Circulation Reports
Circ Rep 2019; 1: 456–461
doi:10.1253/circrep.CR-19-0053

RAPID COMMUNICATION

Association of Serum Amino Acid Concentration With Loss of Skeletal Muscle Mass After 1 Year in Cardiac Rehabilitation Center Patients

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Background: Decreased skeletal muscle mass index (SMI) is a major complication of severe chronic heart failure (HF), but no appropriate indices have been developed to predict decreased SMI.

Methods and Results: We enrolled patients with a structural heart disease or history of HF and collected body composition and blood sample data, including serum amino acid concentration. On multivariate logistic regression analysis and receiver operating characteristic curve analysis, serum branched-chain amino acid (BCAA) concentration was a significant predictor of decreased SMI at 1-year follow-up.

Conclusions: Serum BCAA concentration at baseline was significantly associated with decreased SMI at 1-year follow-up.

Key Words: Amino acid; Heart failure; Muscle; Nutrition

Loss of skeletal muscle mass is frequently present in patients with chronic heart failure (CHF) and may contribute to fatigue and dyspnea.[1] Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of skeletal muscle mass with or without loss of fat mass, while sarcopenia is a condition that involves only muscle loss. Loss of muscle mass and function associated with aging occurs in sarcopenia. Many cases of cachexia are accompanied by sarcopenia. Patients with loss of skeletal muscle mass have poorer prognosis. For therapeutic intervention, accurate assessment of nutritional status of patients with CHF is important.

Body mass index (BMI) is used to define cachexia. In patients with heart failure (HF), however, body weight fluctuates rapidly because of fluid retention and diuretic use. Therefore, to avoid the influence of fluid retention, ideally, skeletal muscle mass should also be measured. Bioelectrical impedance analysis (BIA) provides body composition data non-invasively and allows for assessment of change in muscle or fat mass individually, and its feasibility and diagnostic performance are as accurate as those of dual-energy X-ray absorptiometry.[2]

Regarding serum biomarkers, serum amino acid (AA) concentration has been shown to reflect the nutritional status in several diseases.[3] We previously reported that the concentration of serum branched-chain AA (BCAA) was lower in patients with CHF than in control patients.[4] Furthermore, in patients with HF, an AA supplement improved their exercise capacity.[5] BCAA is mainly catabolized in the skeletal muscle and plays an important role in the formation of skeletal muscle. Serum BCAA concentration has also been positively correlated with the skeletal muscle mass index (SMI).[4]

As mentioned in the previous section, some markers for assessing nutritional status in patients with CHF are being developed. No appropriate indices, however, have been developed to predict future loss of skeletal muscle mass. Therefore, the purpose of this study was to identify serum markers that would be a predictor of loss of skeletal muscle mass.

Here, we found a significant association between serum BCAA concentration at baseline and the incidence of skeletal muscle mass loss after 1 year. To our knowledge, this is the first study to show that serum BCAA concentration can predict loss of skeletal muscle mass.

Methods

Subjects

This was a single-center retrospective case control study. The data were obtained from the heart disease database for 128 patients who visited the Cardiac Rehabilitation Center of Hyogo Prefectural Amagasaki Hospital between April

Received June 21, 2019; revised manuscript received August 19, 2019; accepted August 28, 2019; J-STAGE Advance Publication released online September 27, 2019 Time for primary review: 15 days

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ISSN-2434-0790

2013 and March 2014. From the database, we collected the body composition data and blood sample (including the serum AA concentration) data. Of these patients, 123 patients had body composition data and 72 patients had blood sample data. The body composition and blood sample data of 67 patients were available. All the patients had stage B or C HF according to the American College of Cardiology Foundation/American Heart Association guideline[6] (ischemic heart disease, n=8; cardiomyopathy, n=11; hypertensive heart disease, n=4; atrial fibrillation, n=4; other, n=4; left ventricular ejection fraction, 47.6±14%). Of these patients, we collected repeated body composition data 1 year later. Thirty-one patients had repeated body composition data. At the time of both analyses, the HF patient symptoms remained stable. Patients with acute HF syndrome, acute coronary syndrome in the last 6 months, coronary intervention in the last 6 months, active infection, dialysis, and pacemaker implantation were excluded from the study.

