Serum leptin level is associated with phase angle in CKD5 patients not undergoing dialysis

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ABSTRACT

Serum leptin level is associated with phase angle in CKD5 patients not undergoing dialysis

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Background: Malnutrition has a lot of contributing factors in patients with end-

stage renal disease (ESRD) and is associated with poor prognosis. As uremia is worsening, hemodynamic and hormonal changes, persistent inflammation, and fluid overload are more complicated contributing to the development of malnutrition. Bio-impedance spectroscopy (BIS) is a useful method to estimate fluid balance by measuring fluid excess (overhydration/extracellular water, OH/ECW) and nutritional status by measuring phase angle (PhA). We aimed to evaluate the volume and nutritional statuses using BIS and to investigate the relationships with appetite-regulating hormones in ESRD patients not undergoing dialysis.

Methods: We enrolled a total of 91 patients with stage 5 chronic kidney disease not undergoing dialysis (CKD5-ND). We measured various serum markers including the appetite-regulating hormones, leptin and ghrelin. We categorized the patients with PhA < 4.5˚ into a poor nutritional group, and ones with PhA ≥ 4.5˚ into a proper nutritional group to compare biomarkers. We also evaluated each patient's nutritional status by assessing their geriatric nutritional risk index (GNRI) and their volume status by measuring serum NT-proBNP and OH/ECW.

Results: Forty-one patients (45%) had poor nutritional status. Patients with a poor nutritional status had significantly higher OH/ECW (29.6 ± 12.7 vs. 6.2 ± 10.3%, p<0.001) and lower level of leptin (3.8 ± 3.1 vs. 7.0 ± 6.2 ng/mL, p=0.004) than those with proper nutritional status. PhA was positively associated with GNRI (r=0.597, p<0.001), and OH/ECW has a positive association with NT-proBNP

(r=0.384, p<0.001). Leptin was negatively correlated with OH/ECW (r= -0.288, p=0.006), whereas it was positively correlated with PhA (r=0.263, p=0.012). In multivariate logistic regression, high level of leptin was associated with proper nutrition (odds ratio (OR) 7.00, 95% confidence interval (CI) 1.74-28.10), while an increased OH/ECW was also associated with poor nutrition (OR 0.65, 95% CI 0.51-84).

Conclusion: Our study demonstrates that serum leptin level is positively correlated with PhA in CKD5-ND patients. Low leptin level suggests poor nutrition in CKD5-ND patients. Thus, low leptin level and decreased PhA could be used as a nutritional indicator reflected as malnutrition in CKD5-ND patients.

Key Words: chronic kidney disease, leptin, phase angle

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Ⅰ. INTRODUCTION

Malnutrition is a common problem in patients with end stage renal disease (ESRD) [1] and is associated with higher rate of mortality in this population [2]. After International Society of Renal Nutrition and Metabolism introduced protein energy wasting (PEW), PEW has been commonly used as a term to describe the poor nutritional status in patients with chronic kidney disease (CKD) [3]. According to the diagnostic criteria for PEW, assessment of the nutritional status of CKD patients is difficult as they require several serologic and demographic results, and questionnaires.

The most patients with stage 5 chronic kidney disease not undergoing dialysis (CKD5-ND) are overhydrated [4]. Such overhydration is associated with malnutrition, and furthermore exacerbates the malnutrition, inflammation and atherosclerosis [5]. Thus, when evaluating the nutritional status of CKD5-ND patients, it is worth to evaluate the volume status of the patients at the same time. Both dual energy X-ray absorption spectrometry (DEXA) and bio-impedance spectroscopy (BIS) methods can evaluate the nutritional and volume statuses of patients simultaneously. DEXA, however, is expensive and requires specialized instrumentation, limiting its practical use. In contrast, BIS is easy to use, accurate

and non-invasive method [6-9].

In particular, phase angle (PhA), which is one of the BIS parameters, reflects nutritional status well. PhA is the arctangent of the ratio of reactance (Xc) to resistance (R) measured by current flow [10]. R is the restriction to the flow of an electric current and is primarily related to the amount of water present in the tissues. Xc is the opposition to a change in voltage due to the element's capacitance. It represents the ability of tissues to store energy. Because the cells have a similar electrical capacity, the greater numbers of cells have the larger reactance. R represents body water contents and Xc is related to body cell mass. Theoretically, PhA can be used as a nutritional indicator, because malnutrition is characterized by alterations in fluid balance and changes in cellular membrane integrity [11]. In practice, PhA has been widely used as a nutritional assessment tool in patients with liver cirrhosis, colon cancer and ESRD [8, 10, 12]. Those studies have reported that the decreased PhA is correlated with poor nutritional status and prognosis in ESRD, but no studies have been conducted in CKD5-ND patients.

