 22 September 2016  
Accepted: 14 November 2016

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**Funding:** This research was supported by grants 2011E3300300, 2012E3301100 and 2013E3301600 from Research of Korea Centers for Disease Control & Prevention; by the National Research Foundation of Korea, funded by the Ministry of Science, ICT & Future Planning (2015R1C1A1A01051769); by the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Science, ICT and future planning (2016R1A2B4007870); and by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (HI14C2084).

Adverse changes in nutrition are prevalent and are strong indicators of adverse outcomes in patients with chronic kidney disease (CKD). The International Society of Renal Nutrition and Metabolism (ISRNM) proposed a common nomenclature and diagnostic criteria to identify protein-energy wasting (PEW) in CKD patients. We examined the nutritional status in 1,834 adults with predialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD) study. As there was a need for further understanding of nutritional status and associated factors in CKD, we evaluated the prevalence and associated factors of PEW in adults with predialysis CKD. The prevalence of PEW was about 9.0% according to ISRNM criteria and tended to increase with advanced stage in predialysis CKD. Those who concurrently had PEW, inflammation, and CVD were a small proportion (0.4%). In multivariate logistic regression model, PEW was independently associated with estimated glomerular filtration rate (eGFR) (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.96–0.99), total CO<sub>2</sub> (OR, 0.93; 95% CI, 0.87–0.99), physical activity (OR, 0.43; 95% CI, 0.26–0.69), comorbid diabetes (OR, 1.68; 95% CI, 1.09–2.59), and high sensitivity C-reactive protein (hs-CRP) (OR, 1.03; 95% CI, 1.01–1.06). Our study suggests that PEW increases with advanced CKD stage. PEW is independently associated with renal function, low total CO<sub>2</sub>, low physical activity, comorbid diabetes, and increased hs-CRP in adults with predialysis CKD.

**Keywords:** Nutrition; Protein-Energy Wasting; Inflammation; Chronic Kidney Disease

## INTRODUCTION

Chronic kidney disease (CKD) is recognized as a global health problem (1). The health and economic burdens of CKD are high. Patients with CKD are at increased risk for cardiovascular disease (CVD) and end-stage renal failure. Adverse changes in nutrition are prevalent with decreasing renal function and are a strong indicator of adverse outcomes in patients with CKD (2).

Multiple mechanisms are involved in adverse nutritional changes in CKD patients. Poor food intake caused by uremia-induced anorexia alone does not explain adverse nutritional changes. There are additional contributing causes, such as persistent inflammation, acidosis, multiple hormonal disturbance, comorbidities, and physical inactivity (3). Many studies about nutritional status of CKD patients revealed that wasting and protein-energy abnormalities might be induced by inflammatory processes (2). Simple malnutrition refers to nutritional abnormalities induced by inadequate nutritional intake, whereas wasting caused by CKD refers to nutritional abnormalities that may be associated with inflammation and cannot be corrected solely by increasing the diet. The International Society of Renal Nutrition and Metabolism (ISRNM) (4) proposed a common nomenclature and diagnostic criteria for this adverse nutritional status in the context of CKD. Protein-energy wasting (PEW) was proposed to denote concurrent losses in protein and energy stores in CKD patients.

PEW is a strong indicator of adverse outcome and is associated with CVD. Persistent inflammatory processes in CKD could act as links between inflammation, PEW, and CVD. Several studies (5-8) have reported that strong interactions exist among inflam-

matory parameters, nutritional parameters, and CVD in CKD patients.

In this study, we examined the nutritional status of predialysis CKD in adults enrolled in the KoreaN cohort study for Outcome in patients with Chronic Kidney Disease (KNOW-CKD) study. As there was a need for further understanding of nutritional status and associated factors in CKD, we described nutritional status, inflammatory markers, CVD, and other clinical characteristics according to estimated glomerular filtration rate (eGFR) and PEW parameters. We also explored factors associated with PEW in adults with predialysis CKD.

