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Original Article

Elevated serum leptin levels are associated with low muscle strength and muscle quality in male patients undergoing chronic hemodialysis

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Abstract

Objectives: Low muscle strength and poor muscle quality are highly prevalent in patients with chronic hemodialysis (HD), which lead to an increased risk of poor clinical outcomes. Leptin dysregulation is common in HD patients. Given that leptin receptors are abundant in skeletal muscle, there may be a link between leptin and muscle strength. The cross-sectional study aimed to explore the correlation of serum leptin levels with muscle strength and muscle quality in patients with chronic HD. **Materials and Methods:** A total of 118 chronic HD patients were included in this study. Basic characteristics, handgrip strength, body composition were assessed, and blood samples for serum leptin levels and other biochemical test were obtained. We defined skeletal muscle index (SMI) as skeletal muscle mass/height^2 (kg/m^2) and muscle quality as handgrip strength divided by mid-arm muscle circumference (MAMC). Patients were classified into tertile groups, according to sex-specific leptin levels. **Results:** We observed that patients in the higher leptin tertile tend to have a higher body weight, body mass index (BMI), body fat mass, MAMC, and SMI, while the handgrip strength and muscle quality were significantly lower. Bodyweight (r = 0.30; P = 0.001), BMI (r = 0.45; P = 0.001), body fat mass (r = 0.57; P < 0.001), and SMI (r = 0.22; P = 0.018) were positively and handgrip strength (r = −0.27; P = 0.003) and muscle quality (r = −0.35; P < 0.001) were negatively correlated with serum leptin levels, respectively. After adjusting multiple confounding factors, logarithmically transformed serum leptin levels were independently associated with handgrip strength (β = −3.29, P = 0.005) and muscle quality (β = −0.14, P = 0.009). However, gender-stratified models showed the associations were observed only in male, but not in female. **Conclusion:** We concluded that higher serum leptin levels are associated with low handgrip strength and poor muscle quality in male patients on chronic HD. Further studies are needed to clarify the gender differences and to evaluate the casual relationship between circulating leptin levels and muscle strength.

Keywords: *Hemodialysis, Leptin, Muscle quality, Muscle strength*

Introduction

Protein energy-wasting, defined as decreased body stores of protein and energy fuels, is highly prevalent in patients with end-stage renal disease (ESRD) [1,2], which leads to adverse outcomes, as well as sarcopenia, a progressive loss of skeletal muscle mass and strength [3]. As two major criteria of sarcopenia, however, skeletal muscle strength and mass have different clinical relevance in chronic hemodialysis (HD) patients. In recent observational studies, muscle strength was more closely associated with the risk of mortality than muscle mass did [4,5]. Moreover, poor muscle quality, defined as the ratio of muscle strength to muscle mass, was also regarded as an important predictor for mortality in chronic HD patients [6]. Accordingly, to elucidate the potential mechanisms of muscle weakness and poor muscle quality in chronic HD patients is crucial.

Leptin, a 16-kDa hormone primarily secreted from adipose tissue, is well-established to regulate appetite and energy expenditure, glucose homeostasis, and insulin sensitivity [7]. Furthermore, leptin had been shown to trigger fatty acid oxidation in skeletal muscle [8,9], and its receptors are abundant

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in skeletal muscle [10,11]. These findings indicated that leptin signaling may play a key role in skeletal muscle homeostasis. Recently, high serum leptin levels were observed to be associated with impaired physical function in older adults, midlife women, and patients with knee osteoarthritis [12-14]. In patients with chronic kidney disease and ESRD, leptin is regarded as uremic toxin [15], which was not dialyzable by conventional HD. Thus, compared with healthy controls, serum leptin levels were markedly elevated in patients with ESRD [16]. Despite the high prevalence of both muscle weakness and leptin dysregulation in chronic HD patients, evidence regarding the association between elevated serum leptin levels and muscle weakness is limited.

Therefore, this cross-sectional study aimed to explore the correlation of serum leptin levels with both muscle strength and quality in chronic HD patients.