Loss of appetite is a major and correctable cause of malnutrition in CKD [13]. Appetite is regulated by orexigenic and anorexigenic signals originating from the hypothalamus. Leptin and ghrelin are known to play important roles in regulating appetite by controlling signals [14]. The association between nutritional status and appetite-regulating hormones such as leptin and ghrelin in CKD5-ND patients,

however, is unknown. We aimed to evaluate the body fluid volume and nutritional status by BIS and to investigate the relationship between the appetite-regulating hormones and the parameters of BIS in CKD5-ND patients.

Ⅱ. MATERIALS AND METHODS

1. Patients and data collection

This study included ninety-six patients who visited our hospital between October 2014 and May 2016 to plan either hemodialysis or peritoneal dialysis for renal replacement therapy. We retrospectively reviewed BIS data obtained from the patients on planned visit. Underlying diseases and demographic characteristics were investigated. The laboratory tests, echocardiography, and BIS were performed before the first dialysis session. Patients with malignancy (N=2), liver cirrhosis (N=1), low left ventricular ejection fraction (N=1), and urgent dialysis before BIS analysis (N=1) were excluded. Ninety-one patients were finally enrolled in this study. The study was approved by the Institutional Review Board of Yonsei University Wonju Severance Christian Hospital. All participants provided written informed consent prior to the study.

2. Assessment of volume and nutritional status

Before starting renal replacement therapy, BIS was performed with BCM™ (Body Composition Monitoring™, Fresenius Medical Care, Bad Homburg,

Germany) to assess the body fluid volume and nutritional status of each patient. BCM™ measures intracellular water (ICW), extracellular water (ECW), and total body water (TBW) by sending currents with 50 different frequencies from 5 to 1000 kHz into the body and measuring each current's impedance. It estimates body fluid volume status by reporting the overhydration (OH) value. BCM™ also reports the fat tissue index (FTI), lean tissue index (LTI), and PhA to evaluate the patient's nutritional status. PhA is an angle value of the time delay between the voltage waveform at 50kHz and current waveform. The validity of BIS in healthy individuals and ESRD patients in comparison to standard measurement methods has been demonstrated in previous studies [6,15]. We assigned patients with a PhA less than 4.5˚ (PhA < 4.5˚) to the malnutrition group, and those with a PhA above 4.5˚ (PhA ≥ 4.5˚) to the normal nutrition group [8]. To reduce bias due to the BCM™ machine, we also calculated the geriatric nutritional risk index (GNRI) [16] to determine nutritional status and measured N-terminal prohormone of brain natriuretic peptide (NT-proBNP) [17] to determine volume status. GNRI was calculated using height (H: cm), body weight (BW: kg), and serum albumin (g/L) level. First, ideal weight (WLo: kg) was calculated according to gender from the Lorentz equations as follows:

Men; WLo = H- 100 – [(H-150)/4], Women; WLo = H-100-[(H-100)/2.5]

Then albumin, ideal weight, and body weight were substituted into the following formula

GNRI=[1.489 x albumin(g/L)]+[41.7 x (BW/WLo)]
(BW/BLo=1, when BW exceeded WLo).

3. Laboratory and echocardiographic evaluations

Serum NT-proBNP was measured by electro-chemiluminescence immunoassay (ECLIA) on a Modular Analytics E170 clinical analyser (Roche Diagnostics, Mannheim, Germany). Analytical measurement range for NT-proBNP was 5 to 35,000 pg/mL. All blood samples were collected before initiation of renal replacement therapy and were then immediately centrifuged and stored at -73℃ until analysis. Serum leptin and ghrelin levels were measured with enzyme-linked immunosorbent assay (ELISA) kits. Samples were assayed for leptin (ELISA kit for leptin, Cat. No. CEA084Hu; Cloud-Clone, TX, USA) and ghrelin (ELISA kit for ghrelin, Cat. No. CEA991Hu; Cloud-Clone, TX, USA) in duplicates and the mean value of the two measures was used in the analysis. Analytical measurement range for leptin and ghrelin were 0.156 to 10 ng/mL and 123.5 pg/mL to 10,000 pg/mL, respectively. Reference distributions of this leptin and ghrelin are 2.2-8.6 ng/mL and 161-856 pg/mL in healthy people. Glomerular filtration rate (GFR) was

calculated by modification of diet in renal disease (MDRD) equations. Echocardiography was performed all patients by using 3-MHz transducer and commercial ultrasound system (Vivid-7, General Electric-Vingmed, Milwaukee, WI, USA).

