Adipokines in patients with heart failure under rehabilitation

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Running title: Association of adipokines with frailty in heart failure

Abstract

Background Frailty is a multifactorial physiological syndrome most often associated with age but which has received increasing recognition as a component of chronic illnesses such as heart failure. Patients with heart failure are likely to be frail, irrespective of their age. Adipokine dysregulation, which is associated with frailty, occurs in patients with heart failure. In this study, we tested the hypothesis that adipokines are associated with skeletal muscle and bone mineral density that change lead to frailty in patients with heart failure.

Methods Thirty-five patients with heart failure (age, 67 ± 14 years; 25 males; left ventricular ejection fraction, 45 ± 19%) were included. Serum adipokine levels, physical performance, and body composition were measured.

Results Adiponectin and leptin were inversely correlated with grip strength. Adiponectin was inversely correlated with bone mineral density. Leptin was positively correlated with fat mass. Adipokines were not correlated with skeletal muscle mass.

Conclusions Adipokines were associated with grip strength and bone mineral density in patients with heart failure. Adipokine dysregulation may play a role in the development of frailty in heart failure.

Key words: adipokines, frailty, heart failure, leptin, osteoporosis

Introduction

Frailty is a clinically recognizable state of increased vulnerability mainly resulting from aging-associated decline in reserve and function across multiple physiologic systems. Heart failure is associated with accelerated biological aging,[1] and patients with heart failure are likely to be frail irrespective of their age.[2] A previous systematic review has reported that the prevalence of frailty in heart failure ranges from 18 to 54%, and this has been reported as 45% in a recent meta-analysis.[3, 4] Frailty is an independent predictor of all-cause mortality and hospital readmissions in patients with heart failure.[5] Frailty also increases mortality in patients with acute decompensated heart failure attending an emergency department.[6] Furthermore, frailty has a negative impact on the physical activity, mental state, and quality of life of patients with heart failure.[7, 8]

Frailty is affected by age-related changes in body composition. Skeletal muscle mass, grip strength, and bone density are important factors related to frailty, and sarcopenia and osteoporosis patients have significantly reduced physical activity. [9] Muscle and bone tissues are modified by various factors other than age, such as inflammation.

Inflammation has been implicated in the pathogenesis of both frailty and heart failure, although the pathophysiology of both disorders is complex and includes multiple derangement pathways, which require further elucidation.[10-13] Adipokines secreted by adipose tissue play a role in the regulation of metabolic functions such as lipid metabolism and inflammation, and recent evidence has shown that adipokine dysregulation is associated with frailty in old age.[10, 14-17] Furthermore, adipokine dysregulation has also been reported in

heart failure.[18-20] Here, we tested the hypothesis that adipokines are associated with skeletal muscle and bone mineral density in patients with heart failure.

Methods

Study population

We prospectively included patients admitted with congestive heart failure who underwent phase 2 cardiac rehabilitation in our hospitals (Niigata University Graduate School of Medical and Dental Sciences, Niigata Minami Hospital, Shinrakuen Hospital, Niigata Medical Center, and Saiseikai Niigata Daini Hospital) from February to August 2014. Patients with cardiovascular events such as myocardial infarction, stroke, and thromboembolism within 6 weeks before baseline examination, heart transplantation, or pregnancy were excluded. Patients on dialysis were also excluded. Written informed consent was obtained from all patients. This study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Niigata University Graduate School of Medicine (application number 1788).

Assessment of body composition

Dual-energy X-ray absorptiometry (DEXA; Hologic Discovery QDR Series; Hologic Inc., Bedford, MA) was used to evaluate bone mineral density, lean mass, and fat mass. The lean mass was defined as skeletal muscle mass, and appendicular muscle mass was defined as the combined lean mass of both arms and legs. Appendicular skeletal muscle mass index (ASMI), appendicular fat mass index (AFMI), and appendicular bone mineral density (ABMD) were calculated as each measurement divided by height in meters squared. Grip strength was measured using a Smedley-type handgrip dynamometer.