## MATERIALS AND METHODS

### Study participants

The KNOW-CKD study is an ongoing multicenter prospective, observational study of adults with CKD in Korea. The study design was published previously (9), and is summarized here. Each participating center enrolled a baseline of 2,238 adults with CKD from 2011 to 2015. All enrolled participants were ethnic Korean patients between 20 and 75 years old with predialysis CKD stage 1 to 5, which was staged based on eGFR. Those who had a history of malignancy, liver cirrhosis, advanced heart failure, or who had a single kidney were excluded according to the KNOW-CKD protocol. We included a total of 1,834 participants in the analysis who underwent complete 24-hour urine chemistry, serum high sensitivity C-reactive protein (hs-CRP) concentration measurement, and baseline laboratory tests. All included patients also completed a health questionnaire

### PEW parameters and definition

Using data from the initial KNOW-CKD study, indicators for PEW were created based on the ISRNM diagnostic criteria (4). An ISRNM expert panel recommended four main categories for diagnosing PEW: biochemical parameter, low body mass, decreased muscle mass, and low protein intake. PEW parameters and diagnostic criteria in this study included the following: 1) Biochemical parameter: serum albumin < 3.8 g/dL; 2) Body mass: body mass index (BMI) < 23.0 kg/m<sup>2</sup>; 3) Muscle mass: 24-hour urine creatinine excretion (UCE) < the sex-specific lower quartile; and 4) Dietary intake: dietary protein intake (DPI) < 0.6 g/kg/day. Three or more of these indicators must be present for a diagnosis of PEW. Twenty-four-hour urine collection began after the bladder was emptied in the morning and continued for 24 hours, including the last urination the following morning. We excluded patients from whom less than 500 mL/day of urine was collected, because of concerns regarding urine collection errors. UCE and urine urea excretion were measured. UCE was evaluated according to sex. DPI was calculated using the following formula (10,11):

$$6.25 \times ([24\text{-hour urine urea nitrogen excreted in grams}] +$$

$$[\text{weight in kilograms} \times 0.031 \text{ g nitrogen/kg/day}]) + 24\text{-hour urine proteinuria (g/day, if urinary protein loss} > 5 \text{ g/day})$$

### Other variables

Data regarding demographics, medical history, causes of CKD and comorbid conditions were collected at baseline by a well-trained study coordinator using a standardized case report form and protocol. Serum samples were collected at baseline according to our standardized protocol and sent to a central laboratory for measurement. Serum creatinine concentration was measured using an isotope-dilution mass spectrometry-traceable method. eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula as follows (12):

$$\text{eGFR mL/min/1.73 m}^2 = 175 \times \text{serum creatinine (mg/dL)}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$$

Inflammatory marker was investigated by measuring hs-CRP. Inflammation was defined as hs-CRP > 3 mg/L (13). A patient was defined as an active smoker if a person currently smoked. Alcohol drinking was defined as having more than 2 times of standard drinking (about one bottle of beer, 14 grams of alcohol)/week. Physical activity for health was defined as more than 150 min/week moderate activity, or 75 min/week vigorous activity, or an equivalent combination according to global recommendations on physical activity for health of World Health Organization (14). Cardiovascular disease was defined as having medical history of myocardial infarction, heart failure, peripheral vascular disease, or stroke.

### Statistical analysis

Data were expressed as a percentage for categorical variables and as the mean  $\pm$  standard deviation (SD) for continuous variables. We used  $\chi^2$  test for categorical variables and the analysis of variance (ANOVA) for continuous variables to show differences in baseline characteristics according to CKD stage and PEW score. The covariates for PEW were selected according to our baseline data and other PEW studies of CKD. In logistic analyses of PEW, the associated factors were expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) PASW statistics version 18.0 (IBM, Armonk, NY, USA).