The study conformed to the principles outlined in the Declaration of Helsinki[7] and was approved by the institution ethics committee.

Body Impedance and Laboratory Data

Body composition data were collected using the InBody 720 bioelectrical impedance analyzer (Biospace Japan, Tokyo, Japan). Impedance was measured at frequencies of 1, 5, 50, 250, 500, and 1,000 kHz. The body composition data were derived from 10 sets of impedance data.

Blood samples were collected when the patients visited hospital. We had no data on what time they ate their last meal before visiting hospital or on their daily dietary intake. Blood measurements included hematology, biochemistry, B-type natriuretic peptide (BNP), and 40 AA fractions. AA fraction levels were measured using high-performance liquid chromatography (BML, Tokyo, Japan), using a high-speed AA analyzer (L-9700, Hitachi, Tokyo, Japan). In all patients, the serum concentration of phosphoethanolamine, homocysteine, α-aminoadipic acid γ-amino-n-butyric acid, hydroxylysine, anserine, and carnosine was

Table 1. Subject Characteristics vs. SMI Status

n=31	Decreased SMI (n=17)	Non-decreased SMI (n=14)	P-value	Adjusted P-value
Characteristics				
Age (years)	72.6±8.6	71.1±8.5	0.627	
Male	10 (59)	10 (71.4)	0.479	
BMI (kg/m^2)	22.3±2.9	23.4±3.7	0.389	0.595
SMI (kg/m^2)	8.7±1.5	9.4±1.4	0.206	0.237
FMI (kg/m^2)	5.9±1.6	6.1±2.3	0.774	0.861
ECW/TBW	0.398±0.012	0.391±0.008	0.058	0.082
Laboratory data				
Lymphocyte count (×10^8/L)	15.8±7.2	15.2±4.8	0.771	0.753
Hemoglobin (g/dL)	12.4±1.4	13.4±1.9	0.122	0.144
Alb (g/dL)	4.08±0.41	4.03±0.43	0.755	0.598
T-Bil (mg/dL)	0.70 (0.60–1.00)	0.65 (0.50–0.78)	0.313	0.218
AST (U/L)	22.0 (20.0–28.0)	21.5 (17.5–30.8)	0.946	0.894
ALT (U/L)	16.0 (13.0–21.0)	16.0 (14.0–26.5)	0.453	0.366
eGFR (mL/min/1.72 m^2)	55.6±17.8	62.5±22.9	0.365	0.497
Total cholesterol (mg/dL)	171.6±33.2	181.1±37.4	0.469	0.353
Triglyceride (mg/dL)	111.4±61.3	157.5±83.1	0.098	0.152
HDL-C (mg/dL)	49.7±12.5	45.2±11.9	0.317	0.461
LDL-C (mg/dL)	98.1±32.9	102.4±32.8	0.715	0.678
Hemoglobin A1c (NGSP) (%)	5.89±0.88	6.16±0.72	0.346	0.365
BNP (pg/mL)	146 (74.1–270)	34.0 (17.6–139.4)	0.049	0.304
hsCRP (mg/dL)	0.07 (0.04–0.11)	0.11 (0.05–0.30)	0.133	0.209
AA fraction				
EAA				
BCAA				
Val	238.6 (212.7–262.1)	302.7 (264.1–340.4)	<0.001	0.007
Ile	67.8 (55.6–71.1)	90.6 (81.0–104.3)	<0.001	0.007
Leu	115.7 (102.8–131.7)	156.6 (138.2–182.9)	<0.001	0.013
Met	28.3 (25.9–30.8)	30.3 (27.5–40.3)	0.190	0.105
Lys	214.2 (189.5–223.6)	239.8 (212.0–282.9)	0.109	0.044
Phe	70.9 (65.6–86.4)	84.8 (78.3–97.2)	0.049	0.106
Trp	47.2 (42.3–54.6)	55.6 (48.1–66.2)	0.161	0.179
Thr	120.2 (108.3–144.0)	140.6 (116.8–169.9)	0.250	0.148
His	83.5 (79.9–104.3)	94.8 (85.1–112.6)	0.122	0.231

