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*Original Article*

# Negative correlation between leptin serum levels and sarcopenia in hemodialysis patients

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**Abstract:** Leptin is an adipokine secreted from adipocytes that mediate lipid metabolism and inflammation. This cross-sectional study evaluated association between serum leptin level and sarcopenia in chronic hemodialysis (HD) patients. Blood samples and measurement of muscle mass, handgrip strength, and gait speed were obtained from 76 chronic HD patients. We grouped participants into sarcopenia and non-sarcopenia groups according to the Asian Working Group for Sarcopenia. Eight (10.5%) of the total participants were in the sarcopenia group. Compared to the non-sarcopenia group, patients in the sarcopenia group were lower in height ($P = 0.014$), weighed less ($P < 0.001$), had lower waist circumference ($P < 0.001$), body mass index (BMI, $P < 0.001$), body fat mass ($P = 0.048$), serum triglyceride ($P = 0.032$), creatinine ($P = 0.017$), phosphorus ($P = 0.015$), leptin level ($P = 0.001$), appendicular skeletal muscle mass ($P < 0.001$), and handgrip strength ($P = 0.043$). However, urea reduction rate (URR, $P < 0.001$) and Kt/V ($P < 0.001$) were higher. After multivariate stepwise linear regression, lower logarithmically transformed leptin (log-leptin, β: -0.392, adjusted $R^2$ change = 0.130, $P < 0.001$), lower URR (β: -2.491, adjusted $R^2$ change = 0.054, $P < 0.001$)), lower handgrip strength (β: -0.243, adjusted $R^2$ change = 0.030, $P = 0.013$), lower serum phosphorus level (β: -0.176, adjusted $R^2$ change = 0.023, $P = 0.036$), and higher Kt/V (β: 2.878, adjusted $R^2$ change = 0.319, $P < 0.001$) were the independent predictors of sarcopenia in chronic HD patients. We conclude that low serum leptin level is independently associated with sarcopenia in chronic HD patients. Further studies are needed to establish the casual relationship between circulating leptin levels and uremic sarcopenia.

**Keywords:** Sarcopenia, leptin, hemodialysis

## Introduction

Sarcopenia, first described by I. H. Rosenberg in 1988 in geriatric population, is characterized by a progressive decline of muscle mass and strength and leads to increased morbidity and mortality [1, 2]. In addition to aging, sarcopenia is often observed in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), which is also called uremic sarcopenia [3-5]. Several possible mechanisms for uremic sarcopenia have been described which include an increase in pro-inflammatory cytokines, muscle protein imbalance, inactivity, hormone derangement, decline in satellite cells, metabolic acidosis, and myostatin overexpression [6].

Adipose tissue has been recognized as an endocrine tissue secreting various adipokines involved in lipid metabolism, vascular function, inflammation, and insulin resistance [7]. Moreover, emerging evidence has demonstrated that adipokines also play a role in skeletal muscle homeostasis. As the skeletal muscle mass reduces, intramuscular adipose tissue infiltration and visceral adipose tissue increases, indicating the possible role of adipokines on muscle [8]. Leptin, one of the most well-known adipokines secreted by adipose tissue, is a 16-kDa protein identified as a product of the obesity gene and has important roles in regulation of appetite, inflammation, insulin sensitivity, and fat deposition [7]. Its circulating levels positively correlate with weight, body mass index (BMI), and adipocyte counts in the general population. Moreover, recent studies have shown that leptin is also released from skeletal muscle and that leptin receptors are abundant in human skeletal muscle [9-12]. Thus, skeletal

muscle may be an important target for leptin. Several animal studies have demonstrated that leptin has a pivotal role on muscle metabolism in aged mice [13-16]. However, human data on leptin and sarcopenia are few and inconclusive. In addition, compared to the general population, serum leptin level was significantly increased in patients with ESRD primarily because of decreased renal clearance [17]. Unfortunately, evidence regarding an association between leptin and uremic sarcopenia is limited. Thus, the objective of our study was to examine the association between serum leptin levels and uremic sarcopenia in chronic hemodialysis (HD) patients.