### Ethics statement

The study protocol was approved by the relevant ethics committees, and all participants were informed of their inclusion in this registry. The KNOW-CKD study was supervised by the Korea Centers for Disease Control and Prevention. The design of the present study was approved by Institutional Review Board of the Kangbuk Samsung Hospital (2011-01-076-011).

## RESULTS

### Nutritional and inflammatory status

A total of 1,834 adults with predialysis CKD were included in the study. The mean age was  $53.9 \pm 12.2$  years old, and 60.4% were male. In the study population, 34.5% had diabetes and 96.1% had hypertension.

Characteristics of the patients are shown in Tables 1 and 2. Those with an advanced CKD stage tended to have more CVD, lower Total CO<sub>2</sub>, and greater weight loss. Inflammation prevalence and neutrophil percent increased with CKD stage. PEW prevalence was 2.2%, 4.4%, 8.3%, 6.2%, 15.6%, and 24.6% in CKD stage 1, 2, 3a, 3b, 4, and 5, respectively. Patients with an advanced eGFR stages had lower serum albumin, lower UCE, and lower DPI (Table 1). Those with more PEW parameters tended to have advanced CKD, diabetes, and CVD. They also had lower TCO<sub>2</sub>, low physical activity, and higher weight loss. The hs-CRP were  $1.84 \pm 4.61$ ,  $1.79 \pm 5.01$ ,  $2.32 \pm 5.32$ , and  $2.82 \pm 7.65$  mg/L in patients with 0, 1, 2,  $\geq 3$  PEW parameters, respectively (Table 2).

### Inflammation, CVD, and PEW

In the study population, 11.1% had CVD, 13.6% had inflammation, and 9.0% had PEW. The prevalence of PEW, inflammation, and CVD according CKD stage was shown in Fig. 1. Among patients with CKD 1 and 2 stages, prevalence was 3.8% for PEW, 9.6% for inflammation, and 4.0% for CVD. Among patient with advanced CKD 4 and 5 stages, prevalence was 17.5% for PEW, 17.9% for inflammation, and 14.5% for CVD. Those who had concurrently PEW, inflammation, and CVD were a small proportion (0.4%), but their proportion increased with advanced CKD stage; 0% (CKD 1 and 2 stages), 0.1% (CKD 3a and 3b stages), and 1.1% (CKD 4 and 5 stages).

### The associated factors of PEW

We investigated which factors were predictive of PEW among 1,834 adults with predialysis CKD. In multivariate logistic regression models for PEW, male sex, diabetes, higher hs-CRP levels, lower eGFR, lower total CO<sub>2</sub>, and no physical activity were associated with PEW. PEW was independently associated with the inflammatory marker, hs-CRP in univariate (OR, 1.02; 95% CI, 1.01–1.05) and multivariate analyses (OR, 1.03; 95% CI, 1.01–1.06; Table 3).

