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ORIGINAL

High brain natriuretic peptide is associated with sarcopenia in patients with type 2 diabetes: a cross-sectional study of KAMOGAWA-DM cohort study

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Abstract. Association between heart failure and sarcopenia has been reported, however, the association between sarcopenia and brain natriuretic peptide (BNP) is unclear. Thus, we investigated the association between sarcopenia and BNP in type 2 diabetic patients without heart failure. In this cross-sectional study, skeletal muscle mass index (SMI, kg/m^2) was calculated as appendicular muscle mass, measured by bioimpedance analyzer, by the square of the height. Sarcopenia was defined as having both handgrip strength of <26 kg for men and <18 kg for women, and SMI of <7.0 kg/m^2 for men and <5.7 kg/m^2 for women. To investigate the impact of BNP levels on the presence of sarcopenia, propensity-score matching analysis was used to remove the bias of confounding variables, including age, sex, duration of diabetes, body mass index, exercise, systolic blood pressure, smoking status, hemoglobin A1c, creatinine, energy and protein intake. The area under the curve (AUC) of BNP levels for the presence of sarcopenia was calculated by the receiver operating characteristic curve (ROC). Among 433 patients (236 men and 65.4 (11.1) years), 32 patients (7.4%) were diagnosed as sarcopenia. In the propensity-matched 58 patients, BNP levels (Δ10 pg/mL incremental) were associated with the presence of sarcopenia by logistic regression analysis, (odds ratio: 1.56, 95% confidence interval: 1.14–2.13, $p = 0.002$). The optimal cut-off point of BNP levels for sarcopenia is 27.3 pg/mL (AUC 0.777, 95%CI, 0.691–0.863, sensitivity = 0.813, specificity = 0.736, $p < 0.001$). In conclusion, BNP levels were associated with sarcopenia in type 2 diabetic patients without heart failure.

Key words: Sarcopenia, Muscle mass, Brain natriuretic peptide, Nutrition, Type 2 diabetes

THE NUMBER of patients with type 2 diabetes is sharply increasing, and geriatric syndromes such as frailty and sarcopenia with ageing are common in them [1]. Sarcopenia, which is known as loss of muscle mass and muscle function, leads to motor function disorder, falls, fractures and difficulty in daily life [2, 3]. It has also been reported that sarcopenia is the risk of cardiovascular disease and death [4, 5].

Several studies previously demonstrated that the prevalence and incidence of heart failure in patients with diabetes was higher than that in people without [6, 7]. In addition, cardiovascular disease typified by heart failure is a one of common causes of death in general elderly people [8] and this also applies to patients with type 2 diabetes [6]. In fact, the association between heart failure and sarcopenia has been reported [9, 10].

On the other hand, brain natriuretic peptide (BNP) is often used as a biomarker of heart failure because it is an organs and diseases-specific indicator and useful not only for diagnosis and prognostic predictive index but also for a therapeutic index of heart failure [11, 12]. However, few studies demonstrated the association between sarcopenia and increased BNP levels in patients without heart failure. Thus, we aimed to investigate the association between sarcopenia and BNP levels in patients with type 2 diabetes without chronic heart failure.

Materials and Methods

Study patients

KAMOGAWA-DM cohort study is a prospective cohort study from 2014 and currently in progress [13]. We enrolled patients with type 2 diabetes without physi-

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cal inactivity, who were recruited from the outpatient clinics at the Kyoto Prefectural University of Medicine and Kameoka Municipal Hospital from August 2015 to September 2017 in this cross-sectional study. We excluded obese patients with a body mass index (BMI) of equal to or more than 30 kg/m^2 [14], patients with chronic kidney disease (CKD) of estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 [15] and patients who took diuretics [16] because these conditions would influence BNP levels. Moreover, we defined patients with heart failure as those with class NYHA II–IV cardiac insufficiency [17] and with BNP levels equal to or more than 100 pg/mL [18], and we excluded the patients falling under the definition. In addition, none of the patients had atrial fibrillation in this study. Written informed consent was obtained from all patients and approval for the study was obtained from the local research ethics committee.

