ORIGINAL ARTICLE

Impact of heart failure severity on bone mineral density among older patients with heart failure

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Abstract

The study aimed to identify factors related to bone mineral density (BMD) among older patients with heart failure (HF). A total of 70 consecutive patients with HF aged 65 years or older who were admitted to an acute hospital due to worsening condition were enrolled before discharge. BMD of the femoral neck was evaluated using the DEXA method. Physical function, as well as echocardiographic and laboratory findings including biomarker of HF severity were collected. Bivariate and multiple regression analyses were employed to determine the association between BMD and the clinical variables. Bivariate analysis determined that age, grip strength, walking speed, serum albumin, and N-terminal pro B-type natriuretic peptide (NT-proBNP) were significantly correlated with BMD ($P < 0.01$), whereas other clinical parameters were not. The multiple regression analysis identified NT-proBNP as an independent related factor for BMD after adjusting with confounding clinical variables. NT-proBNP was independently related to BMD among older patients with HF. Our results suggest the inclusion of bone fracture prevention strategies in disease management programs, especially for older patients with HF.

Keywords Osteoporosis · Heart failure · Frailty · Rehabilitation

Introduction

Osteoporosis, which is characterized by compromised bone quality and strength, is a common geriatric disorder leading to increased osteoporotic fractures and disability [1]. Bone fractures, which are well-established geriatric disease due to osteoporosis [1], decreased physical function and activities of daily living, and worsening health-related quality of life.

The number of patients with heart failure (HF), especially older ones, has increased exponentially within this decade and is expected to continuously increase throughout the next decade in worldwide [2]. Despite the dramatic reduction in HF mortality rates, rehospitalization due to worsening HF remains common globally including Japan [2, 3]. Several clinical issues in older people, including mobility loss, falls and fall-related fractures, cognitive impairments, malnutrition, and mental disorders, have been considered as preventable geriatric syndromes [4]. Such geriatric syndromes should have been also considered in the HF management in accordance with the increased number of older patients with HF.

The relationship between HF and bone mineral density (BMD), which is a biomarker of osteoporosis and an established risk factor for fractures, has been pointed [5, 6]. A large-scale clinical trial reported that lower BMD was associated with higher HF risk [5]. A meta-analysis has indicated that patients with HF had significantly lower BMD compared to healthy controls [6]. Furthermore, a hazard ratio of 4.40 for hip fracture after a diagnosis of HF was reported [7]. Despite these previous studies indicating a close association between HF and BMD, most of them had enrolled patients with HF who had reduced systolic function. Considering approximately 40% of patients with HF have preserved systolic function, the study with wider range of HF severity has been required. In addition, previous studies determined HF severity through the New York Heart Association functional class, which places patients

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in one of four categories based on symptom severity and the amount of exertion needed to provoke symptoms [6]. In clinical settings, however, N-terminal pro B-type natriuretic peptide (NT-proBNP), a well-established biomarker for HF severity, is widely used and may be considered a more precise and appropriate index for the HF severity [8]. Considering above-mentioned limitations of the previous studies, the association between HF severity and osteoporosis among older patients with HF remains to be fully elucidated. We hypothesized that HF severity, in addition to other clinical parameters, would be related to BMD among older patients with HF.

This study was aimed to determine the relationship between BMD and HF severity among older Japanese patients with HF.

Materials and methods

Participants

A total of 70 consecutive patients with HF admitted to Fujita Health University Bantane Hospital due to worsening condition between April 2017 and March 2018 were enrolled before discharge. Patients less than 65 years, who could not walk 10 m independently, had severe dementia, had a history of femoral neck fracture or did not agree to participate were excluded. The study protocol was approved by the Research Ethics Committee of Fujita Health University (Approval No: 15-259). All study participants provided written informed consent prior to participation.

Study design and protocol

This study utilized a single-center, observational, cross-sectional design. Baseline medical examinations and physical function tests were conducted within 1 week before discharge.

Bone mineral density measurement

BMD measurements using dual-energy X-ray absorptiometry (DXA) were performed at the femoral neck, which has been reported to be significantly lower in HF patients than healthy controls [6]. DXA scans were performed using PRODIGY Fuga (GE Health Care Japan. Tokyo, Japan) with the array beam mode. Scans were analyzed blindly at our hospital using Hologic software version 7.10. This study used the mean BMD value of both femoral necks for the analyses.

Clinical assessments

Clinical characteristics were collected from patients' medical records for age, gender, body mass index, HF etiology, and medications. Established related variables, including NT-proBNP, serum albumin, serum sodium, and estimated glomerular filtration rate (eGFR) were determined from blood tests [8]. In addition, left ventricular ejection fraction (LVEF) and E/Ea, which is the ratio of the early transmitral flow velocity to the early diastolic mitral annular velocity, were determined from an echocardiography.