Materials and methods

Study participants

From January 2015 to December 2015, 160 patients who were older than 20 years and were maintained on HD using standard bicarbonate dialysate (FX class dialyzer, Fresenius Medical Care, Bad Homburg, Germany) thrice a week for more than 3 months at a medical center in Eastern Taiwan were evaluated as potential study participants. The Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, approved the study, which was conducted under the tenets of the Helsinki Declaration (IRB104-84-B). Exclusion criteria included patients who refused to participate or who had amputated limbs, acute infection, active malignancy, and bed-ridden status. Finally, 118 patients were included in this study. The basic characteristics, HD duration, and medical history included diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease (CAD) were collected through chart review.

Anthropometric analysis

After measuring height and post-HD body weight, body mass index (BMI) was calculated as post-HD body weight (kg) divided by height squared (m). We measured triceps skinfold (TSF) and mid-arm circumference (MAC) at the level of the midpoint between acromion and olecranon from both arms. Mid-arm muscle circumference (MAMC) was calculated as MAC-π × TSF, and the average values of both arms were used for further analysis.

Total skeletal muscle mass and body fat were assessed in standing position before HD, using a portable whole-body bioelectrical impedance device (Tinita BC 706DB, Tanita Corporation, Tokyo, Japan). Skeletal muscle index (SMI) was defined as total skeletal muscle mass/height^2 (kg/m^2).

Muscle strength and quality

Handgrip strength was measured at the arm without vascular access, using a Jamar Plus Digital Hand Dynamometer (SI Instruments Pty Ltd., Hilton, Australia). The patients held the dynamometer in the hand to be tested, with the arm at right angles and elbow at the side of the body. Each measurement was performed with a rest of 1 min, and the average value was recorded. Muscle quality was then defined as handgrip strength (kg) divided by MAMC (cm) [17].

Biochemical investigations

About 5 mL blood sample was obtained before HD in each patient. After determining the blood cell counts (Sysmex SP-1000i, Sysmex American, Mundelein, IL, USA), the remaining blood sample was centrifuged for biochemical analyses. We measured serum levels of blood urea nitrogen, creatinine, albumin, total cholesterol, phosphorus, and C-reactive protein using an autoanalyzer (SiemensAdvia 1800, Siemens Healthcare GmbH, Henkestr, Germany). The fractional clearance index for urea (Kt/V) was calculated using a single-compartment urea kinetic model. Serum intact parathyroid hormone (PTH) levels were measured using enzyme-linked immunosorbent assays (ELISA; Diagnostic Systems Laboratories, Webster, Texas, USA), and serum leptin levels by a commercially available enzyme immunoassay (SPI-BIO, Montigny le Bretonneux, France).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or as median and interquartile range based on data distribution. Categorical variables are expressed as absolute (n) and relative frequency (%). The differences between males and females were compared using independent *t*-test or Mann–Whitney U-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Patients were then classified into three groups according to sex-specific leptin levels. These variables among groups were analyzed by one-way analysis of variance or the Cochran–Armitage test for trend. Clinical variables that correlated with serum leptin levels were evaluated through Pearson's correlation analysis. Serum leptin levels, HD duration, albumin, intact PTH, and C-reactive protein showed skewed distribution and were log-transformed before analysis. Finally, the association of serum leptin levels with handgrip strength and muscle quality were examined through univariate and multivariate linear regression. Statistical analysis was performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the clinical variables of the 118 HD patients. The mean age was 63.2 ± 13.2 years. Among them, 43 (36.4%) had diabetes mellitus, 56 (47.5%) had hypertension, 32 (27.1%) had hyperlipidemia, and 78 (66.1%) had CAD. Compared with males, female patients had longer HD duration, lower height, body weight, BMI, MAMC, SMI, handgrip strength, muscle quality, and serum creatinine levels, while body fat mass, total cholesterol, Kt/V and serum leptin levels were significantly higher.

Clinical characteristics of the study population stratified by sex-specific tertiles of serum leptin levels were exhibited in Table 2. Increasing tertiles of serum leptin levels were significantly associated with greater weight ($P < 0.001$), BMI ($P < 0.001$), body fat mass ($P < 0.001$), MAMC ($P = 0.028$), SMI ($P = 0.001$), and lower handgrip strength ($P = 0.045$) and muscle quality ($P = 0.001$).