(**Table 1** continued the next page.)

n=31	Decreased SMI (n=17)	Non-decreased SMI (n=14)	P-value	Adjusted P-value
NEAA				
Arg	96.7 (89.3–118.6)	109.7 (99.8–146.0)	0.186	0.152
Gly	277.9 (236.6–324.2)	240.8 (215.6–280.1)	0.173	0.188
Ala	483.6 (366.3–589.8)	527.0 (430.9–562.7)	0.518	0.324
Ser	125.3 (117.7–155.9)	138.0 (112.4–149.0)	0.953	0.947
Tyr	79.5 (72.2–97.3)	88.5 (67.5–107.7)	0.984	0.937
Cys	68.8 (63.7–71.8)	64.2 (61.5–80.2)	0.625	0.742
Asn	55.7 (50.0–68.3)	54.9 (49.8–71.1)	0.751	0.673
Gln	693.2 (640.6–741.0)	709.4 (651.8–773.5)	0.570	0.847
Pro	199.2 (170.4–254.6)	242.7 (221.4–285.1)	0.215	0.222
Asp	2.7 (2.0–3.4)	3.5 (2.9–4.3)	0.057	0.416
Glu	48.2 (30.9–76.0)	60.9 (46.5–73.8)	0.316	0.293
Non-proteinogenic AA				
Taurine	64.9 (61.0–84.3)	80.1 (72.0–97.2)	0.341	0.798
Hyp	10.7 (4.6–13.7)	11.9 (4.6–18.4)	0.368	0.049
Sarcosine	7.4 (1.9–9.7)	8.6 (5.7–11.5)	0.296	0.167
Citrulline	58.1 (42.9–65.4)	56.3 (44.2–70.2)	0.860	0.111
AABA	16.7 (14.5–19.6)	19.2 (15.8–21.4)	0.250	0.166
Cystathionine	1.8 (1.1–2.3)	2.8 (1.5–3.5)	0.038	0.052
β-Alanine	3.1 (2.0–4.2)	2.8 (2.2–3.5)	0.874	0.868
BAIBA	4.3 (1.5–7.3)	1.7 (0.7–2.1)	0.056	0.082
Ethanolamine	7.8 (6.7–9.3)	8.5 (7.7–10.1)	0.211	0.256
Ornithine	86.7 (70.9–111.4)	86.4 (83.7–103.4)	0.404	0.122
1-MH	1.2 (0.6–2.4)	3.9 (0.8–14.0)	0.288	0.317
3-MH	5.0 (4.3–8.4)	6.3 (4.5–7.4)	0.953	0.890
NH3	89.6 (73.2–104.1)	89.0 (76.8–100.6)	1.000	0.893
TAA	3,413 (3,328–3,605)	3,812 (3,599–4,216)	0.015	0.044
EAA	911.9 (823.6–977.6)	1,128.2 (1,010.3–1,247.5)	<0.001	0.008
NEAA	2,531 (2,380–2,646)	2,632 (2,518–2,706)	0.200	0.256
BCAA	420.8 (378.9–464.5)	557.8 (486.0–616.4)	<0.001	0.007
FR	2.7 (2.1–2.8)	3.2 (2.9–3.5)	0.004	0.009