Estimation and assessment of habitual food and nutrient intake

In this study, we used the brief-type self-administered diet history questionnaire (BDHQ) to assess the habitual food and nutrient intake [19]. The details of BDHQ were expressed elsewhere [19]. Briefly, the 58 food items intake and calculation of estimated energy, carbohydrate, protein and fat intake were performed by an *ad hoc* computer algorithm for the BDHQ based on Standard Tables of Food Composition in Japan [20]. Dietary total energy (kcal/day), carbohydrate (g/day), total protein (g/day), fat (g/day) and alcohol (g/day) intake were estimated using this calculation program of BDHQ. The patients who reported extremely low (under 600 kcal) or high (over 4,000 kcal) energy intake were also excluded [21].

Lifestyle factors and medications

We performed a standardized questionnaire to all patients. Patients were divided into nonsmoker, ex-smoker and current smoker. In addition, patients reported the kind and frequency of their participation in sports or recreational activities on the questionnaire [22]. We categorized the patients, who performed any kind of sport regularly at least once a week, as regular exercisers [23]. In addition, patients reported the kind of oral hypoglycemic agent and the presence of insulin use on the questionnaire.

Data collection

Patients underwent the measurement of the concentrations of several factors, including fasting plasma glucose, creatinine and C-peptide after an overnight fast, using venous blood. Hemoglobin A1c (HbA1c) was showed as a National Glycohemoglobin Standardization Program unit and analyzed using high-performance liquid chromatography. BNP levels were measured by chemiluminescent enzyme immunoassay. We used the Japanese Society of Nephrology equation for eGFR: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (×0.739 for women) [24].

Body composition of patients was evaluated using the body composition analyzer with a multifrequency impedance called InBody 720 (InBody Japan, Tokyo, Japan) [25]. The multifrequency impedance analyzer is shown a good correlation with the dual-energy X-ray absorptiometry method and was validated [26]. We collected the data of body weight (BW, kg), skeletal muscle mass (kg), appendicular muscle mass (kg) and body fat mass (kg). Then, skeletal muscle mass index (SMI, kg/m^2) was calculated by dividing appendicular muscle mass (kg) by the square of the height (m) [27, 28]. Body mass index (BMI) was defined as body weight (kg) by dividing the square of the height (m). Ideal body weight was defined as the square of the height (m) multiplied by 22 [29].

Definition of sarcopenia

We diagnosed sarcopenia with grip strength and SMI based on algorithms proposed by Asian working group for sarcopenia or Japanese Association on Sarcopenia and Frailty [27]. Grip strength was measured using a Smedley grip dynamometer, and the cut-off values was set to <26 kg for men and <18 kg for women. Moreover, the cut-off values of SMI was set to <7.0 kg/m^2 for men and <5.7 kg/m^2 for women. We diagnosed patients with both of two benchmarks as sarcopenia.

Statistical analysis

Statistical analyses were preformed using JMP version 12.0 software (SAS Institute Inc., Cary, North Carolina) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A p value <0.05 was considered statistically significant. Mean or frequencies of potential confounding variables were calculated, and continuous variables were presented as the mean (standard deviation, SD). Correlation coefficients were analyzed using Spearman's rank correlation coefficient and we calculated correlation coefficient between BNP levels, and skeletal muscle index and grip strength. Univariate logistic regression analyses were performed to investigate the effect of various factors, including BNP levels (Δ10 pg/mL incremental). The number of patients might be small for statistical analysis. Therefore, propensity scores were used to preserve statistical power. The dependent variable was the presence of sarcopenia for the assessment of the propensity score. The propensity score was calculated using multivariable logistic regression models

