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Brain-derived neurotrophic factor is associated with sarcopenia and frailty in Japanese hemodialysis patients

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Aim: We evaluated several sarcopenia-related hormones, cytokines and uremic toxins to identify the humoral factors associated with sarcopenia and frailty in Japanese hemodialysis patients.

Methods: Twenty Japanese patients aged ≥65 years who underwent maintenance hemodialysis therapy at Uonuma Kikan Hospital for more than 6 months were included in this retrospective cross-sectional study. Clinical data, including physical function and mental state, were obtained from the clinical records collected during the regular evaluation at the beginning of each hemodialysis therapy session, 3 days after the previous hemodialysis therapy. The diagnosis of sarcopenia and frailty was based on the Asian Working Group for Sarcopenia 2019 and the Japanese version of the Cardiovascular Health Study, respectively. The mental state of patients was evaluated using the Japanese version of the Patient Health Questionnaire 9 (J-PHQ-9).

Results: In univariate analyses, plasma brain-derived neurotrophic factor (BDNF) levels were significantly lower in patients with severe sarcopenia and frailty. The plasma BDNF concentration was correlated with muscle strength and physical performances, such as the 6-m walk test, Short Physical Performance Battery and 5-time chair stand test. BDNF was also correlated with body weight, hemodialysis vintage, and serum levels of total protein and indoxyl sulfate but not with body mass index, appendicular skeletal muscle mass, serum interleukin 6 levels, or J-PHQ-9 scores. The odds ratio per 100 pg/mL of BDNF for the prevalence of frailty was 0.353.

Conclusions: BDNF is associated with decreased physical performance and the prevalence of severe sarcopenia and frailty in Japanese maintenance hemodialysis patients. **Geriatr Gerontol Int 2021; 21: 27–33**.

Keywords: AWGS, BDNF, J-CHS, kidney, uremic toxin.

Introduction

Sarcopenia is a geriatric syndrome characterized by the age-related loss of skeletal muscle with physiological and clinical consequences. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed a definition of sarcopenia as the progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life and death. In addition, they recommended using the presence of both low muscle mass and low muscle function for the diagnosis of sarcopenia.[1] In 2018, the EWGSOP issued an updated consensus (EWGSOP2) to show that sarcopenia can occur secondary to a systemic disease earlier in life, particularly one that may evoke inflammatory processes, physical inactivity and inadequate intake of energy or protein.[2] In 2014, the Asian Working Group for Sarcopenia (AWGS) proposed a diagnostic algorithm based on Asian data,[3] and the AWGS 2019 consensus revised the diagnostic algorithm in which age cut-offs at either 60 or 65 years old were retained. The AWGS 2019 stated that diagnosing sarcopenia required both muscle quality and quantity measurements, and they newly defined patients with low muscle mass, muscle strength and physical performance as having "severe sarcopenia."[4]

Frailty is defined by the Japan Geriatrics Society as "a state of reduced ability to recover from stress resulting from an age-related decline in reserves" and is sometimes conceptualized as a pre-disability (pre-care dependency) stage.[5] Although there is no generally accepted approach for diagnosing frailty, the Cardiovascular Health Study (CHS) frailty index is the most acceptable tool, and Satake *et al.* proposed a Japanese version of CHS (J-CHS) criteria to assess shrinking, weakness, exhaustion, slowness and low activity. Cut-off values for grip strength and gait speed were also modified to suit aged Japanese adults.[6]

In patients with chronic kidney disease, including end-stage kidney disease, there is an increased occurrence of wasting, malnutrition and inflammation, which leads to a state of decreased body stores of protein and energy fuels termed protein–energy wasting.[7] The accelerated protein catabolism induced by metabolic acidosis, uremia, proinflammatory cytokines, endocrine disorders and the dialysis procedure itself may promote the degradation of lean mass and lead to sarcopenia in patients with chronic kidney disease or ESRD.[7,8] Mori *et al.* reported that the prevalence of sarcopenia was 40% in Japanese patients undergoing hemodialysis.[9] Frailty is also associated with protein–energy wasting and sarcopenia,[10] and Takeuchi *et al.* reported that the prevalence of frailty is 21.4% in Japanese hemodialysis patients.[11]

Hence, the aim of the present study was to evaluate several clinical factors involving sarcopenia-related hormones, cytokines[12–15] and uremic toxins in Japanese hemodialysis patients with and without sarcopenia or frailty and identify the factors characteristic of hemodialysis patients with sarcopenia or frailty.