**Table 1.** Characteristics of 1,834 adults with predialysis CKD based on eGFR stage

Characteristics	All (n = 1,834)	eGFR stage, mL/min/1.73 m <sup>2</sup>						P value
		Stage 1 ( $\geq 90$ ) (n = 231)	Stage 2 (60–89) (n = 339)	Stage 3a (45–59) (n = 327)	Stage 3b (30–44) (n = 405)	Stage 4 (15–29) (n = 418)	Stage 5 (< 15) (n = 114)	
Age, yr	53.9 $\pm$ 12.2	43.7 $\pm$ 11.9	50.9 $\pm$ 11.6	54.8 $\pm$ 11.7	57.2 $\pm$ 10.7	57.3 $\pm$ 11.0	55.9 $\pm$ 11.5	< 0.001
Male sex	60.4	46.8	65.8	67.6	62.5	60.5	43.0	0.872
eGFR, mL/min/1.73 m <sup>2</sup>	51 $\pm$ 30	110 $\pm$ 20	73 $\pm$ 9	52 $\pm$ 4	37 $\pm$ 4	23 $\pm$ 4	12 $\pm$ 2	< 0.001
24-hr UP, g/day	1,340 $\pm$ 2,137	615 $\pm$ 1,103	723 $\pm$ 1,399	1,089 $\pm$ 1,829	1,307 $\pm$ 1,897	2,092 $\pm$ 2,682	2,734 $\pm$ 3,199	< 0.001
Diabetes	34.5	15.7	21.4	30.9	40.7	48.1	50.0	< 0.001
Hypertension	96.1	85.7	95.3	98.2	98.0	98.6	97.4	< 0.001
CVD	11.1	3.9	7.1	11.6	13.8	16.0	8.8	< 0.001
Total CO <sub>2</sub> , meq/L	25.7 $\pm$ 3.6	27.8 $\pm$ 2.9	27.7 $\pm$ 3.0	26.9 $\pm$ 3.0	25.3 $\pm$ 3.1	23.6 $\pm$ 3.2	21.7 $\pm$ 3.3	< 0.001
Active smoker	15.5	16.0	17.1	18.0	12.8	15.6	11.4	0.163
Alcohol consumption $\geq 2$ times/wk	13.0	16.9	17.4	13.8	12.1	10.3	2.6	< 0.001
Physical activity	38.4	40.8	48.0	49.2	40.2	35.5	38.4	0.015
Weight loss > 3 kg/yr	16.7	12.6	14.2	15.6	14.6	22.2	23.7	< 0.001
WBC, cell/ $\mu$ L	6,579 $\pm$ 1,905	6,248 $\pm$ 1,730	6,377 $\pm$ 1,854	6,520 $\pm$ 1,889	6,635 $\pm$ 1,889	6,972 $\pm$ 1,994	6,372 $\pm$ 1,952	0.031
Neutrophil	58.2 $\pm$ 9.0	55.1 $\pm$ 9.6	57.0 $\pm$ 8.6	56.7 $\pm$ 8.6	58.9 $\pm$ 8.7	60.4 $\pm$ 8.6	62.2 $\pm$ 9.6	< 0.001
hs-CRP, mg/L	2.00 $\pm$ 5.23	1.36 $\pm$ 4.80	1.59 $\pm$ 3.44	1.98 $\pm$ 5.57	1.87 $\pm$ 3.99	2.92 $\pm$ 7.33	1.71 $\pm$ 3.47	0.081
hs-CRP > 3 mg/L	13.6	10.0	9.7	11.3	15.8	18.7	13.2	< 0.001
PEW parameters								
Serum albumin, g/dL	4.18 $\pm$ 0.42	4.13 $\pm$ 0.40	4.31 $\pm$ 0.34	4.20 $\pm$ 0.40	4.19 $\pm$ 0.37	4.02 $\pm$ 0.46	3.97 $\pm$ 0.44	< 0.001
Serum albumin < 3.8 g/dL	16.0	9.5	5.0	14.4	14.1	27.3	31.6	< 0.001
BMI, kg/m <sup>2</sup>	24.58 $\pm$ 3.39	24.04 $\pm$ 3.75	24.76 $\pm$ 3.39	24.73 $\pm$ 3.28	24.74 $\pm$ 3.17	24.50 $\pm$ 3.40	24.38 $\pm$ 3.51	0.355
BMI < 23.0 kg/m <sup>2</sup>	33.2	42.4	32.2	29.7	28.6	34.9	37.7	0.321
UCE, g/day	1,179 $\pm$ 416	1,202 $\pm$ 401	1,308 $\pm$ 453	1,243 $\pm$ 425	1,163 $\pm$ 402	1,088 $\pm$ 368	948 $\pm$ 341	< 0.001
Low quartile of UCE (sex-specific)	25.0	13.9	19.2	24.4	25.4	34.4	43.0	< 0.001
DPI, g/kg/day	0.80 $\pm$ 0.35	0.87 $\pm$ 0.28	0.86 $\pm$ 0.33	0.83 $\pm$ 0.36	0.81 $\pm$ 0.39	0.74 $\pm$ 0.36	0.65 $\pm$ 0.28	< 0.001
DPI < 0.6 g/kg/day	26.5	16.5	20.4	25.7	23.7	34.2	49.1	< 0.001
PEW	9.0	2.2	4.4	8.3	6.2	15.6	24.6	< 0.001

Data are represented as mean  $\pm$  standard deviation (SD) or percentage (%).