4. Statistical analysis

All statistical analyses and graphs were performed using IBM Statistics Package for the Social Science (SPSS) version 23.0 (IBM Corporation, Armonk, NY, USA). Categorical data were described as frequencies and percentages. Descriptive statistics were described as means ± standard deviation (SD) for continuous variables. Unpaired Student's t-test was used to determine the significance of differences in clinical variables between the two groups. The chi-square test was used to compare categorical variables. Pearson's correlation test was used to examine relationships between variables. Multivariate logistic regression was performed for leptin, albumin, and OH/ECW. Those variables were chosen considering collinearity among the factors that showed a statistically significant correlation with PhA. Odds ratios (OR), 95% confidence intervals (CI), and p-values are reported. Because there is no definite reference value of leptin, we categorized leptin level into tertiles according to percentiles (<2.59, 2.59-6.05, >6.05 ng/dL). OR was calculated using the lowest tertile as the reference. In model

1, we analyzed variables after adjusting for age and sex. In model 2, we analyzed variables after adjusting for age, sex, C-reactive protein (CRP), creatinine (Cr) and LTI. In model 3, we analyzed variables after adjusting for age, sex, CRP, Cr, LTI, presence of diabetes, use of diuretics, and presence of nephrotic syndrome. Goodness-of-fit of the model was assessed using the Hosmer-Lemeshow test. Predictive accuracy of each logistic regression model was evaluated by calculating the c-statistic (equivalent to the area under the receiver operating characteristic curve). Statistical significance was defined as $p<0.05$.

Ⅲ. RESULTS

1. Baseline characteristics of patients

Mean age of patients was 59.8 ± 11.2 (range 31-79) years. Fifty patients were male. PhA and ECW values were significantly higher in males (4.66 ± 1.31°, 19.1 ± 4.8 L) than in females (3.97 ± 1.20°, 15.6 ± 5.1 L) ($p<0.001$). Other variables were not significantly different between male and female patients. Fifty-seven patients (62.6%) had a history of diabetes. Diabetic patients had lower PhA (4.0 ± 1.24 vs. 4.99 ± 1.17°, $p<0.001$) and serum albumin (3.3 ± 0.5 vs. 3.6 ± 0.7 g/dL, $p=0.010$), and higher ECW (18.6 ± 6.0 vs. 16.0 ± 2.8 L, $p=0.008$) than non-diabetic patients.

2. Comparisons of study parameters according to nutritional status

Normal nutrition group had significantly higher levels of albumin and leptin as well as GNRI compared to malnutrition group. Normal nutritional group had a lower CRP level than the malnutrition group. The difference in ghrelin levels between two groups was marginal. NT-proBNP, OH, and OH/ECW, all of which reflecting volume status, were lower in the normal nutrition group than those in the malnutrition group

(Table 1). In addition, NT-proBNP was significantly associated with OH/ECW ($r=0.384$, $p<0.001$).