Methods

Patients and study design

Twenty patients aged ≥65 years who underwent maintenance hemodialysis therapy at Uonuma Kikan Hospital for more than 6 months were included in this retrospective cross-sectional study. Clinical data, including physical function and mental state, were obtained from the clinical records collected during the regular evaluation at the beginning of each hemodialysis therapy session, 3 days after the previous hemodialysis therapy. The blood samples remaining after regular medical examinations were immediately frozen at −80°C until humoral factor measurements. Body surface area (BSA) was calculated using the following DuBois formula:

$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$ (W, weight in kg; H, height in cm).

The mental state of patients was evaluated using the Japanese version of the Patient Health Questionnaire 9 (J-PHQ-9).[16] The normalized dialysis dose was evaluated by Kt/V, which was calculated using the following Daugirdas formula:

Kt/V = −Ln {(post-dialysis urea/pre-dialysis urea) − (0.008 × duration of dialysis)} + {(4–3.5 × post-dialysis urea/pre-dialysis urea) × (ultrafiltration volume/post-dialysis weight)}.

The protocol of the present study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Uonuma Kikan Hospital (approval number 30–056) and registered in the UMIN Clinical Trial Registry (R000045731). All participants had the opportunity to opt out of the study.

Definition of sarcopenia

Sarcopenia was defined according to the 2019 consensus update on sarcopenia diagnosis and treatment by the AWGS.[4] Low handgrip strength was defined as <28 kg for men and <18 kg for women. The cut-off values associated with physical performance were a 6-m walk of <1.0 m/s, 5-time chair stand test ≥12 s or Short Physical Performance Battery ≤9. Low appendicular skeletal muscle mass (ASM) was measured by dual-energy X-ray absorptiometry (Horizon, Hologic, Sunnyvale, CA, USA) and defined as <7.0 kg/m^2 for men and <5.4 kg/m^2 for women. Low ASM with low muscle strength or low physical performance was defined as sarcopenia, whereas low ASM with low muscle strength and low physical performance was defined as severe sarcopenia.

Definition of frailty

Frailty was defined according to the J-CHS criteria.[6] Shrinking was defined as unintentional weight loss ≥2–3 kg/6 months, weakness was defined as grip strength <26 kg for men and <18 kg for women, exhaustion was defined as constant tiredness in the past 2 weeks, slowness was defined as usual gait speed <1.0 m/s, and low activity was defined as physical exercise <1 day/week and regular physical activities <1 day/week. Frailty, prefrailty and robustness were defined as having 3–5, 1–2 and 0 components, respectively.

Measurement of sarcopenia-related hormones, cytokines and uremic toxins

Plasma hormone concentrations were determined using an acylated ghrelin (human) express enzyme immunoassay kit (Bertin Pharma, Montigny-le-Bretonneux, France), human adiponectin/Acrp30 DuoSet enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA), human/mouse brain-derived neurotrophic factor (BDNF) DuoSet ELISA (R&D Systems), human follistatin DuoSet ELISA (R&D Systems), human leptin DuoSet ELISA (R&D Systems), human GDF-8/myostatin Quantikine ELISA (R&D Systems) and unacylated ghrelin (human) express enzyme immunoassay kit (Bertin Pharma). The concentration of serum indoxyl sulfate was determined using a high-performance liquid chromatography method (Fushimi Pharmaceutical, Kagawa, Japan). The serum level of interleukin 6 (IL)-6 was measured using a human IL-6 Quantikine ELISA (R&D Systems).