## Materials and methods

### *Patients*

This was a single-center cross-sectional study performed from January 2015 until December 2015. A total of 76 patients older than 20 years of age and maintained on HD for at least 3 months at a medical center in Hualien, Eastern Taiwan, were invited to participate in the study. The study was comprised of 43 males and 33 females and the subjects ranged in age from 31 to 91 years. Data about basic characteristics, medical history, and drug usage were collected. Blood pressure before HD was recorded. Blood pressure of all participants was measured by trained staff using standard mercury sphygmomanometers with appropriate cuff sizes, after sitting for at least 5 minutes. All participants signed an informed consent approved by the Institutional Review Board of Tzu-Chi Hospital.

### *Anthropometric analysis*

Height was measured to the nearest half-centimeter while subjects stood erect, barefoot, and with feet together. Body weight was measured to nearest half-kilogram with subjects wearing light clothing and without shoes, before and after hemodialysis. Waist circumference was measured to the nearest half-centimeter at the shortest point between the lower rib margin and the iliac crest. BMI was calculated as dry weight (kilograms) divided by height squared (meters).

### *Sarcopenia diagnosis*

Sarcopenia, defined as having low muscle mass combined with low handgrip strength (HGS) or slow gait speed was diagnosed by applying the Asian Working Group for Sarcopenia (AWGS) criteria [18]. Appendicular skeletal muscle mass (ASMM) was assessed with the patient in the standing position by using a portable whole-body bioelectrical impedance device (Tinita BC 706DB, Tanita Corporation, Tokyo, Japan). The bio-impedance device, a non-invasive and highly available method to assess muscle mass, has a high correlation with thigh muscle cross-sectional areas, the gold standard for detection of sarcopenia [19, 20]. Low muscle mass was defined as less than 7.0 kg/m$^2$ and 5.7 kg/m$^2$ in men and women, respectively. Body fat mass was measured using the same device. HGS was measured on the opposite hand of the arm with the arteriovenous shunt using a Jamar Plus Digital Hand Dynamometer (SI Instruments Pty Ltd, Hilton, Australia). The patients were instructed to apply as much handgrip pressure as possible while sitting with arms along the body. Three trials were performed with a rest period of 1 minute and the average value was recorded. Low handgrip strength was classified as HGS less than 26 kg for men and 18 kg for women. Gait speed was measured by walking for 5 meters in the usual speed. Gait speed < 0.8 m/s was defined as slow gait speed, both in men and women. All three measurements of muscle mass, HGS, and gait speed were performed before and after HD and carried out by the same trained operator. Since bioelectrical impedance measurements may be affected by hydration status in chronic HD patients, post-dialysis measurements of muscle mass, HGS, and gait speed were used in further analysis [21].

### *Biochemical investigation*

Blood samples of approximately 5 mL were immediately centrifuged at 3,000 g for 10 minutes after collection. Serum samples were stored in a 4°C refrigerator and used for biochemical analyses within 1 hour of collection. Serum levels of blood urea nitrogen (BUN), creatinine, glucose, total cholesterol (TCH), triglyceride (TG), total calcium, phosphorus, and C-reactive protein (CRP) were measured using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany). The fractional clearance index for urea (Kt/V) and urea reduction ratio (URR) were measured before dialysis and immediately after dialysis using a formal single-compartment dialysis