Table 1. Comparisons of study parameters according to nutritional status

Variables	Total (N=91)	PhA<4.5˚(N=41)	PhA≥4.5˚(N=50)	p-value
Age (years)	59.8 ± 11.2	60.5 ± 12.8	59.3 ± 9.8	0.656
Gender (male,%)	50 (55%)	20 (49%)	33 (66%)	0.097
HTN (N,%)	81 (89%)	39 (95%)	42 (84%)	0.091
CVD (N,%)	26 (28.6%)	12 (29%)	14 (28%)	0.894
Diuretics (N,%)	54 (59.3%)	25 (61%)	29 (58%)	0.774
NSD (N,%)	27 (30%)	15(37%)	12 (25%)	0.212
Leptin (ng/mL)	5.6 ± 5.3	3.8 ± 3.1	7.0 ± 6.2	**0.004**
Ghrelin (pg/dL)	2,105 ± 2,263	1,597 ± 2,027	2,521 ± 2,379	0.052
BMI (kg/m²)	24.9 ± 4.1	24.8 ± 4.4	25.1 ± 3.8	0.662
LTI (kg/m²)	14.3 ± 3.2	13.1 ± 3.5	15.3 ± 2.7	**0.001**
FTI (kg/m²)	9.1 ± 4.5	9.1 ± 3.9	9.2 ± 5.0	0.962
GNRI	91.4 ± 9.3	85.1 ± 7.1	96.5 ± 7.7	**<0.001**
Albumin (g/dL)	3.4 ± 0.6	3.0 ± 0.5	3.7 ± 0.5	**<0.001**
BUN (mg/dL)	91.2 ± 24.8	92.5 ± 26.7	90.2 ± 23.4	0.669
Creatinine (mg/dL)	9.2 ± 3.4	9.4 ± 3.1	9.0 ± 3.6	0.575
CRP (mg/dL)	1.7 ± 3.2	2.7 ± 4.4	0.8 ± 1.3	**0.009**
Hemoglobin (g/dL)	9.2 ± 1.3	9.0 ± 1.5	9.3 ± 1.2	0.409
NT-proBNP (pg/mL)	9,181 ± 1,667	14,478 ± 12,712	4,965 ± 8,824	**<0.001**
OH (L)	3.6 ± 4.5	6.4 ± 5.0	1.2 ± 1.8	**<0.001**
OH/ECW (%)	16.7 ± 16.3	29.6 ± 12.7	6.2 ± 10.3	**<0.001**
TBW (L)	35.4 ± 8.1	36.2 ± 9.9	34.6 ± 6.2	0.409
ECW (L)	17.7 ± 5.2	19.7 ± 6.4	16.0 ± 3.1	**0.001**
ICW (L)	17.7 ± 3.9	16.5 ± 4.0	18.8 ± 3.5	**0.004**
EF (%)	62.5 ± 0.9	62.9 ± 1.4	62.2 ± 1.1	0.674
GFR (mL/min)	6.6 ± 2.8	6.5 ± 0.4	6.7 ± 2.8	0.738
BP Sys (mmHg)	142.7 ± 19.7	146.0 ± 3.5	140.0 ± 2.5	0.166
BP Dia (mmHg)	78.4 ± 11.6	79.1 ± 1.9	77.9 ± 1.6	0.636

Data are mean±SD. BMI, body mass index; BP Dia, diastolic blood pressure; BP Sys, systolic blood pressure; BUN, blood urea nitrogen; CRP, C-reactive protein; CVD, cardiovascular disease; ECW, extracellular water; EF, ejection fraction; FTI, fat tissue index; GFR, glomerular filtration rate; GNRI, geriatric nutritional risk index; HTN, hypertension; ICW, intracellular water; LTI, lean tissue index; N, number; NSD, nephrotic syndrome; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OH, overhydration; PhA, phase angle; TBW, total body water.

3. Correlations of clinical variables with appetite-regulating hormones (ghrelin and leptin)

Ghrelin was positively associated with leptin and BMI, and negatively associated with NT-proBNP. On the other hand, it was not significantly associated with PhA, albumin, GNRI, OH, and OH/ECW. Leptin was positively associated with ghrelin, PhA, BMI, FTI and GNRI. Whereas it was negatively associated with NT-proBNP, OH, and OH/ECW. LTI, ECW, and ICW, which showed significant differences according to nutritional status, did not show significant association with leptin (Table 2). Hemoglobin was not significantly associated with leptin ($r=0.021$, $p=0.843$), while it was positively associated with ghrelin ($r=0.234$, $p=0.025$).

Table 2. Correlations of clinical variables with ghrelin and leptin

Variables	Ghrelin		Leptin	
	r	p-value	r	p-value
Age (years)	0.181	0.087	0.073	0.694
Leptin (ng/mL)	0.238	**0.023**	-	**-**
Ghrelin (pg/dL)	-	-	0.238	**0.023**
PhA (˚)	0.107	0.315	0.263	**0.012**
BMI (kg/m²)	0.209	**0.047**	0.351	**0.001**
LTI (kg/ m²)	0.109	0.304	0.004	0.973
FTI (kg/ m²)	0.082	0.430	0.407	**<0.001**
GNRI	0.103	0.332	0.281	**0.007**
Albumin (g/dL)	0.061	0.565	0.205	0.051
NT-proBNP (pg/mL)	-0.273	**0.010**	-0.237	**0.026**
OH (L)	0.039	0.713	-0.239	**0.023**
OH/ECW (%)	-0.13	0.902	-0.288	**0.006**
TBW (L)	0.157	0.138	0.030	0.780
ECW (L)	0.118	0.265	-0.096	0.368
ICW (L)	0.155	0.143	0.065	0.540

BMI, body mass index; BUN, blood urea nitrogen; ECW, extracellular water; FTI, fat tissue index; GNRI, geriatric nutritional risk index; ICW, intracellular water; LTI, lean tissue index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OH, overhydration; PhA, phase angle; r: correlation coefficient; TBW, total body water.