Table 1: Clinical variables of the 118 hemodialysis patients

Characteristics	All patients (*n*=118)	Male (*n*=61)	Female (*n*=57)	*P*
Demographics				
Age (years)	63.2±13.2	61.6±12.4	64.8±13.9	0.188
HD duration (years)	4.7 (8.0)	4.0 (7.0)	6.7 (9.0)	0.028*
Examination				
Height (cm)	160.0±8.8	165.5±7.0	154.1±6.3	<0.001*
Body weight (kg)	65.1±15.3	73.1±14.4	56.6±11.2	<0.001*
BMI (kg/m^2)	25.3±4.9	26.6±4.9	23.8±4.5	0.002*
Body fat mass (%)	29.5±7.8	25.8±6.3	33.5±7.2	<0.001*
MAMC (cm)	20.9±3.0	22.6±2.5	19.1±2.4	<0.001*
SMI (kg/m^2)	11.4±4.3	14.0±4.1	8.7±2.4	<0.001*
Handgrip strength (kg)	22.2±9.6	27.7±9.1	16.3±6.0	<0.001*
Muscle quality	1.1±0.4	1.2±0.4	0.9±0.4	<0.001*
Laboratory data				
Hemoglobin (g/dL)	10.4±1.1	10.6±1.1	10.2±1.1	0.066
Albumin (g/dL)	4.1 (0.5)	4.2 (0.4)	4.1 (0.5)	0.137
Total cholesterol (mg/dL)	147.1±34.8	136.7±31.8	158.2±34.8	0.001*
BUN (mg/dL)	61.7±14.0	61.4±13.9	62.0±14.2	0.840
Creatinine (mg/dL)	9.6±2.1	10.3±2.2	8.9±1.6	<0.001*
Phosphorus (mg/dL)	4.7±1.3	4.7±1.3	4.8±1.3	0.848
Intact PTH (pg/mL)	209.4 (389.1)	192.9 (275.7)	265.4 (432.5)	0.246
C-reactive protein (mg/dL)	0.31 (0.80)	0.32 (0.99)	0.28 (0.71)	0.863
Kt/V (Gotch)	1.3±0.2	1.2±0.1	1.4±0.2	<0.001*
Leptin (ng/mL)	12.5 (51.1)	9.5 (41.7)	20.6 (62.6)	0.019*
Comorbid conditions, *n* (%)				
Diabetes mellitus	43 (36.4)	24 (39.3)	19 (33.3)	0.498
Hypertension	56 (47.5)	32 (52.5)	24 (42.1)	0.260
Hyperlipidemia	32 (27.1)	18 (29.5)	14 (24.6)	0.546
CAD	78 (66.1)	37 (60.7)	41 (71.9)	0.196

*P<0.05 is considered statistically significant, comparing differences between male and female. Values for continuous variables are shown as mean±SD after analysis by Student's *t*-test; variables not normally distributed are shown as median and interquartile range after analysis by the Mann-Whitney U-test; values are presented as *n* (%) and analysis after analysis by the Chi-square test. HD: Hemodialysis, BMI: Body mass index, MAMC: Mid-arm muscular circumference, SMI: Skeletal muscle index, BUN: Blood urea nitrogen, PTH: Parathyroid hormone, Kt/V: Fractional clearance index for urea, CAD: Coronary artery disease, SD: Standard deviation

Table 2: Clinical characteristics of the study population stratified by sex-specific tertiles of serum leptin levels

Characteristics	Tertile 1 (*n*=39)	Tertile 2 (*n*=40)	Tertile 3 (*n*=39)	*P* for trend
Demographics				
Age (years)	61.3±13.0	63.6±13.4	64.6±13.4	0.277
HD duration (years)	6.0 (10.0)	5.0 (8.0)	4.3 (7.0)	0.118
Examination				
Height (cm)	159.8±9.7	160.2±8.8	160.1±7.9	0.888
Body weight (kg)	57.5±14.7	66.8±13.6	71.0±14.8	<0.001*
BMI (kg/m^2)	22.3±4.3	25.9±4.3	27.6±4.6	<0.001*
Body fat mass (%)	25.9±8.7	28.9±7.1	33.7±5.2	<0.001*
MAMC (cm)	20.0±3.2	21.3±2.6	21.5±3.1	0.028*
SMI (kg/m^2)	9.7±3.5	11.7±3.6	12.8±5.1	0.001*
Handgrip strength (kg)	25.1±10.1	20.7±8.8	20.8±9.6	0.045*
Muscle quality	1.2±0.4	1.0±0.4	0.9±0.4	0.001*
Laboratory data				
Hemoglobin (g/dL)	10.5±1.1	10.4±1.5	10.3±0.8	0.623
Albumin (g/dL)	4.1 (0.4)	4.2 (0.5)	4.1 (0.5)	0.569
Total cholesterol (mg/dL)	142.2±34.7	149.2±37.3	149.8±32.7	0.340
BUN (mg/dL)	63.5±13.5	62.8±13.9	58.8±14.4	0.140
Creatinine (mg/dL)	9.4±2.2	9.8±2.1	9.6±1.8	0.573
Phosphorus (mg/dL)	4.7±1.5	4.8±1.3	4.7±1.1	0.923
Intact PTH (pg/mL)	184.1 (298.2)	241.9 (366.2)	254.3 (404.1)	0.545