Data given as mean±SD, median (IQR) or n (%). We used t-test to compare patients characteristics and laboratory measurements, and used Wilcoxson rank sum test to compare amino acid fractions. Logistic regression analysis was performed to adjust for sex and age. 1-MH, 1-methyl-histidine; 3-MH, 3-methyl-histidine; AA, amino acid; AABA, α-amino-n-butyric acid; Ala, alanine; Alb, albumin; ALT, alanine aminotransferase; Arg, arginine; Asn, asparagine; Asp, aspartic acid; AST, aspartate aminotransferase; BAIBA, β-amino-iso-butyric acid; BCAA, branched-chain amino acid; BMI, body mass index; BNP, brain natriuretic peptide; Cys, cystine; EAA, essential amino acid; ECW/TBW, extracellular water ratio; eGFR, estimated glomerular filtration rate; FMI, fat mass index; FR, Fischer's ratio; Gln, glutamine; Glu, glutamic acid; Gly, glycine; HDL-C, high-density lipoprotein cholesterol; His, histidine; hsCRP, high sensitivity C-reactive protein; Hyp, hydroxyproline; Ile, isoleucine; LDL-C, low-density lipoprotein cholesterol; Leu, leucine; Lys, lysine; Met, methionine; NEAA, non-essential amino acid; NGSP, National Glycohemoglobin Standardization Program; Phe, phenylalanine; Pro, proline; Ser, serine; SMI, skeletal muscle mass index; TAA, total amino acid; T-Bil, total bilirubin; Thr, threonine; Trp, tryptophan; Tyr, tyrosine; Val, valine.

below the limit of detection. Of these AA, values under the limit of detection were replaced with the limit of detection at 50%.

Statistical Analysis

Because of the positively skewed distributions of BNP, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and high-sensitivity C-reactive protein (hsCRP), these variables were log transformed for analysis. Statistical significance was set at $P<0.05$. Comparison of patient characteristics and blood measurements was performed using the t-test, and comparison of the serum AA concentrations was performed using Wilcoxson rank sum test. To adjust for variables, a logistic regression analysis was performed. To evaluate the predictive ability for decreased SMI, we performed a receiver operating characteristic (ROC) curve analysis and calculated the area under the curve (AUC). Statistical comparisons were performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

First, we analyzed the change in body composition data between baseline and at 1 year. To assess the incidence of skeletal muscle mass loss, we focused on the SMI change. Decreased SMI was observed in 17 of 31 patients at 1 year, and these patients were defined as the decreased SMI group (SMI: 8.7±1.5 kg/m^2 at baseline and 8.3±1.6 kg/m^2 at 1 year). The remaining patients were defined as the non-decreased SMI group (SMI: 9.4±1.4 kg/m^2 at baseline, 9.6±1.3 kg/m^2 at 1 year). There were no significant differences in age or sex between the 2 groups (**Table 1**). To determine if there was an association between laboratory data at baseline and decreased SMI at 1 year later, we compared each laboratory measurement including AA

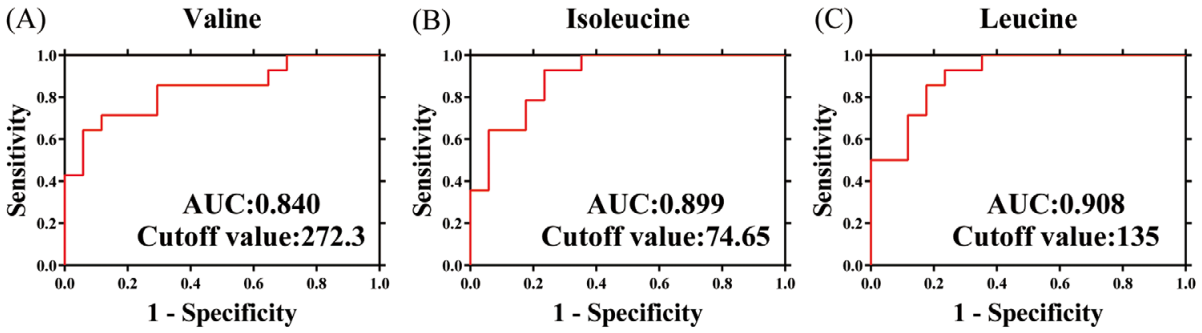

Figure. Receiver operator characteristic curves for (**A**) valine; (**B**) isoleucine; and (**C**) leucine in the prediction of loss of skeletal muscle mass after 1 year in patients in a cardiac rehabilitation center. AUC, area under the curve.

