

Plasma Leptin Concentration and Sympathetic Nervous Activity in Older Adults With Physical Dysfunction

Koji Shibasaki,¹ Shizuru Yamada,² Masahiro Akishita,¹ and Sumito Ogawa¹

¹Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan; and ²Komagane Kogen Ladies Clinic, Nagano 399-4117, Japan

Context: Previous research has shown a positive relationship between plasma leptin and sympathetic nervous activity. High plasma leptin activate inflammatory cytokines and lead to muscle wasting. However, studies have detected low sympathetic nervous activity and high plasma leptin in older adults with muscle wasting, sarcopenia, and frailty. High plasma leptin do not seem to correlate with high sympathetic nervous activity. However, their relationship in older adults remains unclear.

Objective: We investigated the relationship between plasma leptin and sympathetic nervous activity in older adults.

Design, Setting, and Participants: We conducted a cross-sectional study and analyzed the results from 69 participants aged ≥ 75 years. Sympathetic nervous activity was measured by heart rate variability, obtained from 24-hour Holter monitoring. A functional independence measure (FIM) and Barthel index were used to assess physical function.

Results: The plasma leptin was higher in women (men, 3.4 ± 2.8 ng/mL; women, 6.6 ± 6.5 ng/mL; $P = 0.024$). Plasma leptin was negatively and substantially related to the FIM ($\beta = -0.233$; $P = 0.049$) and Barthel index ($\beta = -0.298$, $P = 0.018$) after adjustment for covariates. However, the data showed no relationship between the plasma leptin and sympathetic nervous activity.

Conclusions: We could not detect an association between sympathetic nervous activity and plasma leptin in older adults. This might suggest a failure of the feedback system of the sympathetic nervous system, leading to muscle wasting in older adults.

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Freeform/Key Words: heart rate variability, leptin, older adults, sympathetic nervous activity

Leptin is a type of adipocytokine and is secreted by white adipose tissue [1]. Plasma leptin activates the sympathetic nervous system through the hypothalamus and increases arterial blood pressure. Activation of the sympathetic nervous system, which innervates adipose tissue, has a lipolytic effect [1]. Furthermore, an activated sympathetic nervous system regulates the plasma leptin concentration, causing a decrease.

The plasma leptin levels were substantially related to the C-reactive protein levels, especially in older adults [2]. Moreover, greater plasma leptin concentrations promote other inflammatory cytokines and result in muscle wasting [3]. Thus, a greater leptin concentration has been connected to poor physical performance, independently of age, body mass index (BMI), percentage of skeletal muscle mass, race/ethnicity, economic status, diabetes,

Abbreviations: BMI, body mass index; FIM, functional independence measure; HF, high frequency; LF, low frequency; MMSE, Mini-Mental State Examination.

and other known confounders [4]. Kohara *et al.* [5] demonstrated that the plasma leptin level was greater in older adults with sarcopenia and sarcopenic obesity compared with normal healthy older adults and those with obesity without sarcopenia.

Sympathetic nervous activity gradually decreases with aging [6]. In addition, sympathetic nervous activity is lower in older adults with frailty or sarcopenia than in healthy older adults [7, 8]. Depressed sympathetic nervous activity has been reported to lead to muscle wasting, muscle weakness, and greater mortality [8–10].

Although recent studies revealed a positive correlation between plasma leptin levels and sympathetic nervous activity [1, 11–13], some research has reported greater plasma leptin concentrations in older adults with muscle wasting, sarcopenia, or frailty [4, 5, 14]. In contrast, other studies showed lower sympathetic nervous activity in older adults with frailty or sarcopenia [7, 8, 15]. This suggests that the relationship between the plasma leptin levels and sympathetic nervous activity is different in healthy older adults from that in participants with such geriatric conditions.

A high plasma leptin concentration is also known to elevate the blood pressure [16–19]. However, older adults with frailty who were considered to have high plasma leptin levels were also reported to have low blood pressure and high mortality [20–23]. The positive correlation between the plasma leptin concentration and blood pressure was not found in frail older adults.

The plasma leptin level, sympathetic nervous activity, and blood pressure, therefore, do not seem to correlate positively in older adults with geriatric conditions. Previous research indicated that sympathetic nervous activity was disturbed in frail older adults and led to high mortality [8]. This result was also confirmed by large-scale clinical trials [7, 9]. Therefore, the positive correlation between plasma leptin concentrations and sympathetic nervous activity might disappear in older adults with muscle wasting, sarcopenia, or frailty.