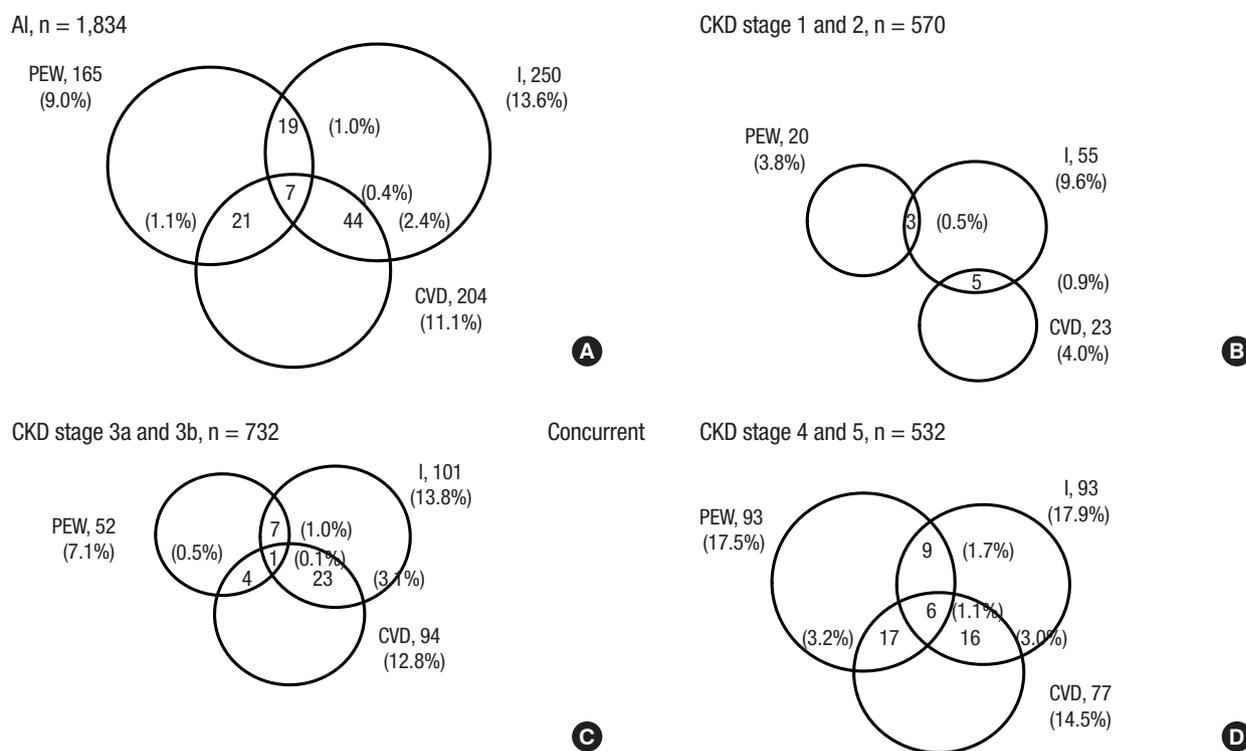
CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, 24-hr UP = 24-hour urine protein, CVD = cardiovascular disease, WBC = white blood cell, hs-CRP = high sensitivity C-reactive protein, PEW = protein-energy wasting, BMI = body mass index, UCE = urine creatinine excretion, DPI = dietary protein intake.