Assessment of serum levels of adipokines

Serum levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured using chemiluminescence enzyme immunoassays (LSI Medience Corporation, Tokyo, Japan). Serum levels of adiponectin and leptin were measured using enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

Statistical analysis

Continuous variables and categorical variables are expressed as mean ± standard deviation (SD) and numbers (percentages), respectively. Linear regression analysis was used to study the relationship between variables. All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY). A two-tailed p-value less than 0.05 was considered statistically significant.

Results

Fifty-six patients underwent phase 2 cardiac rehabilitation during the study period, and 35 patients fulfilled the study inclusion criteria. The baseline characteristics of patients are shown in Table. The study cohort consisted of 25 males (71%). The mean age was 67 ± 14 years and 10 patients (29%) were younger than 60 years. The most common cause of heart failure was ischemic heart disease. The mean left ventricular ejection fraction was 45 ± 19% and there were 29 patients (83%) with New York Heart Association (NYHA) functional class less than III. Physical characteristics are shown in Table. There were 5 overweight or obese patients (14%) (body mass index (BMI) > 25 kg/m^2) and 6 underweight patients (17%) (BMI < than 18.5 kg/m^2). Weight classification by BMI was defined according to World Health Organization criteria.

We investigated the associations of adipokines with physical parameters. Adiponectin and leptin were inversely associated with grip strength (Figure 1 and 2). However, TNF-α and lL-6 were not associated with grip strength. There was no association of four cytokines tested with ASMI (Figure 1-4). Leptin was positively associated with AFMI, but there was no association of AFMI with the other three cytokines evaluated (Figure 1-4). Adiponectin was inversely associated with ABMD (Figure 1).

Discussion

In this study, we found that adipokines were associated with physical performance and body composition in patients with heart failure. This association suggests that deranged inflammatory pathways in adipose tissues may play a role in frailty in patients with heart failure.

Adipose tissue secretes anti-inflammatory adipokines such as adiponectin and pro-inflammatory ones such as TNF-α, IL-6, and leptin.[21] Recent studies have revealed that a decline in immune function with age is associated with frailty, and adipokine dysregulation plays an important role in this association.[10, 14-17] C-reactive protein is positively associated with the severity of frailty in individuals aged over 75 years, and increasing frailty has also been shown with increasing TNF-α and IL-6 levels.[14] Adiponectin and IL-6 are increased in older adults with frailty compared to those without frailty, and are inversely associated with grip strength and gait speed.[17] Leptin is also inversely associated with physical function.[16] Adipokine dysregulation has also been reported in patients with heart failure,[18-20] and in this study we found an inverse association of adiponectin and leptin with grip strength, but there was no association of TNF-α and IL-6 with grip strength. This suggests that adipokine dysregulation, which occurs in association with heart failure, may play a role in development of frailty.

The prevalence of frailty in heart failure patients is high irrespective of age, and frailty is associated with acute exacerbation of heart failure and increased mortality.[2-6] Decreased skeletal muscle mass is associated with impaired cardiorespiratory fitness and quality of life, in addition to weak muscle strength in patients with heart failure.[22] A previous study of patients with heart

failure has found that IL-6 is associated with decreased skeletal muscle mass,[22] while another has demonstrated an inverse association of both adiponectin and leptin with lean mass.[23] In this study, adiponectin and leptin were inversely associated with grip strength, thus suggesting a role of adipokines in frailty in heart failure. However, in this study, the association was negative for adipokines including adiponectin, TNF-α, IL-6, and leptin. These inconsistent results may be explained by the small size of the study cohort and the differences in patient characteristics.

This study also identified an association of adipokines with fat mass and bone mineral density, in addition to that with muscle mass. Leptin is increased in obese patients with heart failure and is correlated with BMI, percentage body fat, and waist circumference.[24, 25] The mean BMI of patients with heart failure in our study group was 22±4, and in these patients, leptin was positively associated with fat mass. Furthermore, leptin is associated with epicardial fat thickness in non-cachectic patients with heart failure.[26] The increased levels of leptin may play a role in disrupted lipid metabolism in heart failure.