We hypothesized that the reason the plasma leptin level and sympathetic nervous activity have not shown positive correlations with muscle wasting, sarcopenia, or frailty in older adults is the disturbance of sympathetic nervous activity in such geriatric conditions. However, these relationships have not been investigated well. The aim of the present study was to investigate the relationships among leptin concentrations, physical function, and the sympathetic nervous system.

1. Participants and Methods

A. Setting and Participants

We conducted a cross-sectional study and analyzed the results from 69 older adults aged ≥ 75 years who lived in the Nagano Prefecture, Japan. We excluded older adults who had undergone treatment of acute phase disease within the previous 2 weeks or malignancy. To minimize the influence of confounders concerning sympathetic nervous activity, patients with arrhythmias, those receiving antiarrhythmic drugs, β -blockers, or anticholinergic drugs, and those with neurodegenerative disease were also excluded, on the basis of the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology [24]. The medical records were reviewed to obtain information on the history of hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, and ischemic heart disease, and this information was confirmed by the patient and/or family. The institutional review board of the Keijinkai Kikyougahara Hospital approved the study protocol. All participants or their families provided written informed consent.

B. Ambulatory Blood Pressure Monitoring and 24-Hour Holter Monitoring

Ambulatory blood pressure monitoring was performed for 24 hours using a TM-2431 device (A&D, Tokyo, Japan). The heart rate variability obtained from ambulatory Holter recording

was performed to assess sympathetic nervous activity. Ambulatory Holter recording was performed for 24 hours using QR2100 (Fukuda ME Kogyo, Tokyo, Japan) and processed with HS1000VL (Fukuda ME Kogyo, Tokyo, Japan). For the time domain analysis, the standard deviations of all NN intervals in all 5-minute segments of the entire recording were calculated, and the frequent domain analysis was calculated using fast Fourier transformation. From the power spectral density, low frequency (LF; 0.04 to 0.15 Hz), high frequency (HF; 0.15 to 0.40 Hz), and the LF/HF ratio were calculated. HF and the LF/HF ratio are considered to reflect parasympathetic nervous activity and sympathetic nervous modulations, respectively [24]. The measured data for systolic blood pressure and diastolic blood pressure were divided into 3 categories: 24-hour, daytime (8:00 AM to 6:00 PM), and night-time (10:00 PM to 4:00 AM) using Asian criteria [25]. Previous studies have shown positive correlations between the plasma leptin levels, blood pressure, and sympathetic nervous activity using the same methods; therefore, we adopted ambulatory blood pressure monitoring and 24-hour Holter recording.

C. Physical Function and Hematological Measures

The patients' height, weight, and BMI were measured. The functional independence measure (FIM) [26] and Barthel index [27] were calculated to assess physical function. We used the Mini-Mental State Examination (MMSE) to examine cognitive function because previous studies have indicated a relationship between low plasma leptin levels and cognitive impairment [28, 29]. Venous blood samples were obtained from the subjects in the morning after an overnight fast. Blood cell counts and plasma levels of chemical parameters were determined by a commercial laboratory (Health Science Research Institute, Yokohama, Japan).

D. Statistical Analysis

The data were analyzed using SPSS software, version 24.0 (SPSS Japan Inc., Tokyo, Japan). The Pearson correlation coefficient was calculated to determine the relationship between the plasma leptin concentration and the other measurements, including age, BMI, MMSE, FIM, Barthel index, blood data, heart rate variability indexes, and blood pressure. The Mann-Whitney *U* test was applied to compare sex differences. Multiple regression analyses were adapted to adjust for age, sex, and BMI.

We divided the participants into four categories according to physical function and BMI as follows (the median was used as the cutoff value): high physical function and low BMI group, low physical function and low BMI group, high physical function and high BMI group, and low physical function and high BMI group. After categorizing, two-factor ANOVA was used to compare the results among the four groups. The Bonferroni method was used for *post hoc* tests after two-factor ANOVA.