Statistical analyses

All data were analyzed using SPSS version 27 (IBM Corp., Armonk, NY, USA). The Mann–Whitney *U*-test was used for continuous variables, and the χ^2-test was used for categorical variables in univariate comparison analyses. The Kruskal–Wallis test was used for comparison among four groups, and the Dunn–Bonferroni test as a *post-hoc* test. Correlations between clinical parameters, physical functions and mental state were assessed using Spearman's rank correlation coefficient. The odds ratio was calculated using binomial logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

Study subject characteristics

Twenty patients aged ≥65 years undergoing maintenance hemodialysis were enrolled in this study. The mean age was 76.5 years (range, 65–88), and six (12%) of the patients were women. The mean dialysis vintage was 91.7 ± 80.1 months, the mean weekly dialysis time was 11.5 ± 1.1 h and the mean Kt/V was 1.32 ± 0.26. The mean body mass index was 21.5 ± 3.3 kg/m^2 and the mean BSA was 1.52 ± 0.18 m^2. Of 11 patients diagnosed with sarcopenia, eight were categorized as severe sarcopenia. In addition, 10 and six patients were diagnosed with frail and prefrail conditions, respectively.

Univariate analyses of clinical and physical parameters for sarcopenia

We compared the demographic and clinical characteristics between patients with and without sarcopenia. Although ASM was significantly decreased in patients with sarcopenia (sarcopenia [−], 6.57 ± 0.49 kg/m^2; sarcopenia [+], 5.68 ± 0.70 kg/m^2; $P = 0.006$), all four physical functions, including handgrip strength (sarcopenia [−], 24.3 ± 10.3 kg; sarcopenia [+], 19.0 ± 5.4 kg; $P = 0.261$), 6-m walk (sarcopenia [−], 1.06 ± 0.40 m/s; sarcopenia [+], 0.94 ± 0.27 m/s; $P = 0.412$), Short Physical Performance Battery (sarcopenia [−], 10.1 ± 3.1; sarcopenia [+], 9.0 ± 2.1; $P = 0.175$) and 5-time chair stand test (sarcopenia [−], 11.6 ± 3.5 s; sarcopenia [+], 18.5 ± 11.7; $P = 0.056$), were not different between the two groups. Considering that the diagnosis for sarcopenia does not require the coexistence of low muscle strength and low physical performance, we speculated that those parameters did not necessarily differ between patients with and without sarcopenia. Then, we compared the clinical characteristics of patients with and without severe sarcopenia (Table 1). Patients

with severe sarcopenia exhibited lower body weight, body mass index and ASM. Muscle strength and all physical performances were also deteriorated in patients with severe sarcopenia. Prevalence of type 2 diabetes mellitus (T2DM) and incidence of cardiovascular disease (CVD) were not different between patients with and without severe sarcopenia. To identify the factors associated with the development of sarcopenia in these patients, we also evaluated clinical parameters and humoral factors reported to affect the prevalence of sarcopenia. Among several sarcopenia-related hormones, we found that the plasma concentration of BDNF was significantly decreased in patients with severe sarcopenia (Table 1). However, the odds ratio per 100 pg/mL of BDNF for the prevalence of severe sarcopenia was not significant (odds ratio: 0.470, 95% confidence interval: 0.212–1.038, $P = 0.062$).

Correlation between each physical function and clinical parameter

Then, we assessed the impact of each humoral factor on physical functions using Spearman's rank correlation coefficient. The plasma BDNF concentration was positively correlated with muscle strength and all physical performances, whereas the serum indoxyl sulfate level was negatively correlated with these physical performances but not with muscle strength. The serum IL-6 level was correlated with the 5-time chair stand test (Table 2, Fig. 1). We also evaluated the correlation between the plasma BDNF concentration and each clinical parameter and humoral factor. BDNF demonstrated a positive correlation with body weight and serum total protein levels and a negative correlation with hemodialysis vintage and serum indoxyl sulfate concentrations. In contrast, body mass index, ASM, serum IL-6 concentrations and J-PHQ-9 scores were not significantly correlated with the plasma BDNF concentration (Fig. 1).

Univariate analyses of clinical and physical parameters for frailty

We compared the demographic and clinical characteristics based on frailty. We categorized robust patients and those with prefrailty as frailty (–) and compared them with the patients with frailty classified as frailty (+). Prevalence of T2DM and incidence of CVD were not different between patients with and without frailty.

