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Original Article

Sarcopenia evaluated by fat-free mass index is an important prognostic factor in patients with chronic heart failure

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ABSTRACT

Background and Aim: Chronic heart failure (CHF) is a major cause of morbidity and mortality, and cardiac cachexia and sarcopenia are serious complications associated with weight loss and increased catabolism. Fat-free mass index (FFMI) is an indicator of resting energy expenditure and is used for the clinical diagnosis of sarcopenia. In the present study, we investigated the impact of sarcopenia, as evaluated by FFMI, on cardiac prognosis in patients with CHF.

Methods and results: We calculated FFMI in 267 CHF patients who were prospectively followed until they died due to cardiac event, or until they were re-hospitalized. Fat-free mass (FFM) was estimated by the formula [FFM (kg) = 7.38 + 0.02908 × urinary creatinine (mg/day)] and normalized by the square of the patient's height in meters to calculate FFMI. During the follow-up periods, there were 83 cardiac events, including 19 cardiac deaths. FFMI was lower in patients with cardiac events than in those without (17.0 kg/m^2 vs. 17.6 kg/m^2, $P = 0.045$). Multivariate Cox hazard analysis revealed that decreased FFMI was associated with an unfavorable outcome (adjusted hazard ratio 0.68, 95% confidence interval 0.47–0.98). The patients were divided into two groups according to their median FFMI. The Kaplan–Meier analysis revealed that significantly higher cardiac event rate was observed in the low-FFMI group (log-rank test, $P = 0.017$).

Conclusions: Decreased FFMI was associated with an unfavorable prognosis in patients with CHF.

1. Introduction

Chronic heart failure (CHF) is an important health issue and still represents a poor prognosis despite advance in treatment [1]. In developed countries, CHF occurs in approximately 1–2% of the general population, but in 10% or more in those aged 70 years or older [2]. Over 60% of patients with CHF are reported to experience muscle weakness and fatigue caused by muscle atrophy, and these are two of the major symptoms in patients with CHF [3,4].

The pathophysiology of CHF is thought to involve detrimental levels of catabolism, since cardiac cachexia and sarcopenia, which both involve catabolic loss of muscle mass, emerge during the advanced stage of CHF [5]. Cardiac cachexia is defined by an overall loss of more than 7.5% of the previous normal weight during a period of more than 6 months, and that is caused by heart disease. Sarcopenia is defined as skeletal muscle loss and dysfunction during aging and affliction with a chronic disease [6,7]. Cardiac cachexia and sarcopenia are associated with metabolic, immune, and neurohormonal factors [8]. The imbalance of immune and neurohormonal systems contributes to the wasting process and leads to cardiac cachexia and sarcopenia.

Fat-free mass index (FFMI), which reflects the masses of skeletal muscle, organs, bone, and connective tissue and which is an indicator of resting energy expenditure, is used for the clinical diagnosis of sarcopenia. In contrast to body mass index (BMI), FFMI is not affected by fluid status in patients with CHF. Thus far, the association between FFMI and the severity of the CHF, as well as its prognosis, has not been fully determined. The purpose of this study was to clarify the relationship between FFMI and cardiac prognosis in patients with CHF.

2. Methods

2.1. Study population

Between September 2009 and October 2011, 469 patients were admitted to the Yamagata University Hospital, some for treatment of worsening CHF, others for diagnosis and pathophysiological investigations of CHF, and the reminder for therapeutic evaluation of CHF. The diagnosis of CHF was based on a history of dyspnea and symptoms of exercise intolerance followed by pulmonary congestion, pleural

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effusion, or left ventricular enlargement as determined by a chest X-ray or echocardiography [9]. Five patients undergoing chronic hemodialysis and 49 patients without data for serum albumin levels were excluded. In addition, 129 patients were excluded for whom data were unavailable to estimate FFMI.

The remaining 294 patients were enrolled in the present study. We also enrolled 30 age- and gender-matched control subjects without signs of significant heart disease to examine the FFMI in patients without CHF. All participants gave written informed consent prior to their participation. The procedures were approved by the institution's Human Investigation Committee and were performed in accordance with the Helsinki Declaration.

2.2. Anthropometry and measurement of blood biomarkers

The measurement of height and body weight was undertaken when the patients had recovered from acute decompensated heart failure. Venous blood samples were acquired on admission for measurement of blood biomarkers. The blood samples were centrifuged at 2,500 g for 15 min at 4 °C within 30 min of collection. Serum brain natriuretic peptide (BNP) concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi & Co., Ltd., Tokyo, Japan) [10].

2.3. Calculation of fat-free mass index

Fat-free mass (FFM) was calculated using the formula FFM (kg) = 7.38 + 0.02908 × urinary creatinine (mg/day), where urinary creatinine (mg/day) = 2.04 × age + 14.89 × body weight (kg) + 16.14 × height (cm) − 2244.45 [11,12]. FFM was then divided by the square of subject's height in meters to obtain FFMI, which normalizes FFM for the effect of height.

Table 1
Baseline characteristics of study participants.