2. Results

We recruited 69 older adults. The characteristics of the participants are listed in Table 1. The mean age was 86.4 ± 6.4 years. Of the 69 adults, 54 were women (78.3%). The average FIM and Barthel index were 52.8 and 37.5, respectively, indicating low physical function. For heart rate variability, the values for the standard deviations of all NN intervals in all 5-minute segments of the entire recording, LF, HF, and LF/HF were 87.2 ± 32.5 ms, 39.2 ± 26.7 ms², 71.7 ± 59.0 ms², and 0.72 ± 0.28 , respectively. The 24-hour systolic and diastolic blood pressures were 131.0 and 73.7 mm Hg, respectively. The night/day ratio was 1.00, indicating the disappearance of the circadian rhythm of blood pressure.

The correlation between the leptin concentration and the other measurements is presented in Table 2. The leptin concentration was substantially and positively correlated with the BMI and total protein using the Pearson correlation coefficient (*r*). A statistically significant difference between the sexes was also detected. In men, the leptin concentration was 3.4 ± 2.8 ng/mL, and in women, it was 6.6 ± 6.5 ng/mL (*P* = 0.024). However, the leptin levels

Table 1. Participant Characteristics

Category	Results
Background data	
Subjects, n	69
Age, y	86.4 ± 6.4
Female sex, %	54 (78.3)
BMI, kg/m ²	19.2 ± 3.7
Disease type	
Cerebrovascular disease, n (%)	37(60.7)
Disuse syndrome, n (%)	14 (23.0)
Fracture, n (%)	10 (16.3)
Blood data	
Leptin, ng/mL	5.9 ± 6.0
Total protein, g/dL	6.6 ± 0.6
Albumin, g/dL	3.6 ± 0.4
Hemoglobin, g/dL	12.1 ± 1.7
Total cholesterol, mg/dL	176 ± 37
C-reactive protein, mg/dL	1.3 ± 3.2
Fasting glucose, mg/dL	90.2 ± 28.4
Adiponectin, µg/mL	19.9 ± 10.9
Physical function	
FIM	55.6 ± 33.7
Barthel index	37.5 ± 33.1
Cognitive function (MMSE)	11.9 ± 10.7
Heart rate variability indexes	
Heart rate, bpm	72.3 ± 11.6
SDANN, ms	87.2 ± 32.5
LF, ms ²	39.2 ± 26.7
HF, ms ²	71.7 ± 59.0
LF/HF ratio	0.72 ± 0.28
Ambulatory blood pressure monitoring	
24-Hour systolic blood pressure	131.0 ± 17.7
Daytime systolic blood pressure	131.0 ± 19.8
Night-time systolic blood pressure	130.0 ± 20.1
24-Hour diastolic blood pressure	73.7 ± 8.5
Daytime diastolic blood pressure	74.5 ± 10.2
Night-time diastolic blood pressure	72.3 ± 10.9
Night/day ratio	1.00 ± 0.13

Data are presented as mean ± SD.

Abbreviation: SDANN, standard deviations of all NN intervals in all 5-minute segments of entire recording.

were not related to the autonomic nervous activity obtained from the Holter monitoring indexes such as LF, HF, and the LF/HF ratio. Moreover, the leptin levels were not related to the blood pressure, including 24-hour systolic and diastolic, daytime systolic and diastolic, night-time systolic and diastolic, or the night/day ratio.

Multiple regression analyses revealed that leptin was substantially and negatively correlated with the MMSE results ($\beta = -0.259$; $P = 0.035$), FIM ($\beta = -0.233$; $P = 0.049$), and the Barthel index ($\beta = -0.298$; $P = 0.018$).

We categorized the participants into four groups according to physical function (FIM and Barthel index) and BMI as follows: high FIM (or Barthel index) and low BMI group, low FIM (or Barthel index) and low BMI group, high FIM (or Barthel index) and high BMI group, and low FIM (or Barthel index) and high BMI group. Two-factor ANOVA revealed that the plasma leptin level was significantly associated statistically with the FIM and BMI (FIM, $F = 4.910$; $P = 0.030$; BMI, $F = 7.942$; $P = 0.006$). In contrast, the interaction effect was not statistically significant [FIM*BMI, $F = 0.853$; $P = 0.359$; Fig. 1(a)]. When we used the Barthel index as the indication of physical function, the results were similar to those with FIM [Barthel index, $F = 1.305$; $P = 0.258$; BMI, $F = 4.260$; $P = 0.044$; Barthel index*BMI interaction, $F = 0.005$; $P = 0.945$; Fig. 1(b)]. The plasma leptin level was not substantially different among the four groups.