Table 1 Demographic and clinical characteristics of patients with and without severe sarcopenia

	Severe sarcopenia (–) $n = 12$	Severe sarcopenia (+) $n = 8$	P value
Age (years)	76.4 ± 7.7	76.5 ± 7.5	0.970
Male/female (n, %)	8 (66.7)/4 (33.3)	6 (75.0)/2 (25.0)	0.690
Type 2 diabetes mellitus (n, %)	2 (16.7)	4 (50.0)	0.111
Cardiovascular disease (n, %)	7 (58.3)	3 (37.5)	0.361
Height (m)	1.57 ± 0.13	1.57 ± 0.04	0.624
Weight (kg)	56.9 ± 10.1	48.1 ± 8.7	0.047
Body mass index (kg/m^2)	22.9 ± 2.6	19.4 ± 3.3	0.031
Body surface area (m^2)	1.56 ± 0.20	1.45 ± 0.13	0.082
Appendicular skeletal muscle mass index (kg/m^2)	6.43 ± 0.59	5.56 ± 0.67	0.005
Dialysis vintage (months)	65.5 ± 45.6	131.0 ± 105.7	0.270
Weekly dialysis time (h)	11.6 ± 0.7	11.3 ± 1.6	0.682
Kt/V	1.27 ± 0.14	1.41 ± 0.38	0.354
Hemoglobin (g/dL)	11.0 ± 0.9	11.4 ± 1.4	0.757
Serum calcium (mg/dL)	8.88 ± 0.22	8.99 ± 0.85	0.228
Serum phosphate (mg/dL)	4.22 ± 1.03	5.58 ± 1.24	0.018
Serum intact PTH (pg/mL)	137.9 ± 99.7	106.1 ± 68.5	0.589
Serum creatinine (mg/dL)	8.38 ± 3.53	9.18 ± 1.72	0.643
Serum urea nitrogen (mg/dL)	47.7 ± 14.2	51.3 ± 11.2	0.487
C-reactive protein (mg/dL)	0.32 ± 0.57	0.27 ± 0.33	0.642
Serum total protein (g/dL)	6.66 ± 0.47	6.04 ± 0.49	0.033
Serum albumin (g/dL)	3.62 ± 0.41	3.25 ± 0.26	0.033
Handgrip strength (kg)	24.3 ± 8.9	17.0 ± 4.9	0.039
6-m walk (m/s)	1.10 ± 0.35	0.83 ± 0.23	0.031
Short Physical Performance Battery	10.5 ± 2.8	8.0 ± 1.4	0.007
5-time chair stand test (s)	11.1 ± 3.1	21.8 ± 12.2	<0.001
J-PHQ-9	5.92 ± 3.75	7.25 ± 4.23	0.414
Acylated ghrelin (pg/mL)	16.2 ± 23.7	1.7 ± 4.9	0.135
Adiponectin (mg/mL)	10.1 ± 4.0	9.3 ± 4.0	0.521
Brain-derived neurotrophic factor (pg/mL)	744 ± 293	509 ± 120	0.025
Interleukin 6 (pg/mL)	6.55 ± 4.31	16.99 ± 21.79	0.076
Follistatin (pg/mL)	183 ± 226	87 ± 98	0.521
Indoxyl sulfate (μg/mL)	28.2 ± 18.1	41.3 ± 8.0	0.069
Leptin (ng/mL)	8.5 ± 11.0	15.2 ± 25.8	0.678
Myostatin (ng/mL)	2.84 ± 1.19	2.41 ± 1.26	0.384
Unacylated ghrelin (pg/mL)	460 ± 662	519 ± 482	0.970

Univariate analysis comparison between patients with and without severe sarcopenia. Data were presented as the mean ± SD and evaluated by the Mann–Whitney U-test or χ^2-test.

PTH, parathyroid hormone.

Table 2 Correlations between clinical parameters and physical functions

		Acylated ghrelin	Adiponectin	Brain-derived neurotrophic factor	Follistatin	Interleukin 6	Indoxyl sulfate	Leptin	Myostatin	Unacylated ghrelin
Handgrip strength	Correlation coefficient	0.413	−0.402	0.55	−0.04	−0.214	−0.35	0.253	0.162	0.37
	P value	0.07	0.079	0.012	0.866	0.386	0.131	0.283	0.494	0.108
6-m walk	Correlation coefficient	0.159	−0.082	0.679	0.133	−0.398	−0.594	0.053	−0.089	−0.131
	P value	0.503	0.731	0.001	0.575	0.082	0.006	0.825	0.71	0.582
Short Physical Performance Battery	Correlation coefficient	0.351	−0.047	0.646	0.142	−0.426	−0.577	0.048	0.181	−0.001
	P value	0.13	0.844	0.002	0.549	0.061	0.008	0.841	0.444	0.997
5-time chair stand test	Correlation coefficient	−0.239	0.065	−0.627	−0.163	0.451	0.499	−0.14	−0.051	−0.062
	P value	0.23	0.787	0.003	0.492	0.046	0.025	0.556	0.83	0.796

Correlations were evaluated using Spearman's rank correlation coefficient.