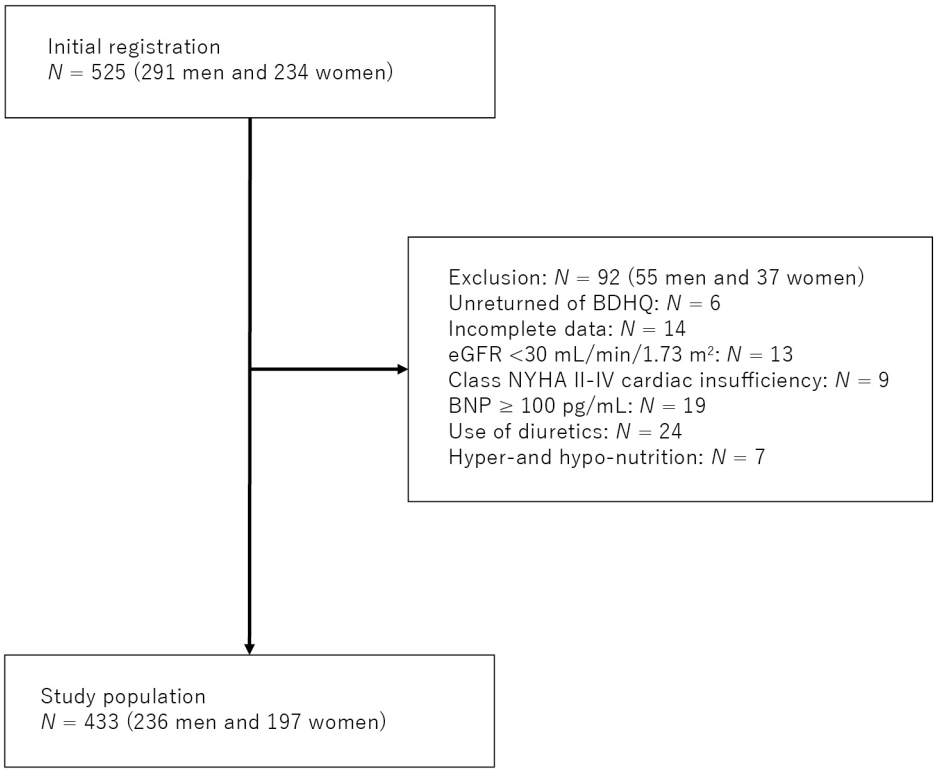

Fig. 1 Study flow diagram for the registration of patients
BDHQ, brief-type self-administered diet history questionnaire; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate

including the following parameters: age, sex, duration of diabetes, body mass index, exercise, systolic blood pressure, smoking status, hemoglobin A1c, creatinine, energy and protein intake [30]. The c-statistic for the propensity score model was 0.80, which shows an acceptable discrimination. Moreover, nearest neighbor matching with a maximum caliper of 0.20 of the propensity score was performed for the propensity score matching. Lastly, 58 patients were selected for the propensity-matched population, and we calculated the odds ratio for the presence of sarcopenia by logistic regression analysis. Furthermore, we calculated the odds ratio for the presence of sarcopenia by logistic regression analysis as sub-analysis by age more than or equal to and less than 75 years old.

Additionally, the area under the curve (AUC) of BNP levels for the presence of sarcopenia was calculated by the receiver operating characteristic (ROC) curve.

Results

In this study, 525 patients (291 men and 234 women) with type 2 diabetes received BDHQ. Among them, a total of 519 patients completed the questionnaire, yielding a collection rate of 98.9 %. We excluded 14 patients with incomplete data of covariates, 13 patients with eGFR less than 30 mL/min/1.73 m^2, 19 patients with BNP levels equal to or more than 100 pg/mL, 24 patients who took diuretics, 9 patients with class NYHA II–IV cardiac insufficiency and 7 patients with hyper- and hypo-nutrition. Finally, the study population was 433 patients (236 men and 197 women) (Fig. 1).