Table 2. Pearson Simple Correlation and Multiple Regression Analysis Between Plasma Leptin and Other Measurements

Variable	All Participants (n = 69)		Male Sex (n = 15)		Female Sex (n = 54)	
	r	P Value	r	P Value	r	P Value
Sex ^a		0.024	NA		NA	
Male	3.4 ± 2.8					
Female	6.6 ± 6.5					
Age	0.011	0.931	-0.108	0.701	0.014	0.917
BMI	0.359	0.002	0.243	0.383	0.461	<0.001
MMSE	-0.194	0.134	-0.320	0.265	-0.168	0.258
FIM	-0.117	0.341	-0.231	0.407	-0.104	0.454
Barthel index	-0.161	0.216	-0.347	0.224	-0.142	0.340
Total protein	0.249	0.039	-0.283	0.307	0.216	0.117
Albumin	0.092	0.475	-0.082	0.771	0.107	0.468
Hemoglobin	-0.146	0.242	-0.194	0.489	-0.079	0.579
Total cholesterol	0.035	0.781	0.600	0.018	-0.182	0.211
Creatinine	0.154	0.220	0.763	0.001	0.176	0.222
C-reactive protein	0.241	0.073	-0.273	0.325	0.272	0.085
Fasting glucose	0.132	0.281	0.765	0.001	0.087	0.533
Adiponectin	-0.174	0.153	0.098	0.727	-0.230	0.094
Heart rate variability from Holter monitoring						
Heart rate	-0.002	0.988	0.471	0.076	-0.075	0.592
SDANN	-0.206	0.098	-0.578	0.024	-0.167	0.228
LF	-0.114	0.363	-0.260	0.349	-0.014	0.918
HF	-0.121	0.331	-0.154	0.585	-0.115	0.409
LF/HF ratio	0.052	0.679	-0.025	0.929	0.129	0.351
Ambulatory blood pressure monitoring						
24-Hour SBP	0.050	0.695	-0.178	0.527	0.082	0.575
Daytime SBP	0.045	0.723	-0.289	0.296	0.096	0.511
Night-time SBP	0.040	0.752	-0.011	0.970	0.045	0.759
24-Hour DBP	0.004	0.973	0.051	0.856	-0.005	0.971
Daytime DBP	-0.020	0.876	-0.176	0.531	-0.002	0.992
Night-time DBP	0.001	0.996	0.331	0.228	-0.048	0.746
Night/day ratio	0.022	0.860	0.423	0.116	-0.043	0.770

Abbreviations: DBP, diastolic blood pressure; NA, not applicable; SBP, systolic blood pressure; SDANN, standard deviations of all NN intervals in all 5-minute segments of entire recording.

^aThe Mann-Whitney *U* test was applied for the comparison of sex differences.

In female subjects, the plasma leptin level was significantly associated statistically with the BMI but not with the FIM (FIM, $F = 2.521$; $P = 0.119$; BMI, $F = 7.329$; $P = 0.009$; FIM*BMI, $F = 0.026$; $P = 0.873$). The plasma leptin level was significantly greater statistically in the low FIM and high BMI group than in the low FIM and low BMI group [$P = 0.048$; Fig. 1(c)]. In male subjects, the FIM and BMI were both substantially associated with the plasma leptin level (FIM, $F = 5.602$; $P = 0.037$; BMI, $F = 9.504$; $P = 0.010$), and the interaction was also statistically significant (FIM*BMI, $F = 6.583$; $P = 0.026$). The plasma leptin level was substantially greater in the low FIM and high BMI group compared with the low FIM and low BMI group and high FIM and high BMI group [Fig. 1(e)]. When using the Barthel index as an indication of physical function instead of the FIM score, a similar association between the plasma leptin level and Barthel index and BMI was observed [Fig. 1(d) and 1(f)].