Contd...

Table 2: Contd...

Characteristics	Tertile 1 (*n*=39)	Tertile 2 (*n*=40)	Tertile 3 (*n*=39)	*P* for trend
C-reactive protein (mg/dL)	0.29 (0.96)	0.24 (0.60)	0.49 (1.15)	0.915
Kt/V (Gotch)	1.4±0.2	1.3±0.2	1.3±0.2	0.198
Comorbid conditions, *n* (%)				
Diabetes mellitus	12 (30.8)	16 (40.0)	15 (38.5)	0.482
Hypertension	19 (48.7)	23 (57.5)	14 (35.9)	0.259
Hyperlipidemia	8 (20.5)	11 (27.5)	13 (33.3)	0.439
CAD	23 (59.5)	29 (72.5)	26 (66.7)	0.475

*$P<0.05$ is considered statistically significant. Values for continuous variables are shown as mean±SD after analysis by Student's *t*-test; variables not normally distributed are shown as median and interquartile range after analysis by the Mann-Whitney U-test; values are presented as *n* (%) and analysis after analysis by the Chi-square test. Sex-specific tertile cut-off points for leptin levels were 5.2 and 26.3 ng/mL in men; 10.3 and 40.5 ng/mL in women. HD: Hemodialysis, BMI: Body mass index, MAMC: Mid-arm muscular circumference, SMI: Skeletal muscle index, BUN: Blood urea nitrogen, PTH: Parathyroid hormone, Kt/V: Fractional clearance index for urea, CAD: Coronary artery disease

The continuous variables correlated with logarithmically transformed serum leptin levels are shown in Table 3. The leptin had a positive correlation with body weight ($r = 0.30$; $P = 0.001$), BMI ($r = 0.45$; $P = 0.001$), body fat mass ($r = 0.57$; $P < 0.001$), and SMI ($r = 0.22$; $P = 0.018$), while had an inverse correlation with handgrip strength ($r = -0.27$; $P = 0.003$) and muscle quality ($r = -0.35$; $P < 0.001$).

Table 4 shows the unadjusted and adjusted linear regression analysis of serum leptin levels with handgrip strength and muscle quality. After fully adjustment of age, sex, HD duration, diabetes mellitus, hypertension, CAD, SMI, body fat mass, albumin, hemoglobin, and C-reactive protein, we demonstrated that logarithmically transformed serum leptin levels were negatively associated with both handgrip strength ($\beta = -3.29$, $P = 0.005$) and muscle quality ($\beta = -0.14$, $P = 0.009$). Sensitivity analyses were performed among 82 patients who had handgrip strength measurement in the dominant arm, which showed similar results [Supplementary Table 1].

Given the significant differences of serum leptin levels and muscle function between males and females, the associations between serum leptin levels, handgrip strength, and muscle quality were further stratified by gender [Table 5]. The negative associations of serum leptin levels with handgrip strength ($\beta = -5.47$, $P = 0.011$ for males; $\beta = -0.57$, $P = 0.642$ for females) and muscle quality ($\beta = -0.22$, $P = 0.021$ for males; $\beta = -0.04$, $P = 0.534$ for males) were only observed in males, not in females.