4. Evaluation of predictive factors for nutritional status

In Pearson's correlation analysis, PhA had a significant positive association with GNRI, while it had significant negative association with OH/ECW (Fig. 1). Similarly, PhA had significant positive correlations with nutrition associated factors such as leptin, LTI, and albumin. On the other hand, it had significant negative correlations with body fluid volume factors such as NT-proBNP, OH, and ECW. Unlike leptin, ghrelin was not significantly associated with PhA (Table 3).

Multivariate logistic regression analysis showed that the increase in serum leptin and albumin predict proper nutrition well. In contrast, the increase in OH/ECW predicts poor nutrition well (Table 4). The Hosmer-Lemeshow test showed significant goodness of fit for model 1 (p=0.505), model 2 (p=0.905), and model 3 (p=0.924). The c-statistics were 0.71 (95% CI 0.61-0.82, p=0.001), 0.79 (95% CI, 0.70-0.89, p<0.001), and 0.84 (95% CI 0.75-0.92, p<0.001), for model 1, model 2, and model 3 respectively ensuring the accuracy of predictive models in the study (Fig. 2).

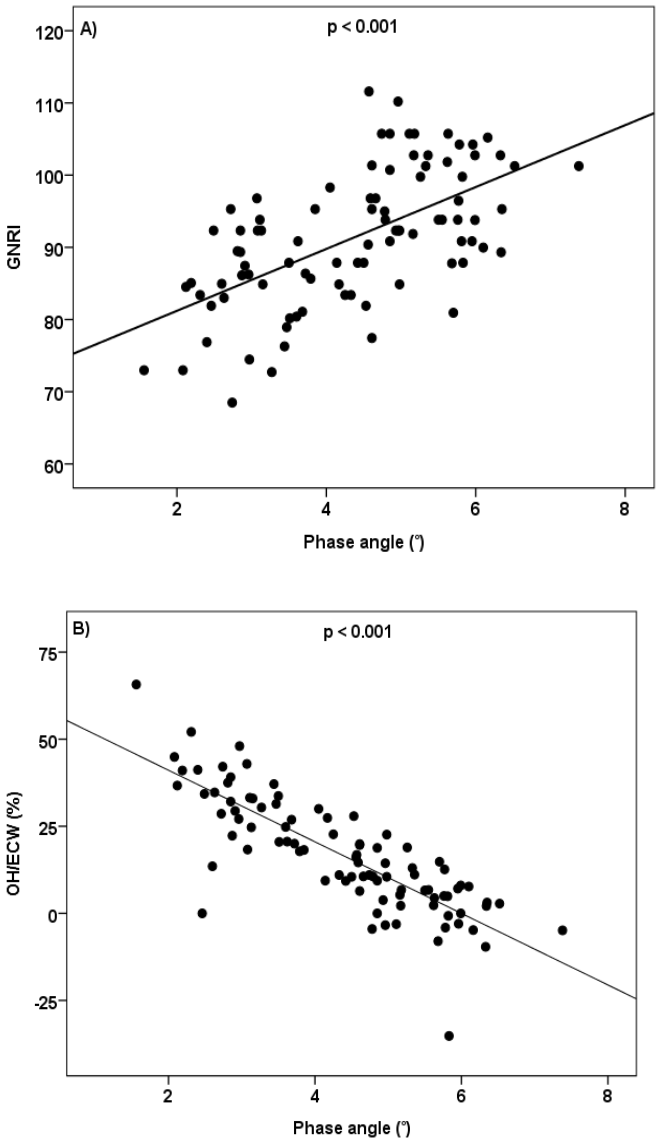

Figure 1. Correlations of phase angle with (A) GNRI (r=0.597, p<0.001) and (B) OH/ECW (r=-0.818, p<0.001).

GNRI, geriatric nutritional risk index; OH/ECW, overhydration/extracellular water.

PhA had a significant positive association with GNRI, while it had significant negative association with OH/ECW.

