The Effects of an Oral Nutritional Supplement with Whey Peptides and Branched-Chain Amino Acids for Cardiac Rehabilitation of Patients with Chronic Heart Failure

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Summary

The aim of the present study was to determine whether the addition of an oral nutritional supplement with whey peptides and branched-chain amino acids for cardiac rehabilitation improves cardiopulmonary function, skeletal muscle function, and metabolism in CHF patients.

In this randomized, parallel-group comparative pilot study, 20 CHF patients were randomly assigned to the nutrition group ($n = 10$) or the control group ($n = 10$). At baseline and 12 weeks, we performed physical examinations, motor function evaluation, clinical laboratory tests, nutritional status assessment, and echocardiography. The primary outcome was exercise tolerance, as determined by the cardiopulmonary stress test (CPX), 6-minute walking test (6MWT), and brain natriuretic peptide (BNP) levels.

During follow-up, body weight, body mass index, total muscle mass, and total lean mass did not change significantly in either group. The total fat mass significantly increased in the nutrition group ($14.3 ± 5.4$ kg versus $16.1 ± 5.5$ kg, $P < 0.001$) but did not change in the control group, and the difference in the changes in total fat mass between groups was significant ($−0.26 ± 0.96$ kg versus $1.49 ± 0.63$ kg, $P < 0.001$). The peakVO$_2$ and 6-minute walk test (6MWT) significantly increased in the nutrition group ($14.6 ± 3.4$ mL/minute/kg versus $15.8 ± 3.8$ mL/minute/kg, $P = 0.029$; $346.9 ± 103.1$ m versus $382.7 ± 102.1$ m, $P = 0.048$; respectively) but did not change in the control group. The changes in peakVO$_2$ and 6MWT did not significantly differ between the groups.

The oral nutritional supplement for the treatment of CHF was effective for cardiac rehabilitation in terms of fat mass and exercise capacity.

The present study demonstrated that oral nutritional supplements with whey peptides and branched-chain amino acid (BCAA) for cardiac rehabilitation in patients with chronic heart failure (CHF) increased fat mass and exercise capacity. We conclude that whey peptides and BCAA supplementation may be a useful treatment for CHF patients.

Key words: Fat, Exercise capacity, Cardiopulmonary stress test, 6-minute walking test

Chronic heart failure (CHF) is the leading cause of death and hospitalization. Patients with CHF have an increased resting energy production rate, which correlates with the severity of their condition. Impaired body metabolism can lead to cardiac cachexia, which is an independent risk factor for mortality. In cardiac cachexia, wasting and weakness of skeletal muscle are observed, and these changes are distinct from those of muscle atrophy due to reduced activity. Nutritional support in patients with CHF should be considered, particularly to prevent progressive weight loss, since restoration of lean and fat body mass may not be achievable. Nutritional support is becoming a mainstay of the comprehensive therapeutic approach to patients with chronic diseases. Branched-chain amino acid (BCAA) supplementation, consisting of valine, leucine, and isoleucine, has already been applied for patients with advanced liver cirrhosis and provides benefit by improving the serum amino acid profile and increasing albumin concentrations. BCAAs play an important role in the formation of skeletal muscle because they account for approximately 35% of the essential amino acids that form these muscles. Indeed, BCAA preparations have been reported to promote postoperative wound healing and recovery from muscle
fatigue after exercise and enhance muscle strength.\textsuperscript{7} Reports from animal experiments have revealed that BCAAs reduced the development of heart failure via improved function of the skeletal muscle mitochondria.\textsuperscript{8} Whey protein and whey peptides, which are enzymatically hydrolyzed whey protein, have considerably higher BCAA content than other proteins such as casein, soy protein, and egg protein.\textsuperscript{9} Provision of adequate amounts of whey protein can also increase muscle protein synthesis.\textsuperscript{9} The incorporation of whey peptides and BCAAs in cardiac rehabilitation is expected to have additional effects on the improvement of cardiopulmonary and skeletal muscle function. Thus, the aim of the present study was to determine whether the addition of an oral nutritional supplement with whey peptides and BCAAs further improves cardiopulmonary function, skeletal muscle function, and metabolism compared with that achieved with conventional cardiac rehabilitation in CHF patients.