Similar to severe sarcopenia, muscle strength and all physical performances used for the diagnosis of sarcopenia deteriorated, and the plasma BDNF level was significantly decreased in frailty (+) patients. However, body weight, body mass index and ASM did not differ significantly between the patients with and without frailty (Table 3). The odds ratio per 100 pg./mL of BDNF for the

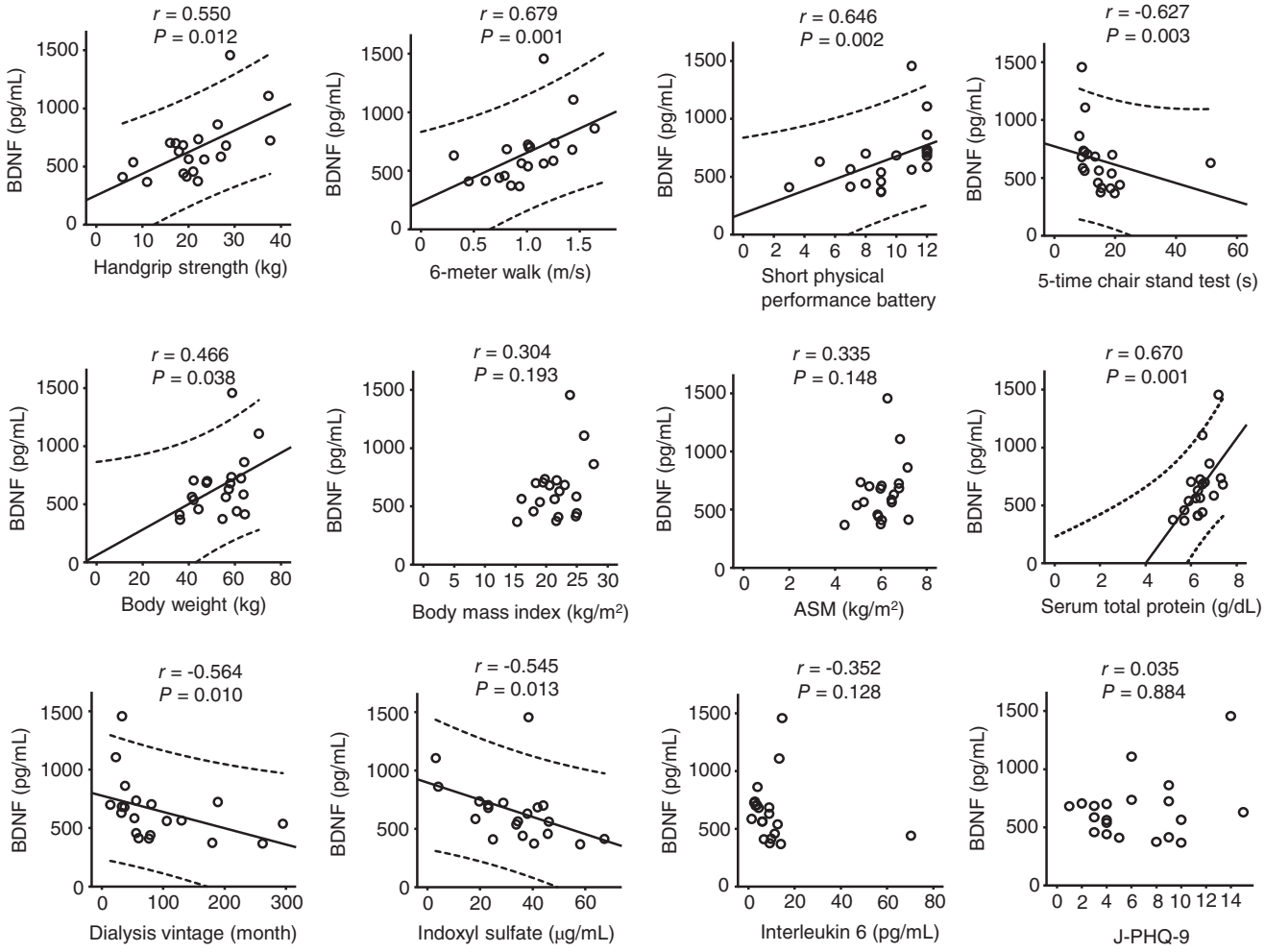

Figure 1 Correlation between plasma brain-derived neurotrophic factor (BDNF) and physical functions or clinical parameters evaluated by Spearman's rank correlation coefficient. Solid and dashed line represent regression line and 95% prediction interval, respectively.

Table 3 Demographic and clinical characteristics of patients with and without frailty

	Frailty (–) n = 10	Frailty (+) n = 10	P value
Age (years)	75.5 ± 6.6	77.4 ± 8.4	0.481
Male/female (n, %)	6 (60.0)/4 (40.0)	8 (80.0)/2 (20.0)	0.329
Type 2 diabetes mellitus (n, %)	2 (20.0)	4 (40.0)	0.329
Cardiovascular disease (n, %)	5 (50.0)	5 (50.0)	1.000
Height (m)	1.57 ± 0.09	1.57 ± 0.11	0.912
Weight (kg)	56.6 ± 9.7	50.2 ± 10.4	0.190
Body mass index (kg/m^2)	22.8 ± 2.9	20.3 ± 3.4	0.165
Body surface area (m^2)	1.56 ± 0.17	1.48 ± 0.19	0.393
Appendicular skeletal muscle mass index (kg/m^2)	6.38 ± 0.63	5.79 ± 0.78	0.075
Dialysis vintage (months)	88.8 ± 88.2	94.6 ± 75.8	0.684
Weekly dialysis time (h)	11.9 ± 0.5	11.1 ± 1.4	0.141