Table 3. Correlations between phase angle and clinical variables

Variables	PhA	
	r	p-value
Age (years)	-0.760	0.472
Leptin (ng/mL)	0.263	**0.012**
Ghrelin (pg/dL)	0.107	0.315
BMI (kg/m²)	-0.023	0.825
LTI (kg/m²)	0.387	**<0.001**
FTI (kg/m²)	-0.038	0.725
GNRI	0.597	**<0.001**
Albumin (g/dL)	0.592	**<0.001**
NT-proBNP (pg/mL)	-0.414	**<0.001**
OH (L)	-0.717	**<0.001**
OH/ECW (%)	-0.818	**<0.001**
TBW (L)	-0.097	0.361
ECW (L)	-0.434	**<0.001**
ICW (L)	0.383	**<0.001**

BMI, body mass index; ECW, extracellular water; FTI, fat tissue index; GNRI, geriatric nutritional risk index; ICW, intracellular water; LTI, lean tissue index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OH, overhydration; PhA, phase angle; r: correlation coefficient; TBW, total body water.

Table 4. Logistic regression analysis; predictive factors for proper nutrition

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Leptin						
- Tertile 1	reference		reference		reference	
- Tertile 2	2.99 (1.00-8.94)	0.050	3.63 (1.01-13.18)	**0.049**	4.20 (1.04-17.24)	**0.044**
- Tertile 3	5.30 (1.68-16.77)	**0.005**	6.51 (1.71-24.85)	**0.006**	7.00 (1.74-28.10)	**0.006**
Albumin (g/dL)	28.67 (6.93-118.59)	**<0.001**	30.47 (6.74-137.65)	**0.017**	28.58 (6.08-134.40)	**<0.001**
OH/ECW (%)	0.77 (0.68-0.86)	**<0.001**	0.65 (0.51-0.83)	**<0.001**	0.65 (0.51-0.84)	**0.001**

- CI, confidence interval; OR, odds ratio.
- Model 1: Adjusted for age and gender.
- Model 2: Adjusted for age, gender, CRP, creatinine, and lean tissue index.
- Model 3: Adjusted for age, gender, CRP, creatinine, lean tissue index, DM, diuretics, and nephrotic syndrome.

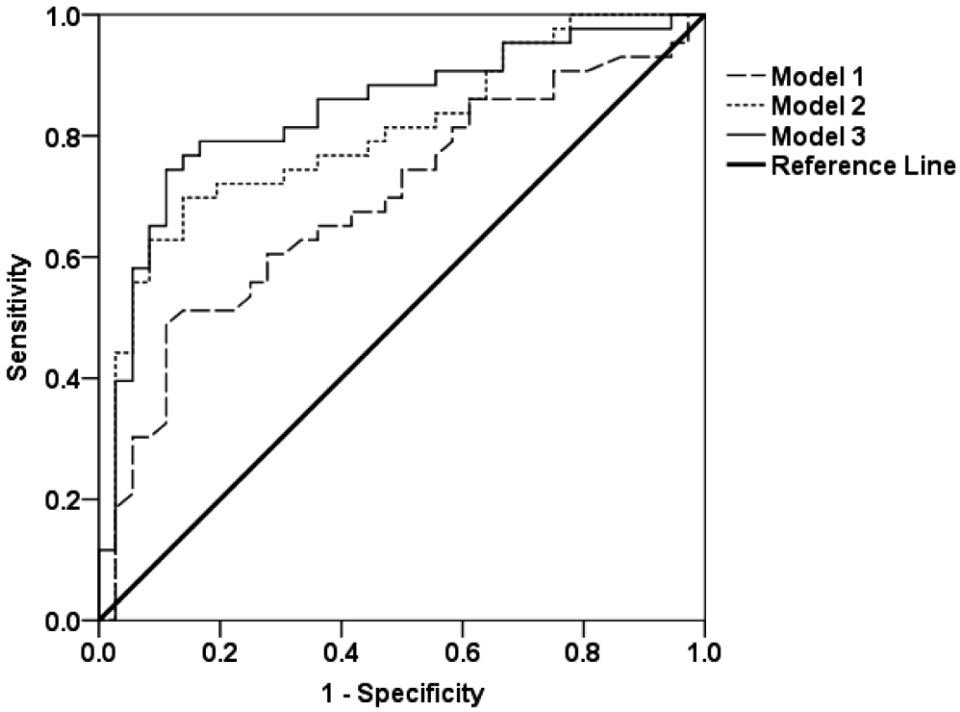

Figure 2. Assessing the predictive accuracy of logistic regression models by using c-statics. The c-statistics were 0.71 (95% CI 0.61-0.82, p=0.001), 0.79 (95% CI 0.70-0.89, p<0.001), and 0.84 (95% CI 0.75-0.92, p<0.001) for each of model 1 (adjusted for age and gender), model 2 (adjusted for age, gender, CRP, creatinine, and lean tissue index), and model 3 (adjusted for age, gender, CRP, creatinine, lean tissue index, DM, diuretics, and nephrotic syndrome). Model 3 has a good predictive power for proper nutrition in the CKD5-ND patients.