Clinical characteristics of 433 patients with type 2 diabetes are shown in Table 1. Among them, 32 patients were diagnosed as sarcopenia. The average (SD) of age and HbA1c were 73.8 (5.8) years and 7.7 (1.5)% in patients with sarcopenia, and 64.8 (11.1) years and 7.6 (1.6)% in patients without sarcopenia, respectively. In addition, the average (SD) of BNP levels in patients with sarcopenia was higher than that in patients without (42.0 (23.3) *vs.* 21.1 (18.1) pg/mL, $p < 0.001$).

In addition, in analyses using Spearman's rank correlation coefficient, BNP levels were negatively associated with skeletal muscle index and grip strength both in men and women (men: $r = –0.454$, $p < 0.001$, $r = –0.376$, $p < 0.001$, women: $r = –0.215$, $p = 0.010$, $r = –0.193$, $p = 0.007$).

Unadjusted ORs and 95% CIs of the presence of sarcopenia are shown in Table 2. BNP levels (Δ10 pg/mL incremental) was positively associated with the presence of sarcopenia (OR: 1.50, 95% CI: 1.29–1.74, $p < 0.001$).

Table 1 Clinical characteristics of study patients

	Total (n = 433)	Patients with sarcopenia (n = 32)	Patients without sarcopenia (n = 401)	p value
Sex (men/women)	236/197	16/16	220/181	0.595
Age (year)	65.4 (11.1)	73.8 (5.8)	64.8 (11.1)	<0.001
Body weight (kg)	64.4 (14.4)	50.7 (9.1)	65.6 (14.2)	<0.001
Body mass index (kg/m^2)	25.0 (4.7)	21.4 (3.2)	25.4 (4.6)	<0.001
Skeletal muscle mass (kg)	24.1 (5.7)	18.7 (3.2)	24.5 (5.7)	<0.001
Appendicular muscle mass (kg)	18.2 (4.7)	13.8 (2.9)	18.6 (4.6)	<0.001
Skeletal muscle mass index (kg/m^2)	7.0 (1.2)	5.7 (0.7)	7.1 (1.2)	<0.001
Grip strength (kg)	29.0 (9.9)	16.9 (5.5)	29.9 (9.5)	<0.001
Body fat mass (kg)	19.2 (8.6)	15.0 (6.2)	19.6 (8.7)	<0.001
Smoking (non-/ex-/current smoker)	339/50/44	29/1/2	310/49/42	0.127
Regular exerciser (no/yes)	370/63	28/4	342/59	0.653
Systolic blood pressure (mmHg)	129.5 (15.5)	123.1 (14.0)	129.9 (15.5)	0.033
Diastolic blood pressure (mmHg)	70.9 (11.6)	60.8 (7.8)	71.8 (11.5)	0.002
Disease duration (year)	10.3 (10.1)	14.6 (14.5)	9.9 (9.6)	0.004
Plasma glucose (mmol/L)	8.6 (3.3)	8.5 (0.4)	9.1 (0.6)	0.147
Hemoglobin A1c (%)	7.6 (1.6)	7.7 (1.5)	7.6 (1.6)	0.348
Creatinine (μmol/L)	69.4 (19.4)	69.9 (13.0)	69.4 (19.8)	0.897
eGFR (mL/min/1.73 m^2)	72.3 (17.9)	68.7 (15.8)	72.5 (18.1)	0.266
C-peptide (nmol/L)	0.7 (0.5)	0.6 (0.1)	0.7 (0.1)	0.002
C-peptide index	8.5 (6.1)	6.3 (1.2)	9.1 (0.6)	0.046
BNP (pg/mL)	22.6 (19.3)	42.0 (23.3)	21.1 (18.1)	<0.001
Energy intake (kcal)	1,762.4 (629.7)	1,500.2 (441.8)	1,779.8 (636.1)	0.037
Protein intake (g/day)	72.2 (30.9)	61.8 (18.8)	72.9 (31.4)	0.123
Animal protein intake (g/day)	42.6 (22.6)	36.4 (14.5)	43.0 (23.0)	0.326
Vegetable protein intake (g/day)	28.6 (10.1)	25.5 (8.3)	28.8 (10.2)	0.276
Fat intake (g/day)	51.7 (21.1)	40.1 (16.3)	52.4 (21.2)	0.027
Carbohydrate intake (g/day)	228.4 (86.9)	204.9 (81.8)	229.9 (87.3)	0.283
Alcohol intake (g/day)	7.4 (16.7)	5.2 (14.4)	7.7 (16.9)	0.328