**Methods**

**Patient enrollment:** Between January 2016 and March 2019, patients with CHF were evaluated at our institution and recruited if they fulfilled the following criteria: (1) aged \( \geq \) 20 years, (2) participating in a monitored cardiac rehabilitation program, and (3) body mass index of \( \leq \) 30. Patients who met any of the following criteria were excluded: (1) severe diabetes, liver disease, kidney disease, infection, or malignant tumor; (2) allergy to milk or soybeans; (3) lactose intolerance; and (4) pregnant or breastfeeding patients. All patients provided written informed consent to participate. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of our institution. All patients were symptomatic for stable HF, with New York Heart Association (NYHA) functional class II or III, and on a stable medication for at least 4 weeks.

**Randomization and intervention:** A Meiji Co., Ltd. staff member not involved in the trial prepared the numbered, opaque (folded paper inside an envelope that was inside a second envelope), sealed envelopes; each contained a letter designating allocation to the control group or nutrition group. The investigator was not allowed to open the envelope until randomization. Upon enrollment, patients were randomized 1:1 to the control or nutrition group. Randomization was performed in our hospital, in which the assignment for each patient was provided in the envelope that was opened at the time of randomization by the investigator. Control group patients were treated with concurrent cardiac rehabilitation. Nutrition group patients were orally supplemented with one pack of an oral nutritional supplement with whey peptides and BCAAs, which was Meiji Mei Balance\textsuperscript{5} Rehasupport Mini (Meiji Co., Ltd. Tokyo; see Supplemental Tables I, II), taken twice daily for 12 weeks, and treated with concurrent cardiac rehabilitation. All patients were instructed to continue their normal diet during the 12-week intervention. Patients in the nutrition group consumed an additional 400 kcal per day, divided into two equal doses taken between main meals to avoid appetite suppression. The exercise component was based on the standards set for cardiac rehabilita-

**Study methods:** This was a randomized, parallel-group comparative study. Patients were evaluated at baseline and after 12 weeks of follow-up. At baseline and 12 weeks post-enrollment, patients underwent the following assessments: (1) physical examinations: height, body weight, and body composition (bioelectrical impedance data for each patient were obtained using an InBody 720 device (Biospace Japan, Tokyo); (2) motor function: grip strength, lower-limb extension power, 6-minute walking test (6MWT), and CPX; (3) clinical lab tests: complete blood count, white blood cells, red blood cells, hemoglobin, hematocrit, platelet, total protein, albumin, cholinesterase, gamma-glutamyl transpeptidase, blood urea nitrogen, creatinine, C-reactive protein (CRP), and brain natriuretic peptide (BNP); (4) nutritional status: Short-Form Mini-Nutritional Assessment (MNA-SF), and Controlling Nutritional Status (CONUT); and (5) echocardiography: left ventricular diastolic diameter, left ventricular ejection fraction (EF), E/A, and left atrial diameter. Bioelectrical impedance analysis provided body composition data and enabled us to assess the changes in muscle or fat mass separately.

**Study outcomes and analysis:** The primary outcome was to evaluate the effects of supplementation on exercise tolerance, as determined by the CPX and 6MWT, and BNP levels. The secondary outcome was to evaluate the effects on body composition, CRP levels, and nutritional status. Quantitative variables were compared between the two groups by Student’s \( t \) test, as appropriate, for unpaired data. Changes in quantitative variables during treatment were evaluated using the paired \( t \) test. Nutritional status indicators such as CONUT and MNA-SF were compared between the two groups by the Mann-Whitney \( U \) test, and between baseline and follow-up outcome measures by the Wilcoxon signed-rank test as appropriate. A \( P \)-value of \(< \) 0.05 was considered significant.