Table 3: Correlation between serum leptin levels and clinical variables among 118 hemodialysis patients

Variables	Log-leptin (ng/mL)	
	r	*P*
Demographics		
Age (years)	0.09	0.329
Log-HD duration (years)	−0.13	0.162
Examination		
Height (cm)	−0.14	0.143
Body weight (kg)	0.30	0.001*
BMI (kg/m^2)	0.45	<0.001*
Body fat mass (%)	0.57	<0.001*
MAMC (cm)	0.13	0.178
SMI (kg/m^2)	0.22	0.018*
Handgrip strength (kg)	−0.27	0.003*
Muscle quality	−0.35	<0.001*
Laboratory data		
Hemoglobin (g/dL)	−0.07	0.484
Log-Albumin (g/dL)	0.04	0.685
Total cholesterol (mg/dL)	0.15	0.112
BUN (mg/dL)	−0.14	0.123
Creatinine (mg/dL)	−0.01	0.938
Phosphorus (mg/dL)	−0.01	0.975
Log-Intact PTH (pg/mL)	0.12	0.202
Log-C-reactive protein (mg/dL)	0.06	0.546
Kt/V (Gotch)	−0.03	0.744

*$P<0.05$ is considered statistically significant. Data of HD duration, albumin, intact PTH, C-reactive protein, and leptin levels showed skewed distributions, and therefore were log-transformed before analysis. HD: Hemodialysis, BMI: Body mass index, MAMC: Mid-arm muscular circumference, SMI: Skeletal muscle index, BUN: Blood urea nitrogen, PTH: Parathyroid hormone, Kt/V: Fractional clearance index for urea

Discussion

In this cross-sectional study of chronic HD adults, higher-serum leptin concentration predicted handgrip strength weakness and poor muscle quality. These associations were independent of body fat mass, skeletal muscle mass, and serum C-reactive protein levels, which suggests the independent role of leptin on handgrip strength and muscle quality. However, these associations were only observed in males but not in females.

Several potential mechanisms explained the association between high leptin levels and muscle weakness in our chronic HD patients. Leptin was well-recognized as a proinflammatory adipokine [18-21], and its high serum levels in patients with ESRD were associated with chronic inflammation status, as well as impaired insulin sensitivity [22-24]. Both of the above conditions have detrimental effects on skeletal muscle homeostasis [25]. Besides, there were well-established links between hyperleptinemia and increased risk of cardio-metabolic diseases [26,27], which has a negative impact on both muscle strength and quality. Despite this, the association between high leptin levels and poor muscle strength and quality remained significant after our full adjustment, included age, sex, HD duration, DM, HTN, CAD, SMI, body fat mass, Kt/V, albumin, hemoglobin, and C-reactive protein. This may implicate an independent role of leptin on skeletal muscle homeostasis.

Table 4: Multivariate linear regression analysis of serum leptin levels correlated with handgrip strength and muscle quality among 118 hemodialysis patients

Variables	Handgrip strength		Muscle quality	
Log-leptin	β (95% CI)	*P*	β (95% CI)	*P*
Model 1	−4.00 (−6.65-−1.35)	0.003*	−0.22 (−0.33-−0.11)	<0.001*
Model 2	−3.14 (−5.34-−0.93)	0.006*	−0.14 (−0.24-−0.04)	0.009*
Model 3	−3.29 (−5.57-−1.01)	0.005*	−0.14 (−0.25-−0.04)	0.009*

*P<0.05 is considered statistically significant. Model 1: Unadjusted, Model 2: Adjusted for age, sex, HD duration, diabetes mellitus, hypertension, CAD, skeletal muscle index and body fat mass, Model 3: Adjusted for age, sex, HD duration, diabetes mellitus, hypertension, CAD, skeletal muscle index, body fat mass, albumin, hemoglobin and C-reactive protein. CI: Confidence interval, HD: Hemodialysis, CAD: Coronary artery disease

Table 5: Multivariate linear regression analysis of serum leptin levels correlated with handgrip strength and muscle quality, stratified by gender

Log-leptin	Handgrip strength		Muscle quality	
	β (95% CI)	*P*	β (95% CI)	*P*
Males				
Model 1	−3.20 (−6.67-0.26)	0.069	−0.22 (−0.37-−0.08)	0.003*
Model 2	−5.50 (−9.44-−1.57)	0.007*	−0.23 (−0.41-−0.06)	0.011*
Model 3	−5.47 (−9.65-−1.29)	0.011*	−0.22 (−0.41-−0.03)	0.021*
Females				
Model 1	−0.73 (−3.48-2.03)	0.600	−0.10 (−0.25-0.06)	0.206
Model 2	−0.79 (−3.10-1.52)	0.495	−0.06 (−0.18-0.06)	0.335
Model 3	−0.57 (−3.04-1.89)	0.642	−0.04 (−0.17-0.09)	0.534