Adiponectin has been shown to increase bone turnover, and therefore, has been implicated in the pathogenesis of osteoporosis.[27] A previous study has demonstrated that adiponectin levels increase as heart failure severity worsens, and that adiponectin was inversely associated with bone mineral density.[28] Patients with heart failure have various risk factors for osteoporosis such as older age, physical inactivity, and therapy with loop diuretics. The increased levels of adiponectin may further contribute to the pathogenesis of osteoporosis in heart failure.

Conclusion

Adipokines were associated with grip strength and bone mineral density in patients with heart failure. Adipokine dysregulation may play a role in the development of frailty in heart failure.

Limitation

There are several limitations to this study. The number of patients was small, and multivariate analysis could not be performed. The etiologies of heart failure in patients were inconsistent. Analysis stratified by age and gender could not be performed. Comorbidities varied and the duration was unknown. The patient's conditions of heart failure were consistent at the time of blood sampling, DEXA and grip strength, although prior therapy and rehabilitation periods were inconsistent.

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Disclosures

None.

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Figure legends

Figure 1. Association of adiponectin with grip strength and body composition. ASMI, appendicular skeletal muscle mass index; AFMI, appendicular fat mass index; ABMD, appendicular bone mineral density.

Figure 2. Association of leptin with grip strength and body composition. ASMI, appendicular skeletal muscle mass index; AFMI, appendicular fat mass index; ABMD, appendicular bone mineral density.

Figure 3. Association of TNF-α with grip strength and body composition. ASMI, appendicular skeletal muscle mass index; AFMI, appendicular fat mass index; ABMD, appendicular bone mineral density.

Figure 4. Association of adiponectin with grip strength and body composition. ASMI, appendicular skeletal muscle mass index; AFMI, appendicular fat mass index; ABMD, appendicular bone mineral density.

Table. Clinical characteristics of 35 patients

Age, years	67 ± 14
Male, n (%)	25 (71)
Cardiovascular diseases	
Ischemic heart disease, n (%)	14 (40)
Dilated cardiomyopathy, n (%)	10 (29)
Hypertrophic cardiomyopathy, n (%)	4 (11)
Valvular heart disease, n (%)	5 (14)
Congenital heart disease, n (%)	2 (6)
Comorbidities	
Hypertension, n (%)	16 (46)
Dyslipidemia, n (%)	17 (49)
Diabetes mellitus, n (%)	14 (40)
Arterial fibrillation, n (%)	12 (34)
NYHA functional class	
I, n (%)	10 (29)
II, n (%)	19 (54)
III, n (%)	6 (17)
Brain natriuretic peptide, pg/mL	427 ± 422
Left ventricular ejection fraction, %	45 ± 19
Medication	
Beta-blocker, n (%)	27 (77)
ACE-I or ARB, n (%)	22 (63)
Spironolactone, n (%)	16 (46)
Loop diuretics, n (%)	28 (80)
Physical characteristics	
Body height, cm	161 ± 9
Body weight, kg	56 ± 14
Body mass index, kg/m^2	22 ± 4
Skeletal muscle mass index, kg/m^2	6.38 ± 1.25
Fat mass index, kg/m^2	2.17 ± 1.05
Bone mineral density, kg/m^2	0.38 ± 0.07
Hand grip strength, kg	29 ± 11

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. Data are mean ± standard deviation or number (%).