Grip strengths were measured using a Jamar dynamometer. Participants were asked to sit with their wrist in a neutral position and elbow flexed at 90° [9]. Grip strength was measured two times for each hand, with the highest value being used for analysis. Walking speed was evaluated through the 10-m walk test. Participants were requested to walk at their comfortable speed for 14 m, of which the middle 10 m was timed. The test was completed twice, with the faster speed being used for the analyses.

Statistical analyses

Data are presented as mean and standard deviation for continuous variables and number and percentages for categorical data. In bivariate analyses, Pearson's or Spearman's correlation coefficients were used to determine the association between BMD scores and clinical variables. Given the right-skewed distribution of NT-proBNP data, logarithmic conversion was performed. Variables with a p value of less than 0.1 upon bivariate analyses were entered into a multiple regression model with a forced entry method to determine independent factors for BMD. All analyses were performed using SPSS 24.0 software package (SPSS Inc., Tokyo, Japan), with a p value of less than 0.05 being considered statistically significant.

Results

Clinical characteristics are summarized in Table 1. Among the 70 patients included (mean age: 81.3 ± 8.5 years), 39 were men. The mean LVEF was 52.4%, while 23 patients (32.8%) had LVEF less than 40%. A total of 57 patients (81.4%) received loop diuretics, while no patient underwent pharmacotherapy for osteoporosis.

Correlations between BMD and clinical variables are presented in Table 2. Age, gender, BMI, serum albumin, HbA1c, log-transformed NT-proBNP, grip strength, and gait speed were significantly correlated with BMD, whereas LVEF and eGFR were not. Prior to multiple

Table 1 Demographic and clinical characteristics of participants

Variables	(N = 70)
Age, years	79.3 (9.3)
Gender, male/female	39/31
BMI, kg/m^2	21.4 (3.9)
MMSE	24.5 (4.9)
GNRI	92.8 (11.9)
Cause of heart failure, *n* (%)	
Ischemic cardiomyopathy	34 (48.6)
Dilated cardiomyopathy	22 (31.4)
Others	14 (20.0)
Comorbidities, *n* (%)	
Hypertension, *n* (%)	29 (41.4)
Diabetes, *n* (%)	22 (31.4)
Dyslipidemia, *n* (%)	14 (20.0)
Pharmacotherapy, *n* (%)	
ACEi/ARB	35 (50.5)
β-Blockers	48 (67.9)
Diuretics	57 (81.4)
Statins	18 (25.7)
Oral anti-diabetic agents	13 (18.5)
Oral anticoagulant agents	16 (22.8)
Serum hemoglobin, g/dL	11.7 (2.1)
Serum albumin, g/dL	3.5 (0.5)
Serum sodium, mEq/L	139 (4.4)
HbA1c, %	6.3 (1.6)
eGFR	50.3 (21.8)
NT-proBNP, pg/mL	5658 (5632)
LVEF, %	52.4 (17.1)
E/Ea	16.6 (7.7)
HFrEF/HFmrEF/HFpEF, *n*	23/12/35
Grip strength, kgF	22.6 (10.4)
Walking speed, m/s	0.92 (0.34)
BMD, g/cm^2	0.71 (0.16)

Data are presented as mean (standard deviation) or number (%)

BMI Body mass index, *MMSE* Mini-Mental State Examination, *GNRI* Geriatric Nutritional Risk Index, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin-II type I receptor blocker, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *NT-pro BNP* N-terminal pro-brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *E/Ea* transmittal to mitral annular early diastolic velocity ratio, *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *BMD* bone mineral density

regression analysis, we excluded gender and grip strength from independent variables because of higher multicollinearity between age and gender ($r = -0.769$, $p < 0.001$), and grip strength ($r = -0.806$, $p < 0.001$). The multiple regression analysis identified that log-transformed NT-proBNP was selected as an independent correlated factor for BMD after adjustment for other several clinical variables. (Table 3).

Table 2 Correlations between bone mineral density and clinical variables

Variables	R	P
Age, years	−0.708	<0.001
Gender	−0.629	<0.001
BMI	0.568	<0.001
GNRI	0.391	0.012
Serum albumin, g/dl	0.508	<0.001
Serum hemoglobin, g/dl	0.159	0.322
HbA1c, %	0.172	0.282
eGFR, mL/min/1.73m^2	0.217	0.162
Log-transformed NT-proBNP	−0.549	0.001
LVEF, %	−0.243	0.116
E/Ea	0.167	0.344
Grip strength, kgF	0.676	<0.001
Walking speed, m/s	−0.576	0.001
Diuretics (furosemide conversion), mg	0.183	0.366

BMI Body mass index, *GNRI* Geriatric Nutritional Risk Index, *HbA1c* hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *NT-pro BNP* N-terminal pro-brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *E/Ea* transmittal to mitral annular early diastolic velocity ratio, *BMD* bone mineral density