**Results**

**Patients:** Twenty patients aged 48-84 years were enrolled and randomly assigned to either the nutrition group (\( n = 10 \)) or the control group (\( n = 10 \)). The baseline characteristics of the two groups are summarized in Table I. No significant differences were observed between the groups in baseline characteristics. The patients were taking similar medications for HF, including angiotensin-converting enzyme inhibitors (ACE) inhibitors, beta-blockers, aldosterone antagonists, and/or loop diuretics.

**Efficacy:** During follow-up, the peak oxygen uptake (\( VO_{2} \)) and 6MWT values increased significantly in the nutrition group (peak\( VO_{2} \): \( 14.6 \pm 3.4 \) mL/minute/kg versus \( 15.8 \pm 3.8 \) mL/minute/kg, \( P = 0.029 \); 6MWT: \( 346.9 \pm 103.1 \) m versus \( 382.7 \pm 102.1 \) m, \( P = 0.048 \)) but did not change in the control group. The changes in peak\( VO_{2} \) and 6MWT values did not significantly differ between the
Table I. Patient Characteristics

| Clinical Characteristics | Control (n = 10) | Nutrition (n = 10) | P-value |
|--------------------------|-----------------|-------------------|---------|
| Age, years               | 71.1 ± 10.2     | 75.3 ± 5.8        | 0.273   |
| Woman                    | 5               | 5                 | N/A     |
| Height, m                | 1.61 ± 0.16     | 1.58 ± 0.10       | 0.527   |
| Body weight, kg          | 56.6 ± 11.2     | 54.1 ± 12.9       | 0.657   |
| BMI, kg/m²               | 21.5 ± 1.3      | 21.5 ± 2.7        | 0.939   |
| Systolic blood pressure, mmHg | 112 ± 10 | 117 ± 19          | 0.47    |
| Diastolic blood pressure, mmHg | 67 ± 9    | 73 ± 15           | 0.324   |
| Heart rate, bpm/minute   | 73 ± 16         | 73 ± 17           | 0.979   |
| SpO₂, %                  | 98 ± 2          | 97 ± 1            | 0.135   |
| LVEF, %                  | 48 ± 15         | 48 ± 13           | 0.974   |
| BNP, median, pg/mL       | 86 ± 70         | 164 ± 133         | 0.115   |
| Serum creatinine, mg/dL  | 0.8 ± 0.3       | 1.0 ± 0.3         | 0.347   |
| Albumin, mean (SD), g/dL | 4.3 ± 0.5       | 4.4 ± 0.4         | 0.811   |

Data are presented as mean ± standard deviation. BMI indicates body-mass index; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; ACE, angiotensin converting enzyme; and ARB, angiotensin II receptor blocker.

Table II. Results of Primary Outcomes: Exercise Tolerance, as Determined by the CPX and 6MWT, and BNP Levels

| | Baseline | Follow up | P value | Change | P value |
|--------------------------|----------|-----------|---------|--------|---------|
| PeakVO₂, mL/min/minute   |          |           |         |        |         |
| Control                  | 17.2 ± 3.9 | 17.4 ± 4.6 | 0.818   | 0.18 ± 2.40 | 0.295   |
| Nutrition                | 14.6 ± 3.4 | 15.8 ± 3.8 | 0.029*  | 1.16 ± 1.30 |         |
| 6MWT, m                  |           |           |         |        |         |
| Control                  | 455.4 ± 81.8 | 470.5 ± 92.9 | 0.927   | 1.22 ± 38.61 | 0.106   |
| Nutrition                | 346.9 ± 103.1 | 382.7 ± 102.1 | 0.048*  | 35.33 ± 45.53 |         |
| BNP, pg/mL               |           |           |         |        |         |
| Control                  | 85.6 ± 70.3 | 112.7 ± 95.1 | 0.127   | 27.1 ± 51.0 | 0.819   |
| Nutrition                | 164 ± 133.1 | 178.1 ± 134.9 | 0.226   | 21.7 ± 49.8 |         |

Data are presented as mean ± standard deviation. *Parameters with significant changes. BNP indicates B-type natriuretic peptide; CPX, cardiopulmonary stress test; and 6MWT, 6-minute walking test.