3. Discussion

The present study has demonstrated that a higher plasma leptin level is significantly associated with low physical function. This finding was independent of age, sex, and BMI. Furthermore, the data showed a substantial relationship between the plasma leptin

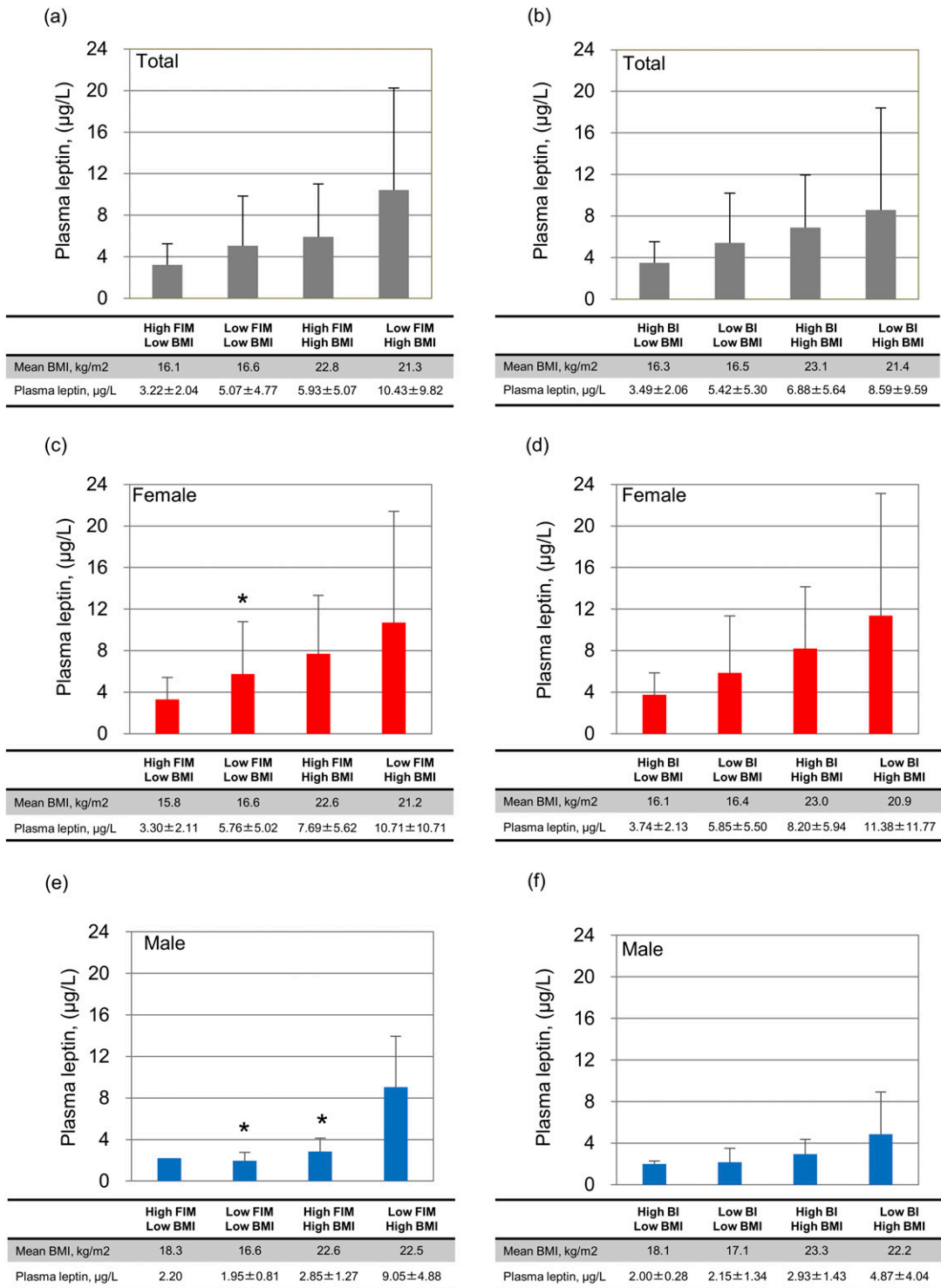


Figure 1. The differences of plasma leptin concentration among four groups divided by physical function and BMI. FIM, Barthel index (BI), and BMI were divided into two groups according to the median values. (a) The data were calculated using FIM and BMI in both sexes. (b) The data were calculated using the BI and BMI in both sexes. (c) The data were calculated using the FIM and BMI in females. (d) The data were calculated using the BI and BMI in females. (e) The data were calculated using the FIM and BMI in males. (f) The data were calculated using the BI and BMI in males. * $P < 0.05$ vs low FIM and high BMI group.

concentration and cognitive function and BMI. These results were consistent with those from previous studies. However, the present study could not detect any relationship between the plasma leptin concentrations and sympathetic nervous activity and blood pressure.