**Table 2.** Characteristics of 1,834 adults with predialysis CKD according to numbers of PEW parameters

Characteristics	No. of PEW parameters				P for trend
	0 (n = 694)	1 (n = 611)	2 (n = 364)	≥ 3 (n = 165)	
Age, yr	54.3 ± 11.9	51.9 ± 12.1	55.4 ± 12.6	55.8 ± 11.7	0.069
Male sex	69.0	51.7	58.1	60.0	0.001
eGFR, mL/min/1.73 m <sup>2</sup>	54 ± 28	56 ± 34	45 ± 29	34 ± 23	< 0.001
24-hr UP, g/day	975 ± 1,223	1,201 ± 2,065	1,712 ± 2,781	2,579 ± 3,056	< 0.001
Diabetes	31.4	30.5	41.0	48.5	< 0.001
Hypertension	97.6	93.5	97.0	97.6	0.799
CVD	8.4	10.3	15.2	17.0	< 0.001
Total CO <sub>2</sub> , meq/L	26.1 ± 3.4	26.1 ± 3.5	25.2 ± 3.8	23.9 ± 3.6	< 0.001
Physical exercise	49.7	41.5	37.1	25.4	< 0.001
Active smoking	16.9	13.9	13.5	19.4	0.842
Alcohol consumption ≥ 2 times/wk	16.3	11.3	11.3	9.1	0.003
Weight loss > 3 kg/yr	13.5	17.5	18.7	23.0	0.001
WBC, cell/μL	6,628 ± 1,795	6,395 ± 1,930	6,663 ± 2,008	6,870 ± 1,994	0.246
Neutrophil, %	56.8 ± 9.1	58.5 ± 8.6	59.2 ± 9.3	61.1 ± 8.6	< 0.001
hs-CRP, mg/L	1.84 ± 4.61	1.79 ± 5.01	2.32 ± 5.32	2.82 ± 7.65	0.021
hs-CRP > 3 mg/L	12.7	12.1	17.1	15.8	0.067
PEW parameters					
Serum albumin, g/dL	4.32 ± 0.28	4.19 ± 0.37	4.07 ± 0.47	3.74 ± 0.56	< 0.001
Serum albumin < 3.8 g/dL	0	14.7	27.3	63.0	< 0.001
BMI, kg/m <sup>2</sup>	26.22 ± 2.47	23.76 ± 3.37	23.77 ± 3.80	22.46 ± 2.95	< 0.001
BMI < 23.0 kg/m <sup>2</sup>	0	49.1	53.2	70.3	< 0.001
UCE, g/day	1,438 ± 389	1,159 ± 321	908 ± 313	756 ± 257	< 0.001
Low quartile of UCE (sex-specific)	0	12.6	65.8	93.9	< 0.001
DPI, g/kg/day	0.95 ± 0.36	0.83 ± 0.31	0.63 ± 0.28	0.48 ± 0.18	< 0.001
DPI < 0.6 g/kg/day	0	23.6	53.7	88.5	< 0.001

Data are represented as mean ± standard deviation (SD) or percentage (%).

CKD = chronic kidney disease, PEW = protein-energy wasting, eGFR = estimated glomerular filtration rate, 24-hr UP = 24-hour urine protein, CVD = cardiovascular disease, WBC = white blood cell, hs-CRP = high sensitivity C-reactive protein, BMI = body mass index, UCE = urine creatinine excretion, DPI = dietary protein intake.

**Fig. 1.** Concurrent prevalence of PEW, I, and CVD in 1,834 adults with predialysis CKD according to eGFR stage. Inflammation is defined as hs-CRP > 3 mg/L.

PEW = protein-energy wasting, I = inflammation, CVD = cardiovascular disease, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, hs-CRP = high sensitivity C-reactive protein.