Groups (Table II). The BNP levels also did not change significantly in either group (Table II). Similarly, body weight, body mass index, total muscle mass, total lean mass, extracellular water ratio (extracellular water/total body water), CRP, CONUT, and MNA-SF did not change significantly in either group (Table III). The total fat mass increased significantly in the nutrition group (14.3 ± 5.4 kg versus 16.1 ± 5.5 kg, \( P < 0.001 \)) but did not change in the control group. The changes in total fat mass significantly differed between groups (−0.26 ± 0.96 kg versus 1.49 ± 0.63 kg, \( P < 0.001 \)) (Table III). The lower-limb extension power (right and left) did not change significantly in either group. Grip strength (right) significantly decreased in the control group but did not change in the nutrition group. Moreover, the changes in grip strength (right) differed significantly between the groups. Grip strength (left) significantly increased in the nutrition group but did not change in the control group. The changes in grip strength (left) did not significantly differ between the groups (Table IV). In this study, patients with CHF administered oral nutritional supplements with whey peptides and BCAAs for 12 weeks for cardiac rehabilitation.
Table III. Results of Secondary Outcomes: Body Composition, CRP Levels, and Nutritional Status

|                | Baseline | Follow up | P value | Change | P value |
|----------------|----------|-----------|---------|--------|---------|
| **Body weight, kg** |          |           |         |        |         |
| Control        | 56.6 ± 11.2 | 56.6 ± 11.4 | 0.943   | 0.03 ± 1.29 | 0.120   |
| Nutrition      | 54.1 ± 12.9 | 56.5 ± 12.7 | 0.083   | 1.21 ± 1.83 |         |
| **BMI, kg/m²**  |          |           |         |        |         |
| Control        | 21.5 ± 1.3 | 21.5 ± 0.9 | 0.786   | -0.05 ± 0.52 | 0.087   |
| Nutrition      | 21.5 ± 2.7 | 22.2 ± 2.4 | 0.084   | 0.47 ± 0.71 |         |
| **Muscles mass, kg** |          |           |         |        |         |
| Control        | 38.4 ± 9.0 | 38.7 ± 9.5 | 0.413   | 0.31 ± 1.14 | 0.392   |
| Nutrition      | 37.4 ± 8.4 | 38.0 ± 8.6 | 0.694   | -0.17 ± 1.22 |       |
| **Fat mass, kg** |          |           |         |        |         |
| Control        | 15.7 ± 3.5 | 15.5 ± 3.1 | 0.415   | -0.26 ± 0.96 | < 0.001* |
| Nutrition      | 14.3 ± 5.4 | 16.1 ± 5.5 | < 0.001* | 1.49 ± 0.63 |         |
| **Lean body mass (LBN), kg** |          |           |         |        |         |
| Control        | 40.8 ± 9.6 | 41.1 ± 10.0 | 0.460   | 0.29 ± 1.19 | 0.423   |
| Nutrition      | 39.7 ± 8.8 | 40.3 ± 9.0 | 0.691   | -0.18 ± 1.29 |       |
| **Extracellular water ratio (ECW/TBW)** |          |           |         |        |         |
| Control        | 0.4 ± 0.0 | 0.4 ± 0.0 | 0.083   | 0.00 ± 0.00 | 0.267   |
| Nutrition      | 0.4 ± 0.0 | 0.4 ± 0.0 | 1.000   | 0.00 ± 0.00 |         |
| **CRP**        |          |           |         |        |         |
| Control        | 0.4 ± 0.5 | 0.1 ± 0.1 | 0.105   | -0.24 ± 0.43 | 0.183   |
| Nutrition      | 0.3 ± 0.3 | 0.5 ± 1.0 | 0.550   | 0.18 ± 0.85 |         |
| **CONUT**      |          |           |         |        |         |
| Control        | 1.6 ± 1.6 | 1.7 ± 1.3 | 0.593   | 0.10 ± 0.57 | 0.193   |
| Nutrition      | 1.0 ± 1.1 | 1.4 ± 1.2 | 0.068   | 0.44 ± 0.53 |         |
| **MNA-SF**     |          |           |         |        |         |
| Control        | 12.5 ± 1.2 | 12.5 ± 1.2 | 1.000   | 0.00 ± 0.47 | 0.053   |
| Nutrition      | 12.1 ± 1.8 | 13.0 ± 1.0 | 0.068   | 0.78 ± 0.97 |         |