Table 2. Significant Indicators of Loss of Skeletal Muscle Mass†

	Estimate	SE	OR	95% CI	P-value
Val	−0.0469	0.0171	0.9542	0.9228–0.9866	0.006
Ile	−0.1764	0.0704	0.8383	0.7302–0.9624	0.012
Leu	−0.1349	0.0619	0.8738	0.7739–0.9865	0.029
TAA	−0.0025	0.0013	0.9975	0.9951–1.0000	0.052
EAA	−0.0097	0.0038	0.9904	0.9831–0.9977	0.010
BCAA	−0.0338	0.0144	0.9668	0.9398–0.9945	0.019
FR	−2.9591	1.1921	0.0519	0.0050–0.5365	0.013

†Logistic regression analysis adjusted for age, sex, BMI, and BNP. Abbreviations as in Table 1.

fractions. In hematology and biochemistry indices, there were no significant differences between the 2 groups. Serum essential AA (EAA) and BCAA (Val, Ile, Leu) concentration, however, was significantly lower in the decreased SMI group (**Table 1**).

Second, to evaluate the ability of laboratory data to diagnose decreased SMI at 1 year later, we performed a ROC analysis. Age and sex were not significant predictors of decreased SMI (AUC, 0.546 and 0.563, respectively; P=0.662 and 0.552, respectively). Lymphocyte count, hemoglobin, albumin, and total cholesterol have been reported as nutritional markers. In addition, the controlling nutritional status (CONUT) score is widely used for evaluating nutritional status.[8] We then assessed whether these existing nutritional markers can diagnose decreased SMI. These indices, however, were also not significant predictors (AUC=0.521, 0.658, 0.544, 0.559, and 0.548, respectively; P=0.843, 0.137, 0.677, 0.578, and 0.648, respectively). With regard to hematology, biochemistry, and BNP, BNP was a significant predictor (AUC, 0.710; P=0.047). Next, we analyzed each AA fraction. Val, Ile, Leu, phenylalanine, and cystathionine were significant predictors of decreased SMI (AUC, 0.840, 0.899, 0.908, 0.710, and 0.721, respectively; P<0.001, <0.001, <0.001, 0.047, and 0.037, respectively; **Figure**).

After adjusting for age and sex, there was no correlation between hematology, biochemistry and BNP, and decreased SMI, but Val, Ile, Leu, total AA, EAA, BCAA, and Fischer's ratio, the ratio of BCAA to aromatic AA (phenylalanine and tyrosine), were significantly correlated with decreased SMI (**Table 1**). In particular, Val, Ile, Leu, EAA, BCAA, and Fischer's ratio were significantly correlated even after adjusting for age, sex, BMI, and BNP (**Table 2**).

Discussion

Here, we have shown that decreased SMI tended to occur in patients with low serum BCAA (Val, Ile, Leu) concentration, and serum BCAA concentration may be used to predict decreased SMI at 1-year follow-up. We think that this may be due to the relationship between BCAA and skeletal muscle, and between BCAA and dietary intake. First, BCAA is mainly metabolized in the skeletal muscle and plays an important role in skeletal muscle formation. This is because this process uses approximately 35% of the EAA to promote the synthesis of skeletal muscle and inhibit protein degradation.[9] Previously, Leu has been shown to stimulate the synthetic action of muscle proteins and promote the repair process of muscle damage.[10] Decline in the serum concentration of BCAA during prolonged exercise was observed previously with or without nutritional supply.[11] In a previous study, cigarette exposure decreased muscle weight and plasma BCAA in rats.[12] Therefore, the low serum BCAA concentration observed in the decreased SMI group might reflect the occurrence of muscle damage and enhanced BCAA catabolism. Second, BCAA are AA that cannot be synthesized in humans, and thus must be supplied in the diet. Therefore, low serum BCAA concentration may reflect the lack of adequate food intake. Supporting our hypothesis, in patients with severe CHF, the ingested calories have been shown to be inadequate for

body needs and the serum BCAA concentration was significantly lower than in healthy controls.[13]