Data was expressed as mean (SD) or number. Wilcoxon test for continuous variables or the chi-square test for categorical variables was performed to assess statistical significance of differences between groups. BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

Clinical characteristics of propensity-matched 58 patients (27 men and 31 women) according to the presence of sarcopenia were showed in Table 3. By logistic regression analysis, BNP levels (Δ10 pg/mL incremental) were associated with the presence of sarcopenia (odds ratio: 1.56, 95% confidence interval: 1.14–2.13, p = 0.002). In addition, we performed sub-analyses by age more than or equal to and less than 75 years old in propensity-matched patients. The unadjusted odds ratio for the presence of sarcopenia in propensity-matched patients aged less than 75 years old was 1.76 (95% CI: 1.13–2.73, p = 0.012), and that in the patients more than or equal to 75 years old was 1.51 (95% CI: 0.93–2.44, p = 0.092).

According to the ROC analysis, the optimal cut-off point of BNP levels for the presence of sarcopenia was 27.3 pg/mL (AUC 0.777 (95%CI: 0.691–0.863, sensitivity = 0.813, specificity = 0.736, p < 0.001) (Fig. 2).

Table 2 Univariate logistic regression analyses for sarcopenia in overall patients

	Unadjusted odds ratio (95%CI)	*p* value
Age (year)	1.12 (1.07–1.18)	<0.001
Men	0.82 (0.40–1.69)	0.596
Duration of diabetes (year)	1.04 (1.01–1.08)	0.007
Body mass index (kg/m^2)	0.75 (0.66–0.85)	<0.001
Regular exerciser	0.77 (0.25–2.36)	0.646
Systolic blood pressure (mmHg)	0.97 (0.95–0.99)	0.029
Ex-smoker	0.19 (0.02–1.44)	0.108
Current smoker	0.44 (0.10–1.96)	0.281
Hemoglobin A1c (%)	1.10 (0.90–1.35)	0.366
Creatinine (μmol/L)	1.05 (0.48–2.33)	0.898
Energy intake (kcal/kg IBW/day)	0.98 (0.93–1.03)	0.496
Protein intake (g/kg IBW/day)	0.99 (0.40–2.45)	0.976
BNP (10 pg/mL)	1.50 (1.29–1.74)	<0.001

BNP, brain natriuretic peptide; IBW, ideal body weight.
Exercise was defined as nonregular exerciser (0) or regular exerciser (1) and smoking status was defined as nonsmoker (0), ex-smoker (1) current smoker (2).

Table 3 Clinical characteristics of propensity-matched patients according to the presence of sarcopenia

	Patients with sarcopenia (n = 29)	Patients without sarcopenia (n = 29)	*p* value
Sex (men/women)	14/15	13/16	0.792
Age (year)	73.1 (5.5)	73.8 (5.8)	0.612
Body mass index (kg/m^2)	21.8 (2.9)	22.1 (3.4)	0.738
Skeletal muscle mass index (kg/m^2)	5.8 (0.6)	6.2 (0.8)	0.059
Grip Strength (kg)	16.9 (9.5)	25.4 (7.1)	<0.001
Smoking (non-/ex-/current smoker)	22/4/3	25/3/1	0.501
Regular exerciser (no/yes)	25/4	23/6	0.486
Systolic blood pressure (mmHg)	124.6 (14.5)	125.4 (14.8)	0.838
Disease duration (year)	14.0 (13.7)	14.2 (12.0)	0.960
Plasma glucose (mmol/L)	9.0 (3.0)	8.1 (2.7)	0.245
Hemoglobin A1c (%)	7.6 (1.3)	7.8 (2.1)	0.717
Creatinine (μmol/L)	68.9 (12.0)	69.4 (18.8)	0.902
eGFR (mL/min/1.73 m^2)	67.7 (16.8)	68.8 (16.1)	0.931
Energy intake (kcal)	1,464.4 (442.6)	1,514.6 (444.9)	0.669
Protein intake (g/day)	61.4 (19.6)	62.5 (23.0)	0.850
BNP (pg/mL)	41.5 (23.0)	24.7 (16.2)	0.002