Data are presented as mean ± standard deviation. *Parameters with significant changes. BMI indicates body mass index; TBW, total body water; and CRP, C reactive protein.

Table IV. Results of Other Strength Parameters, Motor Function, CPX

|                | Baseline | Follow up | P value | Change | P value |
|----------------|----------|-----------|---------|--------|---------|
| **Grip strength (right), kg** |          |           |         |        |         |
| Control        | 25.2 ± 6.9 | 24.2 ± 7.2 | 0.016*  | -0.93 ± 1.00 | 0.047*  |
| Nutrition      | 24.4 ± 8.3 | 24.7 ± 8.1 | 0.505   | 0.38 ± 1.62 |         |
| **Grip strength (left), kg** |          |           |         |        |         |
| Control        | 24.2 ± 6.3 | 24.1 ± 6.9 | 0.863   | -0.11 ± 1.96 | 0.040*  |
| Nutrition      | 22.1 ± 8.3 | 24.6 ± 8.2 | 0.034   | 2.23 ± 2.62 |         |
| **Lower-limb extension power (right), kg** |          |           |         |        |         |
| Control        | 82.3 ± 30.9 | 86.8 ± 34.7 | 0.279   | 4.50 ± 12.36 | 0.994   |
| Nutrition      | 88.9 ± 49.6 | 98.6 ± 48.7 | 0.497   | 4.56 ± 19.21 |         |
| **Lower-limb extension power (left), kg** |          |           |         |        |         |
| Control        | 82.4 ± 32.0 | 85.6 ± 33.8 | 0.430   | 3.20 ± 12.24 | 0.661   |
| Nutrition      | 73.8 ± 45.1 | 82.4 ± 53.3 | 0.289   | 6.11 ± 16.14 |         |
| **AT, mL/minute/kg** |          |           |         |        |         |
| Control        | 11.8 ± 2.7 | 11.0 ± 2.0 | 0.122   | -0.84 ± 1.86 | 0.067   |
| Nutrition      | 9.9 ± 2.2  | 10.8 ± 2.0 | 0.305   | 0.61 ± 1.67 |         |
| **VE/VCO₂ slope** |          |           |         |        |         |
| Control        | 32.9 ± 4.4 | 34.0 ± 4.8 | 0.182   | 1.04 ± 2.2  | 0.702   |
| Nutrition      | 38.0 ± 5.8 | 38.6 ± 5.7 | 0.543   | 0.59 ± 2.7  |         |
| **R values**   |          |           |         |        |         |
| Control        | 1.17 ± 0.09 | 1.20 ± 0.09 | 0.145   | 0.02 ± 0.03 | 0.556   |
| Nutrition      | 1.15 ± 0.07 | 1.16 ± 0.09 | 0.642   | 0.01 ± 0.06 |         |

Data are presented as mean ± standard deviation. *Parameters with significant changes. AT indicates anaerobic threshold; VE, expiratory minute volume; and CPX, cardiopulmonary stress test.

showed significant increases in fat mass and exercise tolerance, as determined by CPX and 6MWT, compared to those in patients who did not receive the supplements.

Discussion
Cardiac rehabilitation includes nutritional interven-
tions in addition to exercise training. Patients with HF have a higher BMI; moreover, a higher fat mass is also associated with a lower risk of mortality. In addition, exercise tolerance is a prognostic factor in patients with CHF and improvement in exercise tolerance leads to improved prognosis. The results of the present study demonstrated that an oral nutritional supplement with whey peptides containing high BCAA content for cardiac rehabilitation in patients with CHF increased fat mass, peakVO₂, and 6MWT values compared to those in patients receiving conventional rehabilitation. These findings suggest that whey peptides and BCAAs may increase the amount of fat and exercise tolerance in patients with CHF, which may reduce the risk of death in patients with CHF, despite the lack of significant change in BNP level.