Sympathetic nervous fibers innervate adipose tissue and mediate the lipolytic effects of leptin [1]. In addition, many studies have demonstrated a positive correlation between the plasma leptin levels and the sympathetic nervous system. Plasma leptin correlated positively with LF and LF/HF, which were considered to reflect sympathetic modulations [30, 31]. Previous research has also shown a correlation between plasma leptin and sarcopenia, physical function, cognitive function, BMI, and C-reactive protein [2, 4, 5, 14, 28, 29]. However, although plasma leptin was significantly associated statistically with physical function (both FIM and the Barthel index), cognitive function (MMSE), and BMI, in the present study, plasma leptin was not associated with LF and the LF/HF ratio. Several reasons could exist for why plasma leptin did not correlate with sympathetic nervous activity in our data. First, aging itself diminishes sympathetic nervous activity [6]. The mean age in the present study was 86.4 years, older than the age of those included in other studies. Thus, greater plasma leptin concentrations could not elevate sympathetic nervous activity. Second, older adults with obesity are thought to have leptin resistance. Previous research has demonstrated that greater plasma leptin levels did not activate sympathetic nervous activity because of lower leptin signaling in the brain in older adults with obesity [32]. Higher plasma leptin levels also did not elevate sympathetic nervous activity in our data. Third, it is known that older adults with frailty or disability have 20% lower sympathetic nervous activity compared with healthy older adults [8]. Therefore, it is possible that elevated plasma leptin could not activate the sympathetic nervous system in these adults. In the present study, the FIM and Barthel index were 55.6 ± 33.7 and 37.5 ± 33.1 , respectively, indicating that the participants almost all had frailty or were disabled. The plasma leptin concentration is decreased by a feedback system of the sympathetic nervous system in healthy adults [13]; however, an inactivated sympathetic nervous system could lead to high plasma leptin concentrations in frail or disabled older adults. Because a high concentration of leptin leads to muscle wasting by elevated inflammatory cytokines, frail or disabled older adults could progress to a state at which they need long-term care. Sympathetic nervous fibers innervate adipose tissue and mediate the lipolytic effect of leptin; therefore, higher plasma leptin and low sympathetic nervous activity could lead, not only to muscle wasting, but also to obesity and, presumably, to low physical function and a high BMI. These results are consistent with a previous study that found that patients with sarcopenia and sarcopenic obesity demonstrated greater plasma leptin levels compared with healthy controls [5].

The present study did not demonstrate a relationship between blood pressure and the plasma leptin concentration. Plasma leptin has shown a positive relationship with blood pressure by simple correlation in previous reports. However, in multiple regression models, the relationship has shown contradictory results [16–19]. Aging and fat mass affect both plasma leptin and blood pressure; however, the importance of the relationship is thought to diminish after adjusting for covariates [18]. Concerning blood pressure variability, Abramson *et al.* [33] demonstrated that plasma leptin was positively associated with blood pressure variability. However, the day/night blood pressure ratio, which indicates blood pressure variability, was not associated with plasma leptin levels in the present study. Because previous research has shown the disappearance of the blood pressure circadian rhythm in older adults with physical dysfunction [34], we assumed that the relationship between plasma leptin and the day/night blood pressure ratio had disappeared owing to the low physical function in the present study participants. We also considered that the low sympathetic nervous activity disturbed the relationship.

The present study had some limitations. First, the present study had a small sample size and was a cross-sectional study and, therefore, could not provide direct evidence. It will be necessary to perform a large-scale clinical trial to evaluate whether decreased sympathetic nervous activity and high plasma leptin concentrations can predict the incidence of sarcopenia, frailty, or muscle wasting in older adults. Second, although we measured C-reactive

protein, other inflammatory cytokines such as IL-6 and TNF- α also affect both leptin and muscle wasting and should be evaluated. Third, we could not evaluate sarcopenia accurately because we did not assess the muscle mass, grip strength, or gait speed. However, allowing for these limitations, the present study has provided valuable evidence concerning the relationship between sympathetic nervous activity, plasma leptin concentrations, and physical function in older adults.

4. Conclusions

Sympathetic nervous activity was significantly and negatively associated with physical function. However, we could not detect a substantial association between sympathetic nervous activity and plasma leptin concentrations in older adults.

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Correspondence: Sumito Ogawa, MD, PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: suogawa-tky@umin.ac.jp.

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