*P<0.05 is considered statistically significant. Model 1: Unadjusted, Model 2: Adjusted for age, HD duration, diabetes mellitus, hypertension, CAD, skeletal muscle index and body fat mass, Model 3: Adjusted for age, HD duration, diabetes mellitus, hypertension, CAD, skeletal muscle index, body fat mass, albumin, hemoglobin and C-reactive protein. CI: Confidence interval, HD: Hemodialysis, CAD: Coronary artery disease

Reduced skeletal muscle mass was observed in leptin-deficient Ob/Ob mice, while leptin administration showed beneficial effect on the growth of skeletal muscle mass [28]. Recently, leptin signaling was also shown to stimulate vascular endothelial growth factor A production by skeletal myocytes, which suggests its regulatory role in skeletal muscle angiogenesis [29]. Hyperleptinemia in ESRD patients may actually implicate leptin resistance, in which normal leptin signaling was blunted. This may explain our observation between high serum leptin levels and low muscle strength. Moreover, leptin resistance impairs fatty acid oxidation in muscle [9] and leads to increase in intramuscular fat infiltration, which contributed to the decrease in muscle quality [8,30]. However, these intramuscular changes may not result in a reduction in either MAMC or total skeletal muscle mass volume.

Several observational studies showed a close link between serum leptin levels and physical function in different populations. In premenopausal mid-life women, high serum leptin levels were independently associated with poor physical performance, included stair climb, sit-to-stand, 2-pound lift times, and forward reach distance [13]. In the seniors-ENRICA cohort, which evaluated community-dwelling older men and women, higher leptin levels were associated with poor self-reported physical performance and lower extremity function, assessed by Short Physical Performance Battery [12]. In patients with knee osteoarthritis, serum leptin levels were inversely related to muscle strength and physical performance [14]. These observations were in line with our findings in chronic HD patients.

Interestingly, the negative associations between serum leptin levels and handgrip strength were only observed in males, but not in females in our study. This finding indicated the potentially different impacts of serum leptin levels on handgrip strength between males and females. The discrepancies may be attributed to gender differences in the leptin biological activity, as well as the differences in the expression of skeletal muscle leptin receptors, which is partly mediated by sex hormones [31,32]. Nevertheless, further studies are needed to clarify this critical issue.

We acknowledged several limitations to our study. First, handgrip strength was measured at the arm without vascular access, not the dominant hand. However, our sensitivity analyses, which included the patients assessed in the dominant arm, showed similar trends. Second, we did not evaluate muscle strength of lower extremities and physical performance, such as 6-min walk test, repeated sit-to-stand, Short Physical Performance Battery test. Third, inflammatory cytokines other C-reactive protein, such as interleukin-6 and TNF-α, were not measured. Finally, this is a cross-sectional study, and the physiologic role of leptin on muscle strength, and quality could not be elucidated in the current study.

Conclusion

We showed that higher serum leptin levels were associated with handgrip strength weakness and poor muscle quality in male patients undergoing chronic HD. The molecular mechanisms by which leptin exerts its effects in skeletal muscle homeostasis in chronic HD patients, as well as the causes of gender differences in the associations between leptin and muscle strength, should be further investigated.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Multivariate linear regression analysis of serum leptin levels correlated with handgrip strength and muscle quality among 82 hemodialysis patients who had handgrip strength measurement in the dominant arm

Variables	Handgrip strength		Muscle quality	
Log-leptin	β (95% CI)	*P*	β (95% CI)	*P*
Model 1	−3.83 (−6.95-−0.70)	0.017*	−0.21 (−0.34-−0.08)	0.002*
Model 2	−3.26 (−5.98-−0.54)	0.020*	−0.11 (−0.24-0.02)	0.083
Model 3	−3.74 (−6.56-−0.91)	0.010*	−0.13 (−0.26-0.01)	0.061

**P*<0.05 is considered statistically significant. Model 1: Unadjusted, Model 2: Adjusted for age, sex, HD duration, diabetes mellitus, hypertension, CAD, skeletal muscle index and body fat mass, Model 3: Adjusted for age, sex, HD duration, diabetes mellitus, hypertension, CAD, skeletal muscle index, body fat mass, albumin, hemoglobin and C-reactive protein. CI: Confidence interval, HD: Hemodialysis, CAD: Coronary artery disease