



Original article

Sarcopenia in adults with congenital heart disease: Nutritional status, dietary intake, and resistance training



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ABSTRACT

Background: This study aimed (1) to assess the nutritional status and dietary intake, (2) compare the body composition and nutritional intake between sarcopenia and non-sarcopenia, and (3) evaluate the effects of resistance training and amino acid intake in adults with congenital heart disease (CHD).

Methods: **Study 1** In total, 172 adults with CHD were prospectively enrolled. The Food Frequency Questionnaire was used, and body composition analysis was conducted. **Study 2:** Thirty of 172 adult patients with CHD were divided into two groups: amino acid intake plus resistance training (group A) and amino acid intake only (group B) for 2 months.

Results: **Study 1:** Skeletal muscle mass index was lower in adults with CHD compared to healthy Japanese. Calorie, protein, and fat intake in adults with CHD was higher than those in the National Nutritive Intake Investigation; however, the difference in carbohydrate or salt intake was non-significant.

Study 2: In adults with CHD in group A, body fat percentage, edema index, and N-terminal pro-hormone of brain natriuretic peptide improved, and body weight, skeletal muscle mass index, and basic metabolism increased after the intervention. There was no improvement after intervention for group B. **Conclusions:** According to this study, adults with CHD have higher calorie, protein, and fat intake than those in a national survey despite decreased skeletal muscle mass. Amino acid intake plus resistance training positively improved body fat percentage, skeletal muscle mass, and edema in adults with CHD. Appropriate nutritional education and resistance training guidelines should be provided.

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Introduction

Most patients with congenital heart disease (CHD) can now be expected to survive until adulthood [1], leading to the emergence of problems associated with aging. Sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life, and death [1–3]. Primary sarcopenia is considered to be age-related when no other cause is evident, except aging itself [2]. Secondary sarcopenia is multi-factorial and

should be considered when one or more other causes are evident, such as activity-, disease-, or nutrition-related sarcopenia [2]. In our previous study, we reported that patients with CHD have lower skeletal muscle and higher body fat percentage than age-matched healthy controls [4]; however, the detailed dietary intake data in sarcopenic patients with CHD are limited so far.

Sarcopenia is also associated with heart failure (HF) [5], which is often accompanied by malnutrition, poor absorption due to gastrointestinal edema, hypermetabolism, systemic inflammation, endocrine imbalances, and oxidative stress [2,6]. HF is a major cause of death in adults with CHD, and therapeutic strategies are needed to prevent the progression of muscle wasting. One of the non-pharmaceutical therapies, resistance training combined with amino acid supplements, is known to be effective for treating

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muscle wasting and weakness in non-CHD patients with HF [7–9]; however, there have been very few reports in CHD patients. Resistance training guidelines specialized for CHD are currently unavailable, and whether non-pharmaceutical therapies can improve sarcopenia in adults with CHD remains unknown.

This study aimed (1) to assess the nutritional status and dietary intake, (2) compare the body composition and nutritional intake between sarcopenia and non-sarcopenia, and (3) evaluate the effects of resistance training and amino acid intake in adults with CHD.

Methods

Study 1: Nutritional status and dietary intake in adults with CHD

Study population

A total of 172 adults with CHD [60 men (34.5 ± 13.7 (18–68) years) and 112 women (36.0 ± 12.0 (19–70) years)] who regularly attended the outpatient clinic at St. Luke's International Hospital were prospectively enrolled in this study, from January to July 2015. A total of 51 and 121 patients had simple (atrial septal defect, ventricular septal defect, pulmonary stenosis, and patent ductus arteriosus) and complex CHD [tetralogy of Fallot: 47, transposition of the great arteries (TGA)/double outlet right ventricle: 27, congenitally corrected TGA: 13, Fontan: 10, cyanotic disease: 10, and others], respectively. Sarcopenia was defined as the skeletal muscle mass index of $<7.0 \text{ kg/m}^2$ in men and $<5.7 \text{ kg/m}^2$ in women based on the previously reported indices [1,6]. We excluded unstable patients who had an episode of frequent hospitalization (at least twice per year) due to HF and/or patients who need regular intravenous infusion of albumin or globulin. The patients who regularly take steroids were also excluded.

Food Frequency Questionnaire

We used the Food Frequency Questionnaire (FFQ) created by a research team supported by the Japanese Ministry of Health, Labour, and Welfare [10]. Participants were instructed to respond to a multifactorial questionnaire consisting of food intake for 3 days.

Body composition analysis

Among the 172 adult patients with CHD, 117 underwent body composition analysis. Patients with pacemaker, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) were excluded because the safety of bioelectrical impedance analysis (BIA) remained unknown. Body mass index (BMI), body fat percentage, skeletal muscle mass index, basic metabolism, and edema index of all patients were measured with BIA using an InBody730 device (InBody, Tokyo, Japan). InBody is widely used to assess body composition, sarcopenia, and edema in gymnasia as well as in geriatric, nephrology, and gastroenterology departments [11–13]. Many studies have also reported that this non-invasive BIA is useful to predict clinical outcomes in patients with HF [9].

Study 2: Effects of amino acid intake plus resistance training in adults with CHD

Study population

In a pilot study, 30 out of 117 adult patients who joined the prospective study on amino acid intake \pm resistance training were enrolled from September 2016 to February 2017, and all patients gave their informed consent. We excluded (1) mentally challenged patients because of their difficulty to continue performing regular exercise for 2 months, (2) those in New York Heart Association (NYHA) functional class (FC) 3 and 4 because of their unstable HF status and the possibility of repeated hospitalization due to HF.