IV. DISCUSSION

Generally, leptin passes through the blood brain barrier (BBB) and binds to receptors in the hypothalamus, resulting in appetite suppression through the inhibition of appetite-promoting substance such as neuropeptide Y (NPY), agouti-related protein (AgRP), or direct blocking of the type 4 melanocortin receptor in the hypothalamus [18,19]. Because leptin is predominantly degraded in renal tubules, leptin levels are generally elevated in patients with ESRD [20]. Today, it is still under debate whether leptin is a main source of anorexia in ESRD patients or not. Previous studies reported that serum leptin levels were positively correlated with PhA in hemodialysis patients and with serum albumin in peritoneal dialysis patients [21,22]. A high calorie diet and appetite stimulant administration increases serum leptin levels in ESRD patients with an increase in the amount of adipose tissues. Nonetheless, increased leptin alone may not sufficiently suppress appetite [23,24]. The ratio of the leptin receptor to leptin was found to be inversely correlated to PhA. While no specific explanations were proposed, this finding suggests that resistance to leptin receptors may affect the nutritional status of patients with ESRD [21]. We found that leptin was positively correlated with nutritional status in ESRD patients. Such a relationship may be due to leptin receptor resistance. Resistance can arise because leptin is inhibited from passing through the BBB and fails to

reach leptin receptors [25]. The extracellular leptin binding domain of the leptin receptor also possesses strong homology to the gp130 signal transducing subunit of the receptor for IL-6, an inflammatory cytokine [26]. This structural similarity downregulates leptin receptor signal transduction in a chronic inflammatory state and impairs counter-regulatory processes due to a change in the conformation of the leptin receptor [27]. More specific research on patients with ESRD is needed.

Ghrelin is a hormone secreted mainly from the stomach that promotes secretion of NPY and AgRP in the hypothalamus, thereby increasing appetite [28]. Because ghrelin is mainly degraded in the kidney, its level is increased in ESRD patients [29]. Ghrelin exists in three forms: acyl-ghrelin, des-acyl ghrelin, and obestatin. Acyl-ghrelin increases appetite, while des-acyl ghrelin and obestatin suppress appetite [30]. In ESRD, total ghrelin is increased but the acyl-ghrelin to des-acyl ghrelin ratio changes with nutritional status [31]. This may explain why total ghrelin level was not associated with nutritional indicators in our study. As another report suggested, the acyl-ghrelin to des-acyl ghrelin ratio may be strongly associate with nutritional indicators [32].

Considering the differences according to PhA in albumin and GNRI, which are generally known as an indicator of nutritional status, PhA could be used as a nutritional indicator in CKD5-ND. In general, NT-proBNP was increased in patients with heart failure and renal failure. In this study EF and GFR did not make significant differences between two groups, suggesting that poor nutrition group’s

NP-proBNP was not increased in by heart failure or renal failure. Hypoalbuminemia, caused by malnutrition increases vascular permeability and decreases colloid oncotic pressure, eventually leading to a hypervolemic status. In addition, hypervolemic status reduces tissue perfusion, resulting in an inflammatory reaction. In this study, PhA was negatively associated with hydration status indicators. Increased CRP, NT-proBNP, and OH/ECW in malnutrition group suggest that nutrition, hydration, and inflammation were associated with one another, but we could not determine the causal relationship.

Unlike previous studies, relatively homogeneous group of dialysis naïve patients with stage 5 CKD (eGFR < 15 ml/min) were enrolled in our study. It is meaningful considering that the dialysis therapy may also affect the general symptoms and signs of the patients. It was also different from the heterogeneous patient population that includes all stage of CKD patients. Stabilization of volume status and removal of uremic toxins by starting hemodialysis can often improve anorexic symptoms of the CKD patients not undergoing dialysis. Therefore, we thought that nutrition and volume status of advanced CKD patients could be different from dialysis patients.