In the present study, lymphocyte count, hemoglobin, albumin, total cholesterol, and CONUT score, which are widely used for evaluating nutritional status, were not associated with decreased SMI. Hemoglobin and albumin have been shown to be associated with skeletal muscle mass,[3,14] but those studies showed the association at the same observation point and did not refer to the association with future changes in skeletal muscle mass. In addition, there are no reports suggesting their direct role in skeletal muscle formation. Therefore, in the present study, these indices did not predict decreased SMI at 1-year follow-up. In the present study, BNP was a significant predictor of decreased SMI. Loss of skeletal muscle mass is a frequent comorbidity in patients with CHF.[15] The pathophysiology of loss of skeletal muscle mass in patients with CHF is less clear. It is suspected that inflammatory processes may be one of the causes. BNP level is associated with the inflammation.[16] In this study, however, there was no correlation between BNP and hsCRP ($R=-0.082$, $P=0.662$). The presence of malnutrition may be another cause of loss of skeletal muscle mass in patients with CHF. BNP level is related to the severity of CHF. Patients with more severe CHF have more severe nutritional problems because of anorexia due to polypharmacy, and hepatic or gastrointestinal congestion and gut malabsorption from gastrointestinal edema or congestion. Diuretics, aspirin, and digoxin could also contribute to the reduction in food intake.[17,18] In this study, high serum BNP concentration correlated with low serum BCAA concentration ($R=-0.407$, $P=0.023$). In patients with severe CHF, the serum BCAA concentration has been shown to be lower than that in healthy controls.[4,13] This suggests that patients with high BNP may have an inadequate diet due to gastrointestinal symptoms, and SMI may decline after 1 year.

There have been several reports of AA supplements in patients with CHF. Rondanelli et al reported that BCAA supplementation is a useful intervention for treating sarcopenia,[19] while Pineda-Juárez et al reported that improvements in physical and functional capacities were attributed to resistance exercise programs but not to the BCAA supplementation,[20] but they did not assess serum BCAA concentration. In the present study, low serum BCAA concentration correlated with a decrease in SMI after 1 year, suggesting the possibility that in patients with low serum BCAA concentration, the ability to synthesize skeletal muscle was decreased, resulting in a loss of skeletal muscle mass. Overall, in the present study, measuring serum AA concentration (especially serum BCAA concentration) was useful for assessing nutritional status and loss of skeletal muscle mass, and patients with low serum BCAA concentration required nutritional intervention from an early stage.

Study Limitations

This study had several limitations. The first limitation is the small number of subjects and the poor follow-up rate. In this study, only 31 of 67 patients had repeated body composition data. Most patients who did not have repeated body composition data had dropped out of the Cardiac Rehabilitation Center visit. Second, this was a retrospective observational study. Although no significant differences were found in age and sex between the groups, other factors that could not be assessed could distort the results. Third, this study had a lack of replication cohorts. We may have overestimated the result due to selection bias and confounding factors. Therefore, these results should be validated in another prospective cohort. Finally, this study lacked drug information at the first measurement.

Conclusions

At the 1-year follow-up, decreased SMI was observed in 55% of patients (17/31 patients) who visited the cardiac rehabilitation center at the present hospital. On comparison of the decreased SMI group and non-decreased SMI group, significant differences were noted in the serum concentration of AA (especially BCAA). Furthermore, serum BCAA concentration at baseline was significantly associated with decreased SMI at 1-year follow-up.

Disclosures

The authors declare no conflicts of interest.

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