Data was expressed as mean (SD) or number. Wilcoxon test for continuous variables or the chi-square test for categorical variables was performed to assess statistical significance of differences between groups. BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

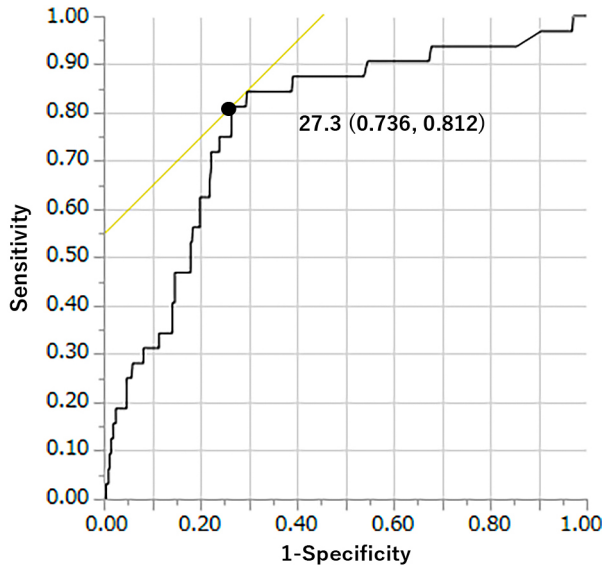

Fig. 2 Area under the receiver operating characteristic (ROC) curve (AUC) [95% confidence interval (CI)] of brain natriuretic peptide (BNP) levels for the presence of sarcopenia

The optimal cut-off point of BNP levels for the presence of sarcopenia is 27.3 pg/mL (AUC 0.777 (95%CI, 0.691–0.863, sensitivity = 0.813, specificity = 0.736, $p < 0.001$).

Discussion

We demonstrated that high BNP levels were associated with the presence of sarcopenia in patients with type 2 diabetes. Although several previous studies revealed the association between muscle loss and heart failure [10, 31, 32], to our knowledge, the present study is the first survey to clarify the association between sarcopenia and BNP levels in type 2 diabetic patients without chronic heart failure.