Our study has several limitations. First, the study was performed on the basis of a single center with a relatively small number of patients. Second, the normal range of PhA values for the Korean population has not yet been defined. The PhA value varies by age, gender, and race [13]. Third, we did not measure the sub-

forms of ghrelin, therefore we could not categorize ghrelin into its sub-forms such as the ratio of acyl-ghrelin to des-acyl ghrelin. Fourth, although patients received diet education, we could not control the patients' dietary intake (total energy intake and nutrient ratio). Despite these limitations, our study included only patients with stage 5 CKD who had not begun dialysis. We also objectively assessed the volume status of the patients which was not affected by dialysis therapy at the time of blood sampling using BIS.

V. CONCLUSION

In conclusion, we found that CKD5-ND patients with poor nutrition have also excessive body fluids through BIS and serum NT-proBNP tests. Because we demonstrate that low leptin level suggests poor nutrition in CKD5-ND patients, and leptin level is positively correlated with PhA in CKD5-ND patient, we believe that PhA of BIS test and serum leptin level could be used as a good nutritional indicator for ESRD patients.

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국 문 요 약

투석치료를 하지 않은 만성 신질환 5 단계 환자의 혈청 렙틴 농도와 위상각과의 관계

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배경: 말기 신부전 환자에서 영양실조는 많은 유발 요인을 가지며 불량한 예후와 관련된다. 요독증이 심해질수록 혈역학과 호르몬의 변화, 지속적인 염증, 그리고 수분 과잉은 점점 악화되고 영양실조의 발생에 기여하게 된다. 생체 임피던스 분광법 (bioimpedance spectroscopy, BIS)은 과수분상태 (overhydration/extracellular water, OH/ECW) 측정을 통해 체수분 균형을 평가하고 위상각 (phase angle, PhA) 측정을 통해 영양 상태를 평가하는 유용한 검사 방법이다. 본 연구에서는 투석 치료를 받지 않은 말기 신부전 환자들에게서 생체 임피던스 분광법을 사용하여 체수분 및 영양 상태를 측정하고 혈청 내의 식욕 조절 호르몬들과의 상관관계를 알아보고자 하였다.

방법: 본 연구는 총 91 명의 투석 치료를 받지 않은 5 단계의 만성 신질환 환자들을 대상으로 하였다. 식욕 조절 호르몬인 렙틴과 그렐린을 포함하여 여러 혈청 표지자들을 측정하였다. 그리고 위상각이 4.5 ° 미만인 군을 영양 불량군, 위상각이 4.5 ° 이상인 군을 정상 영양군으로 분류하여 여러 생체 표지자들을 비교하였다. 또한 환자들의 영양 상태를 Geriatric nutritional risk index (GNRI)를 통해 추가로 평가하였고, 체수분 상태를 OH/ECW 와 혈청 NT-proBNP 를 통해 평가하였다.

결과: 41 명의 환자(45%)가 영양 불량군에 속하였다. 영양 불량군의 환자들은 정상 영양군의 환자들에 비해 높은 OH/ECW (29.6 ± 12.7 vs. 6.2 ± 10.3%, p<0.001), 낮은 혈청 렙틴 농도 (3.8 ± 3.1 vs. 7.0 ± 6.2 ng/mL, p=0.004)를 보였다. 위상각은 GNRI 와 양의 상관관계가 있었고 (r=0.597, p<0.001), OH/ECW 는 NT-proBNP 와 양의 상관관계를 보였다 (r=0.384, p<0.001). 혈청 렙틴 농도는 OH/ECW 와 음의 상관관계를 보였고 (r=-0.288, p=0.006), 위상각과는 양의 상관관계를 보였다 (r=0.263, p=0.012). 다변량 로지스틱 회귀분석에서 혈청 렙틴 농도가 높을수록 영양상태가 좋았고 (odds ratio (OR) 7.00, 95% confidence interval (CI) 1.74-28.10), OH/ECW 가 증가할수록 영양 상태는 좋지 않았다 (OR 0.65, 95% CI 0.51-0.84).

결론: 본 연구에서 투석치료를 받지 않는 말기 신부전 환자들에게서 낮은 혈청 렙틴 농도는 나쁜 영양 상태를 시사하고, 혈청 렙틴 농도가 위상각과 유의한 양의 상관관계를 보여 위상각은 투석을 시작하지 않은 말기 신부전 환자들에서 영양 상태를 평가하는 유용한 지표가 될 수 있다.

핵심 되는 말: 렙틴, 만성 신부전, 위상각