Figure 1

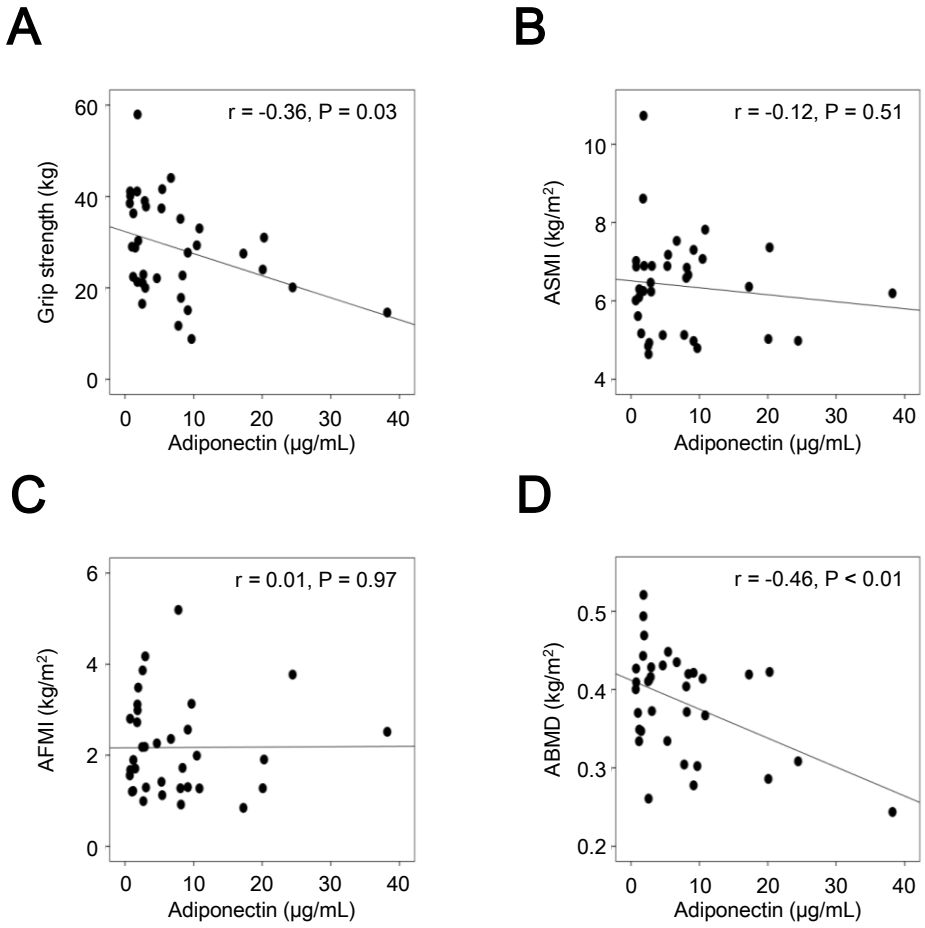

A
r = -0.36, P = 0.03
Grip strength (kg)
Adiponectin (μg/mL)
B
r = -0.12, P = 0.51
ASMI (kg/m²)
Adiponectin (μg/mL)
C
r = 0.01, P = 0.97
AFMI (kg/m²)
Adiponectin (μg/mL)
D
r = -0.46, P < 0.01
ABMD (kg/m²)
Adiponectin (μg/mL)