Table 3 Multiple regression analysis for bone mineral density

	B	SE	B	t	P
Age	−0.910	0.190	−0.558	−4.778	<0.001
BMI	0.011	0.005	0.254	1.933	0.056
Serum albumin	0.037	0.052	0.092	0.706	0.486
HbA1c	0.001	0.001	0.063	0.52	0.507
Log-transformed NT-proBNP	−5.524	2.002	−0.266	−2.759	0.009
Walking speed	15.625	7.551	0.247	2.069	0.019
(Constant)	179.813	26.532		6.777	

Dependent variables: BMD

Gender and grip strength were removed from multiple regression analysis because of multicollinearity

BMI Body mass index, *GNRI* Geriatric Nutritional Risk Index, *HbA1c* hemoglobin A1c, *NT-proBNP* N-terminal pro-brain natriuretic peptide

Discussion

The current study showed that NT-proBNP, a well-establish biomarker of HF severity, was closely correlated with BMD among older patients with HF. To the best of our knowledge, this has been the first study to demonstrate that HF severity was an independent related factor for BMD among older patients with HF.

Although lower BMD [6] and higher risk of hip fracture [7] were observed in patients with HF, no study has

addressed the association of BMD and HF severity. After adjusting for several clinical variables including age, medication, and physical function, our results demonstrated that log-transformed NT-proBNP was an independent correlated factor for BMD. The finding could be attributed to hormonal abnormalities and inflammatory activation among patients with HF. The patients with HF frequently develop significant bone loss over time related to testosterone depletion [10]. Healthy controls with high CRP and tumor necrosis factor-α group had lower BMD values and higher risk for hip fracture as compared to low group [11], while inflammatory cytokines have been well known and relevant markers of HF severity and prognosis [12]. These pathophysiological changes related to HF support the close association between HF severity and BMD among older patients with HF.

Age and walking speed were independent correlated factors for BMD in the study. Clinical guidelines have indicated that increasing age, female sex, low body weight, rheumatoid arthritis, current smoking, alcohol intake, vitamin D deficiency, low calcium intake, physical inactivity, and polypharmacy or long-term use of certain medications, such as glucocorticoids, anticoagulants, and diuretics, are all risk factors for osteoporosis [1]. Our data support previous findings suggesting aging and physical function as risk factors for osteoporosis. It is well known that physical function decreases with heart failure severity [8]. In our result, we could find independent association between BMD and NT-proBNP after adjustment for grip strength and walking speed. Thus, our data also showed that older patients with HF were more likely to develop osteoporosis due to not only aging or physical inactivity but also HF severity.

There was no relationship between BMD and pharmacotherapy. The current study included 16 patients on oral anticoagulants (six receiving a vitamin K antagonist and 10 receiving a non-vitamin K antagonist oral anticoagulant). Previous reports have shown that non-vitamin K antagonists promote lower risk for osteoporosis than vitamin K antagonists [13]. Moreover, most of our patients (approximately 80%) had been placed on loop diuretics, a first-line medication for patients with HF. Considering our patients' pharmacological background, the much lower rate of anticoagulant use and much higher rate of loop diuretic use could perhaps explain why we detected no relationship between BMD and pharmacotherapy.

Previous guidelines and scientific statements have provided several disease management strategies for older patients with HF. Some lifestyle-related factors, such as salt intake, physical activity, and medication [14], could help manage HF conditions and prevent future rehospitalization due to HF deterioration. However, no information has been available regarding non-HF-related rehospitalizations, including those due to bone fracture or other diseases. Given that HF is a risk factor for bone fractures, as previously discussed, preventing all-cause rehospitalizations is important for improving health-related quality of life. Our results suggest that increased bone loss in conjunction with HF could likely increase fracture risk, especially among older patients with HF. Thus, strategies for optimal HF treatment and for optimizing physical activity or physical function among older patients with HF who have double the disease burden are critical.

Some potential limitations of the present study are worth noting. First, considering that this study was performed on patients with HF from a single institution, generalization of the results should be done with caution. Second, the cross-sectional design of our research does not allow for determining causal relationships. Then, longitudinal studies are needed to prove that strategies aimed at preventing bone fractures should be an integral component of disease management programs. Finally, we could not determine hormonal, inflammatory, and nutritional status. Thus, this study may serve as only preliminary research regarding the impact of HF severity on BMD among older patients with HF. Nevertheless, the results presented herein provide novel information about the relation between HF severity and BMD, and also suggested the optimal management of older patients with HF to prevent not only HF-related rehospitalizations but also all-cause hospitalizations.

In conclusion, the present study showed that NT-proBNP was an independent related factor for femoral neck BMD among older patients with HF. The results of this study suggest that strategies aimed at preventing bone fractures *could be an* integral component of disease management programs especially for older patients with HF.

Declarations

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