	Control subjects ($n = 30$)	CHF patients ($n = 267$)	*P* value
Age, years	70 ± 3	71 ± 12	0.719
Male, *n* (%)	15 (50)	160 (60)	0.295
NYHA functional class, I/II/III, IV	–	59/99/109	–
Etiology, *n* (%)			–
Hypertensive heart disease	–	59 (22)	
Dilated cardiomyopathy	–	52 (20)	
Ischemic heart disease	–	50 (19)	
Valvular heart disease	–	41 (15)	
Other causes	–	65 (24)	
Presentation profile			
BMI, kg/m^2	23.0 ± 3.3	21.6 ± 3.6	0.059
FFMI, kg/m^2 (IQR)	18.3 (18.1–19.3)	17.3 (16.2–18.6)	<0.001
eGFR, ml/min/1.73 m^2	74.7 ± 15.4	62.4 ± 25.0	0.008
Blood biomarkers			
Albumin, g/dl	–	3.6 (3.1–4.0)	–
Fasting blood sugar, mg/dl	102 ± 35	113 ± 32	0.102
Total cholesterol, mg/dl	199 ± 25	168 ± 37	<0.001
Triglyceride, mg/dl	105 ± 51	91 ± 48	0.125
LDLc, mg/dl	122 ± 21	101 ± 34	<0.001
HDLc, mg/dl	58 ± 12	53 ± 20	0.154
Hemoglobin, g/dl	13.4 ± 1.3	12.2 ± 2.3	0.005
BNP, pg/ml (IQR)	26.3 (11.7–37.1)	390 (142–965)	<0.001
Echocardiographic data			
LV end-diastolic diameter, mm	–	55 ± 10	–
LV ejection fraction, %	–	50 ± 18	–
Medications, *n* (%)			
ACE inhibitors and/or ARBs	–	167 (63)	–
beta-Blockers	–	173 (65)	–

Data are presented as means ± SD or % unless otherwise indicated; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; FFMI, fat-free mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; LV, left ventricular; NYHA, New York Heart Association.

Table 2
Comparison of patients with or without cardiac events.

	Event (−) ($n = 184$)	Event (+) ($n = 83$)	*P* value
Age, years	69 ± 12	74 ± 12	0.003
Male, *n* (%)	107 (58)	53 (64)	0.379
NYHA functional class, I/II/III, IV	50/71/63	9/28/46	<0.001
Etiology, *n* (%)			0.401
Hypertensive heart disease	45 (24)	14 (17)	–
Dilated cardiomyopathy	33 (18)	19 (23)	–
Ischemic heart disease	33 (18)	17 (20)	–
Valvular heart disease	29 (16)	12 (15)	–
Other causes	44 (24)	21 (25)	–
Presentation profile			
BMI, kg/m^2	21.9 ± 3.8	21.1 ± 3.5	0.104
FFMI, kg/m^2 (IQR)	17.6 (16.2–18.9)	17.0 (16.0–18.0)	0.045
eGFR, ml/min/1.73 m^2	66.9 ± 25.8	52.4 ± 20.2	<0.001
Blood biomarkers			
Albumin, g/dl	3.8 (3.1–4.0)	3.0 (2.4–3.3)	<0.001
Fasting blood sugar, mg/dl	112 ± 29	113 ± 37	0.808
Total cholesterol, mg/dl	173 ± 36	156 ± 38	<0.001
Triglyceride, mg/dl	98 ± 52	77 ± 32	<0.001
LDLc, mg/dl	104 ± 31	95 ± 37	0.036
HDLc, mg/dl	55 ± 21	50 ± 15	0.055
Hemoglobin, g/dl	12.5 ± 2.3	11.5 ± 2.2	0.001
BNP, pg/ml (IQR)	334 (128–890)	512 (221–1137)	0.507
Echocardiographic data			
LV end-diastolic diameter, mm	54 ± 9	56 ± 11	0.128
LV ejection fraction, %	52 ± 18	45 ± 17	0.003
Medications, *n* (%)			
ACE inhibitors and/or ARBs	116 (63)	51 (61)	0.947
beta-Blockers	109 (59)	64 (77)	0.081

Data are presented as means ± SD or % unless otherwise indicated; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FFMI, fat-free mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; LV, left ventricular; NYHA, New York Heart Association.

2.4. End points and follow-up

The enrolled patients were prospectively followed for a median duration of 10.7 months (interquartile range 3.0–20.3 months). For 83 patients, the studies ended upon cardiac death including death due to progressive CHF, myocardial infarction, and sudden cardiac death, as well as re-hospitalization for worsening CHF. The remaining 211 patients were ended upon the closure of the observation period. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was confirmed by the attending physician. Two cardiologists, who were blinded to the blood biomarker data, reviewed the medical records and conducted telephone interviews to survey the incidence of cardiac events [10].

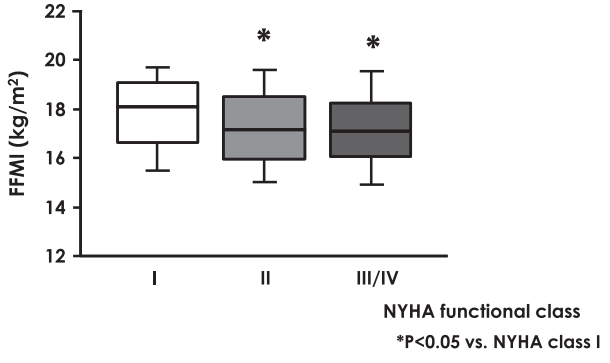

Fig. 1. The association between FFMI and NYHA functional class. Values of FFMI in NYHA functional class II and class III/IV patients were significantly lower than in class I patients (17.2 vs. 17.9, $P = 0.028$ and 17.3 vs. 17.9, $P = 0.010$, respectively). FFMI, fat-free mass index; NYHA, New York Heart Association.