**Table 3.** Logistic regression analysis model for PEW in 1,834 adults with predialysis CKD

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, yr	1.02 (1.01–1.03)	0.033	1.00 (0.98–1.02)	0.997
Male	0.98 (0.71–1.36)	0.921	1.46 (0.93–2.29)	0.099
eGFR, mL/min/1.73 m <sup>2</sup>	0.97 (0.96–0.98)	< 0.001	0.98 (0.96–0.99)	< 0.001
Total CO <sub>2</sub> , meq/L	0.86 (0.82–0.91)	< 0.001	0.93 (0.87–0.99)	0.043
Physical exercise	0.43 (0.29–0.66)	< 0.001	0.43 (0.26–0.69)	< 0.001
Diabetes	1.90 (1.38–2.62)	< 0.001	1.68 (1.09–2.59)	0.020
Hypertension	0.59 (0.21–1.62)	0.303	1.30 (0.37–4.66)	0.684
CVD	1.73 (1.12–2.68)	0.013	1.09 (0.61–1.95)	0.783
hs-CRP, mg/L	1.02 (1.01–1.05)	0.043	1.03 (1.01–1.06)	0.044

PEW = protein-energy wasting, CKD = chronic kidney disease, OR = odds ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate, CVD = cardiovascular disease, hs-CRP = high sensitivity C-reactive protein.

## DISCUSSION

As a baseline study of KNOW-CKD, the nutritional status in predialysis CKD adults has been described here. This study demonstrates the prevalence of PEW is increased with advanced CKD stage. The relationships between the nutritional status and inflammatory status and CVD are getting closer in advanced CKD. PEW is associated with metabolic acidosis, low physical activity, comorbid diabetes, and inflammation.

Adverse nutritional changes are serious consequences and a strong indicator of adverse outcomes in CKD. This abnormality is often associated with diminished functional capacity related to uremic metabolic stress (2). Several terms used to describe the adverse nutritional changes in kidney disease include “uremic malnutrition” (15), “malnutrition-inflammation atherosclerosis syndrome” (16), or “malnutrition-inflammation complex syndrome” (17). Ill-defined terminologies and non-uniform definitions may lead to conceptual errors and data misinterpretation. In 2008, ISRN experts panel recommended the term “PEW” to describe the state of decreased body stores of protein and energy in CKD patients (4). The ISRN proposed that 4 main categories be recognized for diagnosing PEW: biochemical criteria, low body mass, decreased in muscle mass, and low protein intake. Among biochemical indicators, serum albumin is a strong and consistent indicator for PEW. BMI is the most common measure of body mass, and is often used to predict outcomes in CKD. Muscle mass is the most valid criterion for diagnosing PEW, and is often difficult to diagnose low muscle mass. There are no clinical uniform and reproducible measures of muscle mass especially in patients with catabolic status. However, UCE remains the method for assessing total muscle mass because of its lower cost and easier reproducibility. Recent studies (18,19) showed that UCE effectively predicted clinical outcomes in CKD. In the Chronic Renal Insufficient Cohort (CRIC) study (19), UCE and appendicular muscle mass were modestly correlated. In the NephroTest cohort study (20), lower gender-specific quartile of UCE was associated with high-

er risk for mortality in early stage CKD. DPI is a reliable marker of nutritional intake and can be estimated by 24-hour urine urea nitrogen in clinically stable CKD patients (10). There have been a few studies of nutritional status in predialysis CKD patients using the ISRN criteria. In this study, we defined the PEW according to the ISRN criteria, and we described the nutritional status in CKD patients. The prevalence of PEW was 9.0% and was increased with advanced CKD stage.