Figure 2

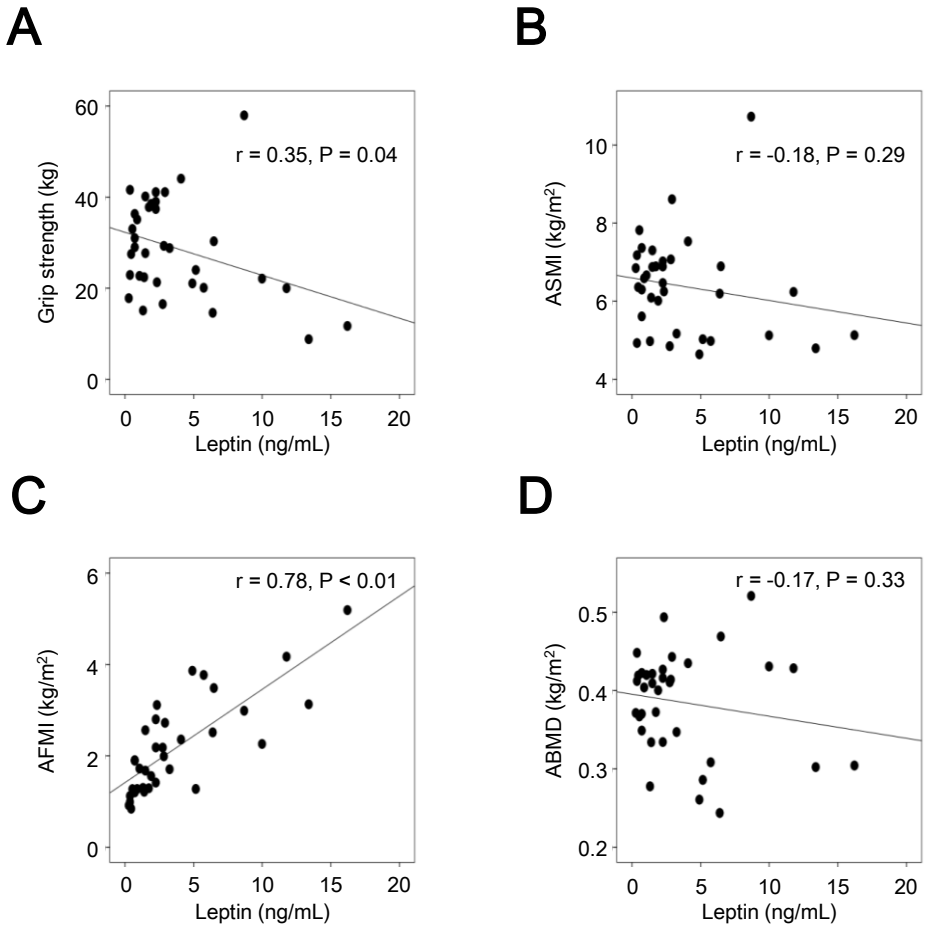

A
B
C
D
Grip strength (kg)
ASMI (kg/m²)
AFMI (kg/m²)
ABMD (kg/m²)
Leptin (ng/mL)
r = 0.35, P = 0.04
r = -0.18, P = 0.29
r = 0.78, P < 0.01
r = -0.17, P = 0.33