Kt/V	1.30 ± 0.20	1.35 ± 0.32	0.791
Hemoglobin (g/dL)	11.3 ± 0.7	11.0 ± 1.4	0.130
Serum calcium (mg/dL)	8.91 ± 0.22	8.93 ± 0.76	0.148
Serum phosphate (mg/dL)	4.68 ± 1.40	4.84 ± 1.22	0.596
Serum intact PTH (pg/mL)	133.7 ± 99.7	116.7 ± 78.9	0.880
Serum creatinine (mg/dL)	8.67 ± 3.77	8.72 ± 1.91	0.705
Serum urea nitrogen (mg/dL)	51.3 ± 15.8	47.0 ± 9.52	0.406
C-reactive protein (mg/dL)	0.45 ± 0.62	0.15 ± 0.23	0.129
Serum total protein (g/dL)	6.59 ± 0.50	6.23 ± 5.79	0.184
Serum albumin (g/dL)	3.56 ± 0.53	3.38 ± 0.15	0.323
Handgrip strength (kg)	25.2 ± 9.2	17.5 ± 5.2	0.043
6-m walk (m/s)	1.19 ± 0.25	0.79 ± 0.28	0.004
Short Physical Performance Battery	11.3 ± 1.1	7.7 ± 2.4	0.001
5-time chair stand test (s)	10.9 ± 3.1	19.9 ± 11.6	0.002
J-PHQ-9	5.50 ± 4.04	7.40 ± 3.72	0.159
Acylated ghrelin (pg/mL)	17.9 ± 25.6	3.0 ± 6.4	0.190
Adiponectin (mg/mL)	9.3 ± 4.0	10.2 ± 4.0	0.684
Brain-derived neurotrophic factor (pg/mL)	791 ± 287	509 ± 137	0.011
Interleukin 6 (pg/mL)	7.18 ± 4.85	14.28 ± 19.97	0.326
Follistatin (pg/mL)	152 ± 173	137 ± 212	0.739
Indoxyl sulfate (μg/mL)	26.1 ± 14.8	40.9 ± 14.2	0.063
Leptin (ng/mL)	12.5 ± 14.0	9.8 ± 22.1	0.105
Myostatin (ng/mL)	2.86 ± 0.93	2.48 ± 1.45	0.353
Unacylated ghrelin (pg/mL)	485 ± 730	482 ± 430	0.684

Univariate analysis comparison between patients with and without frailty. Data were presented as the mean ± SD and evaluated by the Mann–Whitney U-test or χ^2-test.