PEW, inflammation, and CVD clearly contribute to poor outcomes in CKD patients. Persistent, low-grade inflammation has been recognized as a component of CKD. Inflammation plays a contributing role in CVD as well as contributing to PEW. Stenvinkel et al. (5) reported a strong association between malnutrition, inflammation, and atherosclerosis in 109 patients with terminal chronic renal failure (mean eGFR  $7 \pm 1$  mL/min). The concurrent prevalence of PEW, inflammation, and CVD in their study was 22.0%. They assessed PEW by subjective global assessment (SGA), inflammation by C-reactive protein (CRP)  $\geq 10$  mg/L, and CVD by the presence of carotid plaque. Another study (6) suggested that inflammation, malnutrition, and CVD appear to be interrelated, each additionally contributing to high mortality in 128 hemodialysis patients; the concurrent prevalence of PEW, inflammation, and CVD was 23.0%. This study assessed CVD according to CVD history. The Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD) study (7) reported PEW interacted with inflammation and CVD in 815 patients with dialysis. In the NECOSAD study, the concurrent presence of PEW, inflammation, and CVD was a small proportion of 6%, but was strikingly increased the mortality. In our study, we defined PEW according to ISRN criteria, inflammation as hs-CRP  $> 3$  mg/L, and CVD as having medical history of CVD. The prevalence of PEW, inflammation, and CVD was 9.0%, 12.7%, and 8.4% respectively, while concurrent presence of PEW, inflammation, and CVD was uncommon (0.4%), but increased with advanced CKD stage. There are possible explanations of the discrepancy between our study and the previous studies. First, non-uniform definitions of PEW, inflammation, and CVD have

been assessed in the studies. Second, the study populations of these studies varied in terms of comorbidities and CKD stages.

The mechanisms involved in PEW are multiple and complicated (3). Although insufficient food intake due to poor appetite and dietary restrictions contribute to PEW, uremia-induced alterations such as increased energy expenditure, persistent inflammation, acidosis, and multiple catabolic endocrine disorders lead to excessive wasting of muscle and fat. We examined the predictors of PEW in 1,834 adults with predialysis CKD. In our multiple adjusted logistic regression models, comorbid diabetes, advanced CKD stage, metabolic acidosis, lack of physical activity, and inflammation were independently associated with PEW. Among the PEW predictors, metabolic acidosis and physical non-exercise are important modifiable factors. Metabolic acidosis induces release of branched-chain amino acids from muscle, also leads to insulin resistance, and induces adrenal glucocorticoid production (21,22). Bicarbonate therapy or low dietary acid load can reduce metabolic acidosis and muscle degradation. Muscle weakness is a reliable marker of poor outcome in CKD and is measured simply by grip strength or gait speed. Exercise-induced benefits include improvement in insulin sensitivity, decrease the muscle degradation, and improvement in cardiovascular functions (23,24). Decreased physical activity likely plays a major role in PEW.

A few considerations are important in the interpretation of our results. First, we sincerely defined the PEW according to ISRNM criteria; however, the cut-off value for each criterion is not validated in our Korean population. Racial differences in nutritional and inflammation status have been observed in CKD patients (25). Second, our study population is all CKD stage of CKD. Adults with CKD stage 1 and 2 (eGFR > 60 mL/min/1.73 m<sup>2</sup>) made up 31% of the study population. Third, a single hs-CRP measure may not be a standard method for defining the inflammation in CKD patients. The optimal cut-off value of hs-CRP is also uncertain (13,26). Fourth, there are many risk factors associated with PEW; thus may have an unknown potential bias. However, our study also has several distinct strengths. The KNOW-CKD study has well-designed protocol and is a nationally representative prospective cohort study. We used a rigorous protocol to measure demographics, comorbidities, and laboratory data. We are following the adults with various CKD stage and will evaluate the roll of inflammation, metabolic acidosis, and physical activity in PEW.

In summary, nutritional status in predialysis CKD adults indicated that the prevalence of PEW is about 9.0% according to ISRNM criteria and increased with advanced CKD stage. PEW was associated with metabolic acidosis, low physical activity, comorbid diabetes, and inflammation. Future studies are needed to evaluate the complex interaction between PEW, CVD, and inflammation. New strategies to improve metabolic acidosis or physical activity in at-risk adults with CKD are needed to reduce

the burden of CKD.

## DISCLOSURE

The authors have no potential conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

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