Cardiac cachexia, defined as weight loss ≥ 6% within 6 months, has been estimated to affect 12-15% of CHF patients with New York Heart Association (NYHA) class II-IV. The incidence of cardiac cachexia in CHF patients with NYHA class III/IV is approximately 10% per annum. CHF affects nutritional state, energy, and sub-state metabolism. The mortality rate among CHF patients is 2-3-fold higher among those with cardiac cachexia than those without it. Patients with cardiac cachexia experience a general loss of fat, lean body mass, and bone tissues. Cachectic CHF patients are weaker and become fatigued more quickly owing to both reduced skeletal muscle mass and impaired muscle quality. Anorexia, insulin resistance, immune abnormalities, neurohormonal abnormalities, and abnormal metabolic balance between catabolism and anabolism are frequently associated with cardiac cachexia. In patients with pre-cachexia or early cachexia, for example, those with chronic obstructive pulmonary disease, there is strong evidence that nutritional support can improve patient outcomes. CHF patients develop a deficit of amino acids that are necessary for the failing heart as an energy source and for protein synthesis. One of the key mechanisms of cachexia is highly complex and not fully understood; therefore, we cannot provide definitive conclusions regarding the mechanistic explanations of our results. Nonetheless, our study findings indicate a positive association between BCAA supplementation and improved exercise capacity among CHF patients.

Our study has some limitations. First, this was a single-center study, with a limited number of patients who participated in a monitored cardiac rehabilitation program and were followed up, consistent with a study by the Hyogo Prefectural Amagasaki General Medical Center. Thus, we anticipated that approximately 20 patients would agree to participate in our trial. This sample size was similar to that used in previous studies. Moreover, the follow-up period was short. In addition, the peakVO₂ and 6 MWT significantly increased in the nutrition group, but those changes did not significantly differ between groups. Future studies with larger sample sizes should evaluate the long-term clinical outcomes, including those in outpatients, and particularly whether BCAA supplementation not only increases the peakVO₂ and 6MWT distance between groups with significance, but also reduces repeated admissions and mortality. Second, we did not collect data on caloric and nutritional intake during the study; therefore, no conclusions can be drawn regarding the optimal dose and composition of the nutritional support. Third, our study was conducted using the envelope method. The study was conducted using a robust envelope method to avoid bias, however, future studies with a larger sample size using a more robust and secure randomization method (i.e. computer randomization) would be warranted to ensure a fair comparison between like groups.

In conclusion, oral nutritional supplements with whey peptides and BCAAs for cardiac rehabilitation in patients with CHF can increase fat mass and exercise capacity. We conclude that BCAA supplementation may be a useful treatment for CHF patients. Future studies with larger sample sizes and longer follow-up periods are needed to determine whether this treatment strategy has a direct benefit by itself. Furthermore, the assessment of cardiac cachexia might elucidate the underlying mechanisms of BCAA treatment of CHF.
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Disclosure

Conflicts of interest: The authors have no conflicts of interest that might be relevant to this work.