**Table 1.** Clinical variables of the 76 hemodialysis patients with or without sarcopenia

| Characteristics | All Patients (n = 76) | No Sarcopenia Group (n = 68) | Sarcopenia Group (n = 8) | *P* value |
|---|---|---|---|---|
| Age (years) | 60.39 ± 12.36 | 60.06 ± 10.92 | 63.25 ± 22.031 | 0.493 |
| HD duration (months) | 49.08 (22.44-132.06) | 46.62 (20.46-122.34) | 122.64 (34.62-179.25) | 0.104 |
| Height (cm) | 161.30 ± 8.69 | 162.13 ± 8.67 | 154.25 ± 5.04 | 0.014* |
| Pre-HD body weight (Kg) | 67.26 ± 16.44 | 70.05 ± 15.03 | 43.51 ± 3.63 | < 0.001* |
| Post-HD body weight (Kg) | 65.25 ± 15.37 | 68.01 ± 13.79 | 41.78 ± 2.57 | < 0.001* |
| Waist circumference (cm) | 91.91 ± 12.82 | 94.17 ± 11.52 | 72.75 ± 4.71 | < 0.001* |
| Body mass index (Kg/m$^2$) | 24.83 ± 4.71 | 25.68 ± 4.22 | 17.63 ± 0.92 | < 0.001* |
| Body fat mass (%) | 29.20 ± 7.96 | 29.81 ± 8.12 | 23.963 ± 3.38 | 0.048* |
| SBP (mmHg) | 143.42 ± 27.07 | 143.57 ± 27.43 | 142.13 ± 25.44 | 0.887 |
| DBP (mmHg) | 79.08 ± 17.57 | 77.88 ± 16.59 | 89.25 ± 23.24 | 0.083 |
| Albumin (mg/dl) | 4.25 ± 0.40 | 4.26 ± 0.40 | 4.18 ± 0.45 | 0.592 |
| Globulin (mg/dl) | 3.07 ± 0.51 | 3.08 ± 0.49 | 3.00 ± 0.72 | 0.671 |
| Total cholesterol (mg/dl) | 150.63 ± 30.84 | 150.82 ± 31.51 | 149.00 ± 26.14 | 0.876 |
| Triglyceride (mg/dl) | 117.50 (86.25-184.00) | 123.50 (95.25-199.25) | 86.50 (58.75-122.00) | 0.032* |
| Glucose (mg/dl) | 124.00 (103.00-145.75) | 126.00 (101.50-153.75) | 119.00 (114.00-131.25) | 0.451 |
| Blood urea nitrogen (mg/dl) | 62.25 ± 13.42 | 62.13 ± 13.51 | 63.25 ± 13.50 | 0.825 |
| Creatinine (mg/dl) | 9.90 ± 2.22 | 10.11 ± 2.23 | 8.15 ± 1.07 | 0.017* |
| Total calcium (mg/dl) | 9.08 ± 0.84 | 9.10 ± 0.83 | 8.96 ± 0.97 | 0.655 |
| Phosphorus (mg/dl) | 4.82 ± 1.30 | 4.94 ± 1.22 | 3.78 ± 1.57 | 0.015* |
| Intact parathyroid hormone (pg/ml) | 259.50 (129.03-479.98) | 259.50 (143.05-479.98) | 198.60 (58.30-453.38) | 0.509 |
| C reactive protein (mg/dl) | 0.25 (0.08-0.73) | 0.28 (0.08-0.77) | 0.14 (0.06-0.29) | 0.209 |
| Leptin (ng/ml) | 10.28 (5.76-55.23) | 11.35 (6.28-61.42) | 3.10 (1.86-7.54) | 0.001* |
| Kt/V (Gotch) | 1.33 ± 0.17 | 1.29 ± 0.14 | 1.61 ± 0.15 | < 0.001* |
| Urea reduction rate | 0.73 ± 0.04 | 0.72 ± 0.04 | 0.80 ± 0.03 | < 0.001* |
| ASMM (kg/m$^2$) | 11.12 ± 4.30 | 11.81 ± 4.01 | 5.29 ± 0.39 | < 0.001* |
| Handgrip strength (kg) | 23.46 ± 9.27 | 24.19 ± 9.36 | 17.22 ± 5.80 | 0.043* |
| Gait speed (m/s) | 0.85 ± 0.38 | 0.88 ± 0.38 | 0.61 ± 0.28 | 0.060 |

Values for continuous variables given as means ± standard deviation and test by Student's *t*-test; variables not normally distributed given as medians and interquartile range and test by Mann-Whitney U test. HD, hemodialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Kt/V, fractional clearance index for urea; ASMM, appendicular skeletal muscle mass. *$P < 0.05$ was considered statistically significant.

urea kinetic model. Serum intact parathyroid hormone levels (iPTH, Diagnostic Systems Laboratories, Webster, Texas, USA) and leptin (SPI-BIO, Montigny le Bretonneux, France) concentrations were measured using enzyme-linked immunosorbent assays and enzyme immunoassay, respectively [22-24].