The possible explanation of the association between BNP levels and sarcopenia is as follows. The common pathogenesis of sarcopenia and heart failure include inflammatory cytokines. Several studies revealed the association between elevation of inflammatory cytokines, such as TNF-α, IL-β and IL-6, and heart failure [33, 34]. In addition, the increase of inflammatory cytokines was revealed to be the prognosticator for heart failure [35, 36] and severe cardiac disease [37]. One of the reasons that the inflammatory cytokines increase in patients with heart failure is inflammatory response of adipose tissue which is provoked by the upregulation of sympathetic nervous system because of the chronic pressure overload [38]. Moreover, BNP levels themselves are associated with the inflammation and it was reported that the secretion of BNP is induced by increased TNF-α [39, 40]. BNP is known as an anti-inflammatory hormone [41-43]. Therefore, the association of high BNP and sarcopenia apparently seems contradictory. However, there is a possibility that BNP is elevated in order to reduce the function of inflammatory cytokines induced by sarcopenia. Therefore, elevating BNP level is associated with inflammation, even without having heart failure. On the other hand, some previous studies reported that the inflammatory cytokines activate NF-κβ in skeletal muscles and increase the ubiquitin ligase, *i.e.* MuRF-1 and Atrogin-1, which promote protein catabolism [37, 44]. TNF-α is associated with muscle loss in animal studies [33]. In fact, BNP levels were negatively associated with BMI in men ($r = –0.373$, $p < 0.001$) and women ($r = –0.185$, $p = 0.011$) in this study. A previous study reported that BNP levels is negatively associated with BMI [45]. Adipocytes highly express natriuretic peptide clearance receptors-C, which is the basis for low serum BNP levels is associated with fat mass [46]. In fact, body fat mass is negatively associated with BNP levels both in men ($r = –0.373$, $p < 0.001$) and women ($r = –0.185$, $p = 0.011$). In addition, BNP levels were negatively associated with SMI both in men ($r = –0.404$, $p < 0.001$) and women ($r = –0.244$, $p < 0.001$) in this study. Other groups demonstrated the direct association between elevation of inflammatory cytokines and sarcopenia with heart failure [10, 47, 48]. Taken together, the inflammatory cytokines are supposed to be associated with pathogenesis both of heart failure *i.e.* increased BNP levels and sarcopenia. In sub-analyses by age, BNP levels were significantly associated with the presence of sarcopenia in patients less than 75 years old, whereas it was not significant in those more than or equal to 75 years old. This might be because the number of more than or equal to 75 years old patients with type 2 diabetes was small (only 78 patients). Moreover, Sayama, *et al.* [49] reported that BNP levels in elderly patients, mean age of which was 82 years old, without heart failure are greater than those in younger patients because of renal dysfunction and systolic dysfunction. Therefore, there might not be a significant association between BNP levels and the presence of sarcopenia in more than or equal to 75 years old patients.

In this study, we showed that the value of BNP levels of 27.7 pg/mL is a cut-off value for the presence of sarcopenia in patients without heart failure. The value of BNP levels less than 40 ng/mL is extremely unlikely to have heart failure, which is seemingly normal level [18]. However, it was revealed that there is a possibility of sarcopenia even with such low BNP levels.

The strength of our study was to assess nutrient intake using BDHQ. Reduced energy and protein intake were demonstrated to be associated with decreased skeletal muscle mass [50-52] and the assessment of nutrient intake is necessary to discuss sarcopenia. In our study,

BNP levels were significantly associated with sarcopenia even after adjusting for energy and protein intake and the other covariates. Our study has some limitations. First, we defined heart failure by BNP levels and symptom. The mean value of BNP was 42 pg/mL in patients with sarcopenia in this study, suggesting that there was a possibility that some of them were slight heart failure. Thus, to rule out heart failure, including heart failure with preserved ejection fraction, the cardiac echocardiogram is desirable. Second, the accuracy of diet survey depends on the memorial power of patients, because the data were based on the self-reported questionnaires. However, BDHQ was correlated with energy and protein intake evaluated by the 16-day-weighed dietary record [19]. Third, we did not use walking speed for diagnose sarcopenia. Thus, there is a possibility of underestimation of sarcopenia. Fourth, this study was a cross-sectional design; thus, this study did not permit the determination of causality. Additionally, although it has been postulated that diabetes may be an important factor in sarcopenia development, the relationship is unclear since the opposite maybe also true [53]. To clarify these causal relationships, follow up data are necessary. Sixth, we used dichotomous value for exercise, because we did not have detailed data of exercise or physical activity. Lastly, it is unclear whether this result applies to patients other than Japanese.

In conclusion, BNP levels were associated with the presence of sarcopenia in patients with type 2 diabetes. In addition, the value of BNP levels of 27.7 pg/mL is a cut-off for the presence of sarcopenia in patients without heart failure. We should pay attention to the possibility of the presence of sarcopenia even in patients with slightly increasing BNP levels. Further prospective studies are needed to better asses the relationship between sarcopenia and the severity of heart failure in patients with type 2 diabetes.

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Disclosure

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Conflict of Interenst

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