PTH, parathyroid hormone.

prevalence of frailty was significant (odds ratio: 0.353, 95% confidence interval: 0.134–0.929, P = 0.035).

Association between severe sarcopenia and frailty

Finally we categorized the patients into four groups; severe sarcopenia (–) and frailty (–) as S (–) F (–) (n = 9, 45%), severe sarcopenia (–) and frailty (+) as S (–) F (+) (n = 3, 15%), severe sarcopenia (+) and frailty (–) as S (+) F (–) (n = 1, 5%), and severe sarcopenia (+) and frailty (+) as S (+) F (+) (n = 7, 35%). Among the clinical parameters, significant differences were observed in the physical performances between F (–) S (–) and F (+) S (+) (Table 4).

Discussion

In this retrospective cross-sectional study, we focused on BDNF as a factor associated with deterioration in muscle strength and physical performances and the prevalence of severe sarcopenia and frailty in Japanese maintenance hemodialysis patients.

BDNF is a member of the neurotrophin family and is involved in the regulation of neuronal and glial development, neuroprotection, and both short- and long-lasting synaptic interactions through regulation of presynaptic release of neurotransmitters and postsynaptic receptors, which are critical for cognition and memory.[17] BDNF also induces synaptic potentiation at neuromuscular junctions,[18] survival of motor neurons,[19] and muscle development and metabolism.[20] BDNF is present in almost all brain regions and detected in plasma. BDNF is also produced and secreted by human and rodent skeletal muscles and regulated by exercise; however, muscle BDNF is not considered as the source of circulating BDNF, and appears to be mainly involved in autocrine and paracrine signaling to promote muscle fiber fat oxidation and potentially muscle development.[12] Most circulating BDNF originates from megakaryocytes[21] and physical exercise activates platelets to release BDNF into the circulation.[20] Alterations of BDNF levels may reflect changes occurring in megakaryocytes and platelets induced by physical exercise, accompanied by local

Table 4 Demographic and clinical characteristics of patients with and without severe sarcopenia and/or frailty

	S (–) F (–) n = 9	S (–) F (+) n = 3	S (+) F (–) n = 1	S (+) F (+) n = 7	P value	*Post-hoc* test
Age (years)	75.2 ± 6.9	80.0 ± 10.6	78.0	76.3 ± 8.0	0.771	
Male/female (n, %)	6 (66.7)/3 (33.3)	2 (66.7)/1 (33.3)	0 (0.0)/1 (100.0)	6 (85.7)/1 (14.3)	0.359	
Type 2 diabetes mellitus (n, %)	2 (22.2)	0 (0.0)	0 (0.0)	4 (57.1)	0.219	
Cardiovascular disease (n, %)	5 (55.5)	2 (66.7)	0 (0.0)	3 (42.9)	0.662	
Height (m)	1.58 ± 0.09	1.54 ± 0.23	1.49	1.59 ± 0.03	0.720	
Weight (kg)	58.2 ± 8.7	52.9 ± 14.9	42.1	49.0 ± 9.0	0.218	
Body mass index (kg/m^2)	23.2 ± 2.7	22.2 ± 2.5	19.0	19.5 ± 3.6	0.175	
Body surface area (m^2)	1.58 ± 0.09	1.49 ± 0.33	1.33	1.47 ± 0.12	0.308	
Appendicular skeletal muscle mass index (kg/m^2)	6.54 ± 0.40	6.12 ± 1.04	4.95	5.64 ± 0.68	0.039	0.079
Handgrip strength (kg)	27.1 ± 7.3	15.8 ± 8.8	8.0	18.3 ± 3.6	0.043	0.163
6-m walk (m/s)	1.21 ± 0.26	0.77 ± 0.43	1.01	0.80 ± 0.24	0.040	0.042
Short Physical Performance Battery	11.6 ± 0.7	7.3 ± 4.5	9.0	7.9 ± 1.5	0.008	0.008
5-time chair stand test (s)	10.0 ± 1.5	14.5 ± 4.5	18.8	22.3 ± 13.1	0.005	0.004
Brain-derived neurotrophic factor (pg/mL)	819 ± 290	520 ± 187	538	505 ± 129	0.051	