*Statistical analysis*

Continuous variables were expressed as mean ± standard deviation (SD) and were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between patients were made using Student's independent t test (two-tailed) for normally distributed data or the Mann-Whitney U test for parameters that presented with non-normal distribution (HD duration, TG, glucose, iPTH, CRP, and leptin). Categorical data were expressed as the number of patients and analyzed by Chi-square test. Clinical variables that correlated with serum leptin levels in HD patients were evaluated using univariate linear regression analysis. Variables that were significantly associated with leptin levels in HD patients were tested for independency in multivariate forward stepwise regression analysis. Because of HD duration, TG, glucose, iPTH, CRP, and leptin were not normally distributed and underwent base 10 logarithmic transformations to achieve normality. Variables that were significantly associated with sarcopenia in the HD patients were tested for independence by multivariate stepwise linear regression analysis. Data were analyzed using SPSS for Windows (version 19.0; SPSS

**Table 2.** Distribution of hemodialysis patients with or without sarcopenia in subgroup analysis

| Characteristics | | No Sarcopenia Group (%) | Sarcopenia Group (%) | *P* value |
|---|---|---|---|---|
| Gender | Male | 40 (58.8) | 3 (37.5) | 0.250 |
| | Female | 28 (41.2) | 5 (62.5) | |
| Diabetes | No | 45 (66.2) | 7 (87.5) | 0.220 |
| | Yes | 23 (33.8) | 1 (12.5) | |
| Hypertension | No | 37 (54.4) | 4 (50.0) | 0.813 |
| | Yes | 31 (45.6) | 4 (50.0) | |
| ARB use | No | 44 (64.7) | 6 (75.0) | 0.562 |
| | Yes | 24 (35.3) | 2 (25.0) | |
| β-blocker use | No | 51 (75.0) | 7 (87.5) | 0.432 |
| | Yes | 17 (25.0) | 1 (12.5) | |
| CCB use | No | 40 (58.8) | 3 (37.5) | 0.250 |
| | Yes | 28 (41.2) | 5 (62.5) | |
| Statin use | No | 61 (89.7) | 7 (87.5) | 0.848 |
| | Yes | 7 (10.3) | 1 (12.5) | |
| Fibrate use | No | 58 (85.3) | 8 (100.0) | 0.244 |
| | Yes | 10 (14.7) | 0 (0) | |

Data are expressed as number of patients and analysis was done using Chi-square test.

**Table 3.** Clinical characteristics and serum leptin levels of 76 hemodialysis patients

| Characteristic | | Number (%) | Log-Leptin (ng/ml) | *P* value |
|---|---|---|---|---|
| Sex | Male | 43 (56.6) | 1.07 ± 0.56 | 0.104 |
| | Female | 33 (43.4) | 1.29 ± 0.57 | |
| Diabetes | No | 52 (68.4) | 1.14 ± 0.58 | 0.600 |
| | Yes | 24 (31.6) | 1.22 ± 0.56 | |
| Hypertension | No | 41 (53.9) | 1.27 ± 0.62 | 0.093 |
| | Yes | 35 (46.1) | 1.04 ± 0.49 | |
| ARB | No | 50 (65.8) | 1.20 ± 0.60 | 0.508 |
| | Yes | 26 (34.2) | 1.10 ± 0.51 | |
| β-blocker | No | 58 (76.3) | 1.18 ± 0.59 | 0.625 |
| | Yes | 18 (23.7) | 1.11 ± 0.51 | |
| CCB | No | 43 (56.6) | 1.22 ± 0.63 | 0.352 |
| | Yes | 33 (43.4) | 1.09 ± 0.49 | |
| Statin | No | 68 (89.5) | 1.15 ± 0.56 | 0.527 |
| | Yes | 8 (10.5) | 1.29 ± 0.69 | |
| Fibrate | No | 66 (86.8) | 1.14 ± 0.58 | 0.409 |
| | Yes | 10 (13.2) | 1.30 ± 0.54 | |

Data of leptin levels showed skewed distribution and, therefore, were log-transformed before analysis. Data are expressed as mean ± standard deviation and test by Student's *t*-test. ARB, angiotensin-receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker.

Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

## Results

The clinical and laboratory characteristics in 76 HD patients with or without sarcopenia are presented in **Table 1**. The mean age of total participants was 60.39 ± 12.36 years, with 34% of patients aged > 65 years. Among these patients, 36 (47.4%) patients had low HGS, 30 (39.5%) patients had slow gait speed, and 8 (10.5%) patients had low muscle mass. Eight (10.5%) patients were defined as having sarcopenia according to AWGS criteria. Compared to the non-sarcopenia group, patients in the sarcopenia group were lower in height ($P = 0.014$) and weighed less ($P < 0.001$), had lower waist circumference ($P < 0.001$), BMI ($P < 0.001$), body fat mass ($P = 0.048$), serum TG ($P = 0.032$), serum creatinine ($P = 0.017$), serum phosphorus ($P = 0.015$), leptin level ($P = 0.001$), ASMM ($P < 0.001$), and HGS ($P = 0.043$) while the Kt/V ($P < 0.001$) and URR ($P < 0.001$) were higher. **Table 2** depicts the subgroup distribution of HD patients with or without sarcopenia. Among the 76 total participants, 24 (31.6%) patients had DM and 35 (46.1%) patients had hypertension. In comparing the sarcopenia with the non-sarcopenia group, there were no statistically significant differences in distribution by gender, diabetes, hypertension, angiotensin receptor blocker, β-blocker, calcium channel blocker (CCB), statin, or fibrate drugs used. **Table 3** shows serum leptin levels and clinical characteristics among HD patients. There were no statistical differences on log-leptin level in comparing sex, diabetes, hypertension, and the drugs used (angiotensin receptor blocker, β-blocker, CCB, statin, or fibrate).

**Table 4** shows the correlation between serum leptin levels and clinical variables among 76 HD patients using univariate linear regression analyses or multivariate stepwise linear regression analysis. Univariate correlation analysis showed log-leptin levels positively correlated with pre-HD body weight ($r = 0.314$; $P = 0.006$), post-HD body weight ($r = 0.316$; $P = 0.006$), waist circumference ($r = 0.502$; $P < 0.001$), BMI ($r = 0.440$; $P < 0.001$), body fat mass ($r = 0.577$; $P < 0.001$), globulin ($r = 0.255$; $P =$

**Table 4.** Correlation between serum leptin levels and clinical variables among 76 hemodialysis patients

| Variables | Log- Leptin (ng/ml) | | | |
|---|---|---|---|---|
| | Univariate | | Multivariate | |
| | r | *P* value | Beta | *P* value |
| Age (years) | 0.036 | 0.760 | | |
| Log-HD duration (months) | -0.092 | 0.431 | | |
| Height (cm) | -0.104 | 0.373 | | |
| Pre-HD body weight (Kg) | 0.314 | 0.006* | | |
| Post-HD body weight (Kg) | 0.316 | 0.006* | | |
| Waist circumference (cm) | 0.502 | < 0.001* | 0.328 | 0.001* |
| Body mass index (Kg/m$^2$) | 0.440 | < 0.001* | | |
| Body fat mass (%) | 0.577 | < 0.001* | 0.450 | < 0.001* |
| SBP (mmHg) | -0.131 | 0.258 | | |
| DBP (mmHg) | -0.231 | 0.045* | | |
| Albumin (mg/dL) | 0.018 | 0.875 | | |
| Globulin (mg/dL) | 0.255 | 0.026* | | |
| Total cholesterol (mg/dL) | 0.146 | 0.209 | | |
| Log-Triglyceride (mg/dL) | 0.263 | 0.022* | | |
| Log-Glucose (mg/dL) | 0.110 | 0.345 | | |
| Blood urea nitrogen (mg/dL) | -0.159 | 0.170 | | |
| Creatinine (mg/dL) | 0.043 | 0.711 | | |
| Total calcium (mg/dL) | 0.052 | 0.653 | | |
| Phosphorus (mg/dL) | 0.014 | 0.904 | | |
| Log-Intact parathyroid hormone (pg/mL) | 0.166 | 0.152 | | |
| Log-C reactive protein (mg/dL) | 0.202 | 0.080 | | |
| Kt/V (Gotch) | -0.044 | 0.712 | | |
| Urea reduction rate (%) | -0.029 | 0.805 | | |
| ASMM (kg/m$^2$) | 0.251 | 0.029* | | |
| Handgrip strength (kg) | -0.233 | 0.043* | | |
| Gait speed (m/s) | -0.132 | 0.256 | | |

Data of HD duration, triglyceride, glucose, iPTH, C reactive prottein, and leptin levels showed skewed distribution and, therefore were log-transformed before analysis. Analysis data was done using the univariate linear regression analyses or multivariate stepwise linear regression analysis (adopted factors: pre-HD body weight, post-HD body weight, waist circumference, body mass index, body fat mass, DBP, globulin, log-triglyceride, handgrip strength, and ASMM). HD, hemodialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Kt/V, fractional clearance index for urea; ASMM, appendicular skeletal muscle mass. *$P$ < 0.05 was considered statistically significant.