Figure 3

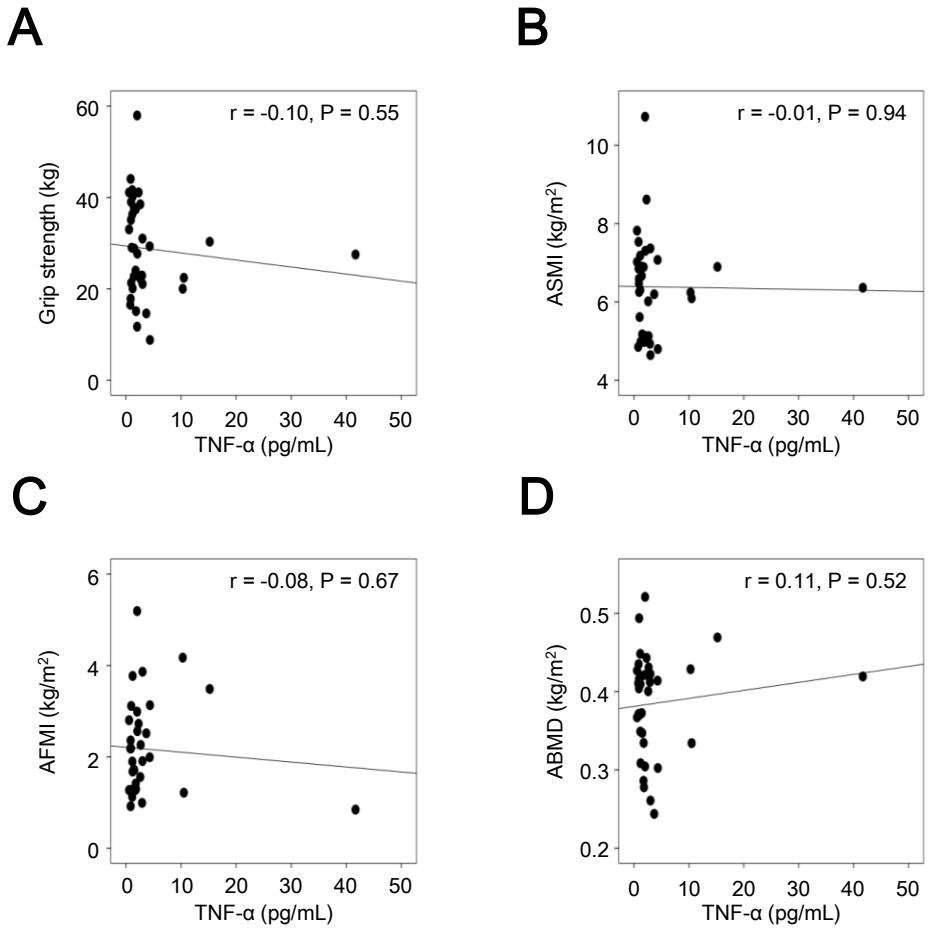
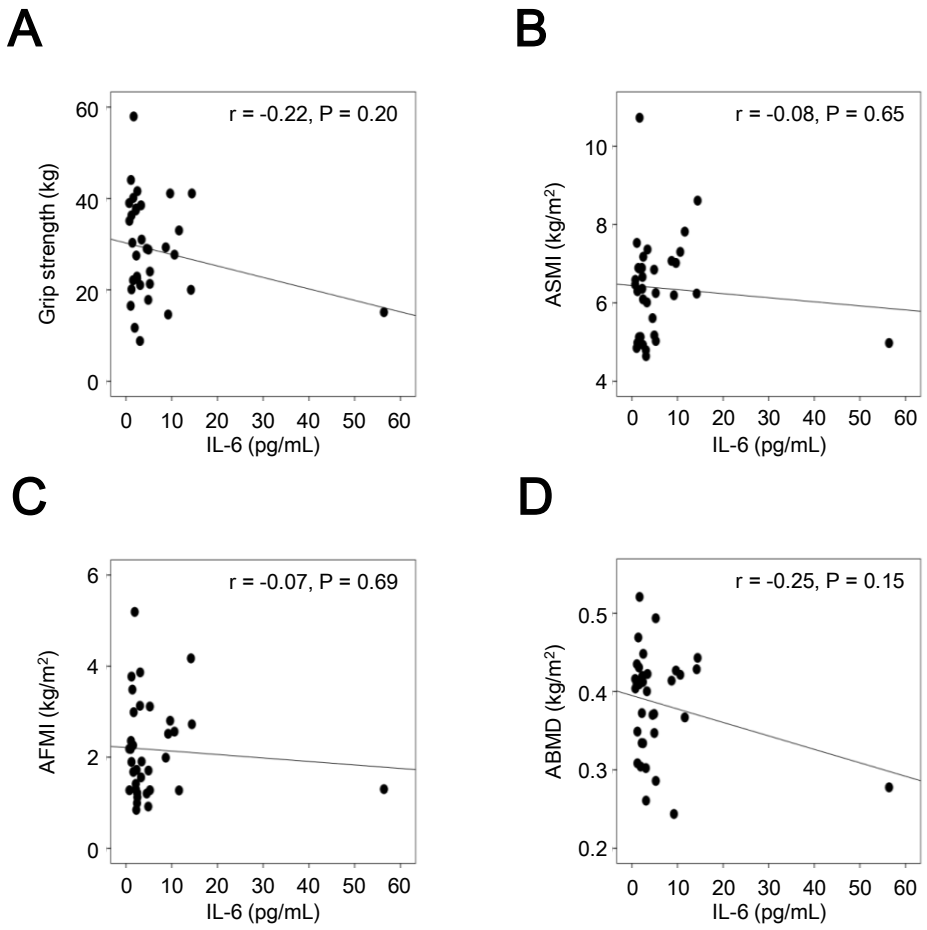

A
B
C
D
r = -0.10, P = 0.55
r = -0.01, P = 0.94
r = -0.08, P = 0.67
r = 0.11, P = 0.52
Grip strength (kg)
ASMI (kg/m²)
AFMI (kg/m²)
ABMD (kg/m²)
TNF-α (pg/mL)
0
10
20
30
40
50
60
4
6
8
2
0.2
0.3
0.4
0.5

Figure 4


A
B
C
D
r = -0.22, P = 0.20
r = -0.08, P = 0.65
r = -0.07, P = 0.69
r = -0.25, P = 0.15
Grip strength (kg)
ASMI (kg/m²)
AFMI (kg/m²)
ABMD (kg/m²)
IL-6 (pg/mL)
0
10
20
30
40
50
60
2
4
6
8
0.2
0.3
0.4
0.5