Univariate analysis comparison between patients with and without severe sarcopenia and/or frailty. Data were presented as the mean ± SD and evaluated by the Kruskal–Wallis test or χ^2-test. The Dunn–Bonferroni test was used as a *post-hoc* test and its P values represent those between F (–) S (–) and S (+) F (+). F (–), frailty (–); F (+), frailty (+); S (–), severe sarcopenia (–); S (+), severe sarcopenia (+).

production and secretion of BDNF in skeletal muscle.[20] In the present study, we revealed that the plasma BDNF level was significantly lower in patients with severe sarcopenia or frailty and that a lower BDNF level was correlated with deteriorated physical functions. Lower BDNF was also correlated with longer dialysis vintage and higher serum indoxyl sulfate levels. Indoxyl sulfate is derived from the metabolism of tryptophan and is a protein-bound uremic toxin.[22] The kidneys achieve a high clearance of indoxyl sulfate by tubular secretion, and the removal of indoxyl sulfate by current hemodialysis is limited due to its high plasma protein binding rate. Indoxyl sulfate contributes to renal disease progression, vascular disease, and adverse effects on bones and the central nervous system.[23] No consistent association of various uremic toxin levels, including indoxyl sulfate, with physical performance have been reported, but inflammation is one of the pathways contributing to physical impediment in hemodialysis patients.[24] Considering that higher central or peripheral level of proinflammatory cytokines reduce central BDNF expression and thus impact on neurogenesis and neurotransmitter release,[12] we presume that increased indoxyl sulfate concentrations due to declining kidney function along with longer hemodialysis vintage would be accompanied by proinflammatory responses, which would negatively affect the production of BDNF in skeletal muscles and megakaryocytes, indirectly resulting in impaired physical performances.

BDNF is also related to many psychiatric disorders, such as major depressive disorder, in humans. Several studies reported that lower serum/plasma BDNF levels were observed in depressed patients, and peripheral BDNF levels were increased after antidepressant treatment.[25] However, the association between serum BDNF levels and depressive or anxiety symptoms in hemodialysis patients is still controversial.[26] In addition, in the present study, the plasma BDNF concentration was not correlated with the J-PHQ-9 score. In hemodialysis patients, circulating inflammatory mediators would likely contribute to the development of depressive and anxiety symptoms to a greater extent than BDNF.[26] Reduced plasma level of BDNF is also observed in T2DM[27] and acute coronary syndrome,[28] which are related to systemic or peripheral inflammatory conditions. In the present study, the prevalence of T2DM and the incidence of CVD were not different between patients with severe sarcopenia or frailty.

The present study had several limitations. First, this is a single-center study involving a small study population. The aim of this study was to identify the humoral factors among several sarcopenia-related hormones and clarify the correlations between clinical parameters. Although this small population was appropriate for the screening of a variety of factors reported to be associated with sarcopenia or frailty, this small population was inadequate for multivariate analyses. Second, as this was a cross-sectional study, it was difficult to discuss cause and effect relationships. Particularly, logistic regression analysis did not show a significant association between plasma BDNF and the prevalence of severe sarcopenia. We predict that BDNF is associated more closely with physical functions than ASM. To verify this prediction, we categorized the patients into four groups and compared those with S (–) F (+) and S (+) F (–) (Table 4). However, most patients with severe sarcopenia presented frailty and vice versa, and enough populations of S (–) F (+) or S (+) F (–) were not available for statistical evaluation. A future large-scale prospective study focusing on BDNF is required to determine the causal relationship between BDNF levels and the prevalence of sarcopenia or frailty. Third, as peripheral BDNF concentrations fluctuate during each hemodialysis session and are affected by inflammatory conditions concomitant with hemodialysis,[29,30] hemodialysis conditions or complications of inflammatory diseases should be carefully adjusted.

In conclusion, we reported that BDNF is associated with decreased physical functions and the prevalence of severe sarcopenia and frailty in Japanese maintenance hemodialysis patients. The plasma BDNF concentration was correlated with serum indoxyl sulfate levels (one of the uremic toxins) and hemodialysis vintage, which are findings specific to hemodialysis patients. We hope that the present study provides evidence clarifying the mechanisms underlying hemodialysis-specific sarcopenia and frailty.

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Disclosure statement

The authors declare no conflict of interest.

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