0.026), log-TG ($r$ = 0.263; $P$ = 0.022), and ASMM ($r$ = 0.251; $P$ = 0.029) while negatively correlating with diastolic blood pressure ($r$ = -0.231; $P$ = 0.045) and HGS ($r$ = -0.233; $P$ = 0.043). Multivariate correlation analysis showed log-leptin levels positively correlated with waist circumference ($r$ = 0.328; $P$ = 0.001) and body fat mass ($r$ = 0.450; $P$ < 0.001).

After adjusting the factors significantly associated with sarcopenia (height, pre-HD body weight, post-HD body weight, waist circumference, BMI, body fat mass, log-TG, creatinine, phosphorus, ASMM, HGS, URR, Kt/V, and log-leptin), we found that lower log-leptin (β: -0.392, adjusted $R^2$ change = 0.130, $P$ < 0.001), lower URR (β: -2.491, adjusted $R^2$ change = 0.054, $P$ < 0.001)) , lower HGS (β: -0.243, adjusted $R^2$ change = 0.030, $P$ = 0.013), lower serum phosphorus level (β: -0.176, adjusted $R^2$ change = 0.023, $P$ = 0.036) and higher Kt/V (β: 2.878, adjusted $R^2$ change = 0.319, $P$ < 0.001) were the independent predictors of sarcopenia in chronic HD patients (**Table 5**).

## Discussion

In the current cross-sectional study, we investigated the relationship between leptin and sarcopenia in 76 chronic HD patients. Our study shows that serum leptin is significantly lower in the sarcopenia group. Moreover, the lower log-leptin level is an independent predictor for the presence of sarcopenia in our chronic HD patients, after adjusting possible confounding factors.

Several animal studies have demonstrated that leptin has a pivotal role on muscle metabolism. The study of Hamrick et al. revealed that leptin receptor expression in skeletal muscle was declined in aged mice and recombinant leptin treatment significantly increased hind limb muscle mass and extensor digitorum longus fiber size [13]. Neira S´ainz et al. observed an improvement of inflammation and muscle loss after leptin administration in obese leptin-deficient ob/ob mice [14]. Nguyen et al. showed that muscle regeneration was delayed in ob/ob and db/db mice partly because of the lack of

**Table 5.** Multivariate stepwise linear regression analysis of the factors correlated to sarcopenia among the 76 hemodialysis patients

| Variable | Beta | Adjusted R square | Adjusted R square change | *P* value |
|---|---|---|---|---|
| Kt/V (Gotch) | 2.878 | 0.319 | 0.319 | < 0.001* |
| Log-Leptin (ng/ml) | -0.392 | 0.449 | 0.130 | < 0.001* |
| Urea reduction rate (%) | -2.491 | 0.503 | 0.054 | < 0.001* |
| Handgrip strength (kg) | -0.243 | 0.533 | 0.030 | 0.013* |
| Phosphorus (mg/dl) | -0.176 | 0.556 | 0.023 | 0.036* |

*$P < 0.05$ is considered statistically significant in the multivariate stepwise linear regression analysis (adopted factors: height, pre-HD body weight, post-HD body weight, waist circumference, body mass index, body fat mass, log-triglyceride, creatinine, phosphorus, appendicular skeletal muscle mass, handgrip strength, urea reduction rate, Kt/V, and log-leptin). HD, hemodialysis; Kt/V, fractional clearance index for urea.

leptin signaling [25]. In the mouse model lacking all functional leptin receptor isoforms, skeletal muscle mass and fiber diameter were reduced 30-40% in relation to wild-type controls [15]. Taken together, leptin is an important factor in the regulation of skeletal muscle, likely through regulation of insulin sensitivity, oxidative stress, intramuscular fatty acid oxidation, and irisin-induced myogenesis [16, 26, 27].