References

1. Pechlman ET, Scheffers J, Gottleib SS, Fisher ML, Vaitkevicius P. Increased resting metabolic rate in patients with congestive heart failure. Ann Intern Med 1994; 121: 860-2.
2. ObiseseAN TO, Toth MJ, Donaldson K, et al. Energy expenditure and symptom severity in men with heart failure. Am J Cardiol 1996; 77: 1250-2.
3. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997; 349: 1050-3.
4. Drexler H, Riede U, Münzel T, König H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation 1992; 85: 1751-9.
5. Tajiri K, Shimizu Y. Branched-chain amino acids in liver diseases. World J Gastroenterol 2013; 19: 7620-9.
6. Shimomura Y, Yamamoto Y, Bajotto G, et al. Nutraceutical effects of branched-chain amino acids on skeletal muscle. J Nutr 2006; 136: 529-32.
7. Choudry HA, Pan M, Karinch AM, Souba WW. Branched-chain amino acid-enriched nutritional support in surgical and cancer patients. J Nutr 2006; 136: 314-8.
8. Tanada Y, Shioi T, Kato T, Kawamoto A, Okuda J, Kimura T. Branched-chain amino acids ameliorate heart failure with cardiac cachexia in rats. Life Sci 2015; 137: 20-7.
9. Hulmi JJ, Lockwood CM, Stout JR. Effect of protein/essential amino acids and resistance training on skeletal muscle hypertrophy: A case for whey protein. Nutr Metab (Lond) 2010; 7: 51.
10. Thomas E, Gupta PP, Fonarow GC, Horwich TB. Bioelectrical impedance analysis of body composition and survival in patient with heart failure. Clin Cardiol 2019; 42: 129-35.
11. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013; 1: 93-102.
12. Florea VG, Henein MY, Anker SD, et al. Prognostic value of changes over time in exercise capacity and echocardiographic measurements in patients with chronic heart failure. Eur Heart J 2000; 21: 146-53.
13. Anker SD, Laviano A, Filippatos G, et al. ESPEN Guidelines on Parenteral Nutrition: On Cardiology and Pneumology. Clinical Nutr 2009; 28: 455-60.
14. Evans WJ, Morley JE, Argilés J, et al. Cachexia: A new definition. Clinical Nutr 2008; 27: 793-9.
15. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol 1997; 30: 527-32.
16. Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999; 115: 836-47.
17. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997; 96: 526-34.
18. van Wetering CR, Hoogendoorn M, Broekhuizen R, et al. Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. J Am Med Dir Assoc 2010; 11: 179-87.
19. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999; 99: 1173-82.
20. Beyramvand MR, Khalafi MK, Roshan VD, Choobineh S, Parsa SA, Piranfar MA. Effect of taurine supplementation on exercise capacity of patients with heart failure. J Cardiol 2011; 57: 335-7.
21. Aquilani R, Viglio S, Iadarola P, et al. Oral amino acid supplements improve exercise capacities in elderly patients with chronic heart failure. Am J Cardiol 2008; 101: 104E-10E.
22. Lombardi C, Carubelli V, Lazzarini V, et al. Effects of oral amino Acid supplements on functional capacity in patients with chronic heart failure. Clin Med Insights Cardiol 2014; 8: 39-44.
23. Rennie MJ. Influence of exercise on protein and amino acid metabolism. In: Rowell LB, Shepherd JT, eds. Handbook of Physiology, Section 12: Exercise: Regulation and Integration of Multiple Systems. Bethesda, MD: American Physiological Society; 1996: 995-1035.
24. Tsuji S, Koyama S, Taniguchi R, Fujiwara T, Fujiwara H, Sato Y. Nutritional status of outpatients with chronic stable heart failure based on serum amino acid concentration. J Cardiol 2018; 72: 458-65.
25. Rozentryt P, von Haelthing S, Lainscak M, et al. The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: a randomized, double-blind pilot study. J Cachexia Sarcopenia Muscle 2010; 1: 456-61.
26. Tsuji S, Koyama S, Taniguchi R, Fujiwara T, Fujiwara H, Sato Y. Association of serum amino acid concentration with loss of skeletal muscle mass after 1 year in cardiac rehabilitation center patients. Circ Res 2019; 1: 456-61.
27. Uchino Y, Watanabe M, Tanaka M, et al. Branched-chain amino acids ameliorate heart failure with chronic heart failure patients with hypoalbuminemia: Results of a preliminary study. Am J Cardiovasc Drugs 2018; 18: 327-32.

Supplemental Files

Supplemental Tables I, II

Please see supplemental files; https://doi.org/10.1536/ihj.21-102