Despite strong evidence from animal studies, several observational studies of leptin effects on skeletal muscle mass and function in human subjects have been conflicting. The study of Waters et al. showed that ASMM was negatively correlated with leptin and sarcopenic participants had elevated leptin concentration in elderly participants [28]. Similarly, in middle-aged to elderly participants with sarcopenic obesity, which is characterized by low skeletal muscle mass and high body fat component, Kohara et al. found that plasma leptin levels were negatively related to thigh muscle cross-sectional area [29]. In patients with CKD stage 3-4, Castaneda-Sceppa et al. showed that high serum leptin levels were significantly associated with low arm muscle area [30]. However, some studies have shown a paradoxically inverse association between serum leptin and sarcopenia. Gómez et al. observed a positive correlation between leptin and fat-free mass in the general population [31]. Hubbard et al. also noted low leptin levels in frail elderly subjects with reduced mid-arm muscle area [32]. Another study conducted from 1,573 individuals without diabetes mellitus, aged ≥ 60 years, showed that higher leptin concentration was associated with greater risk of frailty in older adults [33]. Our study showed a similar result in patients with chronic HD. Two possible factors may contribute to the discrepancy in these studies. First, leptin may exert different effects in diverse populations such as HD patients, healthy, elderly, and obese subjects. Second, few clinical studies have concerned leptin receptor function or the number which may be important determinants to the action of leptin signals. The higher serum leptin level in sarcopenia subjects observed in some studies may be attributed to leptin resistance in these patients. Thus, we propose that deficiency of serum leptin, as well as leptin resistance, is associated with sarcopenia.

Recently, emerging studies have shown that serum leptin concentration seems to be a marker of good nutritional status, rather than an appetite-suppressing uremic toxin in patients with ESRD, and that decreased leptin levels are associated with protein-energy wasting [34-37]. Our study shows serum leptin is significantly lower in the sarcopenia group, indicating the poor nutrition status in this group. Moreover, serum albumin and TCH, two traditional nutritional markers in ESRD patients, were not associated with the presence of sarcopenia in our study and previous studies have shown similar results [3]. Kim et al. reported that only subjective global assessment (SGA) was significantly associated with sarcopenia among nutritional markers but not albumin. Despite its prognostic value, serum albumin is an insensitive indicator of malnutrition in ESRD patients [38].

In our study, the prevalence of muscle dysfunction, measured by HGS and gait speed, was much higher than the prevalence of low muscle mass. Therefore, the diagnosis of sarcopenia in our study was mainly driven by low muscle mass. This finding is similar with the previous study conducted by Bataille et al. which showed that low muscle strength was presented in the large majority of 111 HD patients while a low muscle mass index was present in 33.3% of the population [39]. Prevalence of sarcopenia was

31.5% in that study and the diagnosis of sarcopenia was mainly driven by muscle mass measurement.

Our study had some additional findings. Pre-HD serum creatinine, a surrogate marker of muscle mass in chronic HD patient [40], was lower in the sarcopenia group compared to non-sarcopenia group. Our study showed that patients in sarcopenia group had significantly lower serum phosphorus and serum phosphorus was a negative predictor for sarcopenia. Serum phosphorus level is positively correlated with protein intake in HD patients, therefore lower serum phosphorus level in the sarcopenia group indicated low protein intake. Moreover, Kt/V was higher in the sarcopenia group and was a positive predictor for sarcopenia, which was possibly due to the small body size in the sarcopenia group.

The negative impact of diabetes on muscle mass and strength had been demonstrated in many of the previous studies, both in older population and ESRD population [3, 41]. In addition to insulin resistance, an increase in circulating inflammatory cytokines and elevation of plasma fatty acid concentration, is commonly observed in patients with diabetes, leading to impairment of muscle protein anabolism and accelerated loss of muscle mass and strength [42, 43]. However, our study did not show a significant association between diabetes and sarcopenia in chronic HD patients, which may have been concealed due to the small number of study subjects.

Ours is the first study to explore the possible association between serum leptin level and uremic sarcopenia in chronic HD patients, using the AWGS criteria. However, the study has several limitations. First, the sample size is small and only a small proportion of patients were classified as sarcopenia. Second, the cross-sectional nature of the study did not prove a causative relationship between serum leptin level and uremic sarcopenia. Third, misclassification bias may be likely in our study by using AWGS criteria, which was developed originally for Asian geriatric population. Unfortunately, in ESRD population, the consensus on the diagnosis of uremic sarcopenia is lacking and the best cut-offs to predict clinical outcomes are yet to be defined. Fourth, SGA or malnutrition inflammation score, two reliable scores for nutritional evaluation in chronic HD patients, were not assessed.

In conclusion, our study shows that low serum leptin is an independent predictor of sarcopenia in chronic HD patients. The findings suggest that leptin may play an important role in the development of sarcopenia in chronic HD patients. Further larger scale prospective studies are needed to confirm the association and to establish the causative relationship between leptin and uremic sarcopenia.

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## Disclosure of conflict of interest

None.

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