Therefore, edema index and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and (3) patients with severe cyanosis (SPO₂ of $<85\%$) and unmanaged arrhythmias were difficult to assess because an official exercise guideline specialized for those with CHD is unavailable; therefore an appropriate exercise program is difficult to arrange and maintain at home.

Thirty patients with CHD were randomized and divided into two groups: amino acid intake plus resistance training (group A) and amino acid intake alone (group B). Patients were randomized according to a computer-generated randomization sequence with 1:1 distribution using randomly permuted block method. A total of 10 age-matched healthy controls who took amino acid plus resistance training were also recruited (group C).

Amino acid intake and resistance training

Patients took an amino acid jelly every day for 2 months. Ingredients of amino acid were as follows: Amino care 100 g jelly/day (Nestle Japan Ltd. Nestle Heath Science, Tokyo. Ajinomoto Ltd. Tokyo) of 30 kcal, protein 3.0 g (leucine 3000 mg), no fat, vitamin B 1 (0.2 mg), vitamin B6 (0.2 mg), vitamin B12 (0.4 μg), and vitamin D (20 μg). Leucine is an essential amino acid and can promote protein assimilation.

In resistance training, patients underwent a home exercise program every other day for 2 months. Patients exercised with elastic bands for arm and leg exercises. The load of each maneuver was individually adapted based on a heart rate that does not exceed >30 beats than the resting value, as measured using a heart rate monitor. According to a physiotherapist's instruction, the home-based training group was instructed to perform a regular exercise at home 3 times a week. Each maneuver was repeated 15 times for two sets, following the resistance exercise guidelines for general HF, not specialized for CHD. During follow up, the load could be adjusted, but patients could contact the physiotherapist at any time if necessary. Patients were instructed to fill in an exercise diary comprising the date and duration of each session to monitor adherence. Physiotherapists or doctors followed up each patient through e-mail for 2 months.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. A priori approval was received from the institution's research committee. The ethical committee of our hospital also approved the study. All patients signed a written informed consent for this study.

Statistical analysis

Data were evaluated using Student's *t* tests, Mann–Whitney *U* tests, paired *t*-tests, chi-square tests, or one-way analysis of variance (SPSS ver. 20; SPSS Inc., Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant (two-tailed).

Results

Comparison of nutritional status: adults with CHD vs. National Nutritive Intake Investigation

In 172 outpatients, 102 were in NYHA FC1, 66 in NYHA FC2, and 4 in NYHA FC3. All patients in NYHA FC 3 were severe cyanotic patients (SPO₂ $<85\%$) with a palliative repair, but in a stable condition. There was no patient in NYHA FC 4 or patients who showed active protein-losing enteropathy (PLE) with low serum albumin level. Two patients had a history of PLE when they had suffered from severe infection or acute pulmonary thromboembolism. Their serum albumin levels were within the normal range in this study and they were not treated with steroids.

The difference in body height, weight, and BMI was not significant between the two groups (Table 1). Intake of calories,

Table 1
Body composition analysis patients and national nutritive intake investigation.

	Males with CHD 60 patients	Male in national survey 3112 people	p Value	Females with CHD 112 patients	Females in national survey 3615 people	p Value
Age (yrs)	37.5 ± 14.4 (18–68)	>20		36.6 ± 12.5 (19–70)	>20	
Body height (cm)	169.3 ± 7.8	167.2 ± 7.0	ns	157.3 ± 7.0	153.3 ± 6.9	ns
Body weight (kg)	64.5 ± 11.6	65.8 ± 10.9	ns	50.6 ± 8.6	52.9 ± 9.3	ns
BMI (kg/m ²)	22.6 ± 3.6	23.5 ± 3.3	ns	21.4 ± 3.2	22.4 ± 3.7	ns
Calories (kcal)	2207 ± 250	2123 ± 591	<0.05	1829 ± 91	1661 ± 441	<0.01
Protein (g)	87.0 ± 6.1	76.0 ± 25.2	<0.01	73.5 ± 5.5	62.0 ± 19.4	<0.01
Fat (g)	64.5 ± 5.0	59.2 ± 26.8	<0.05	57.6 ± 3.8	50.0 ± 21.4	<0.01
Carbohydrate (g)	291.4 ± 48.8	289.5 ± 86.3	ns	242.6 ± 15.7	231.8 ± 67.2	ns
Salt (g)	10.6 ± 2.4	10.9 ± 4.1	ns	9.7 ± 0.6	9.2 ± 3.5	ns

Abbreviations. CHD: congenital heart disease, BMI: body mass index.

protein, and fat in adults with CHD in this study was higher than those in the National Nutritive Intake Investigation [14]. No difference in intake of carbohydrates or salt was observed between the two groups.

Skeletal mass index in men and women with CHD were $7.7 \pm 0.4 \text{ kg/m}^2$ and $6.2 \pm 0.4 \text{ kg/m}^2$, respectively. Skeletal mass index in Japanese healthy young population are $8.67 \pm 0.9 \text{ kg/m}^2$ in men and $6.78 \pm 0.66 \text{ kg/m}^2$ in women [15] and there were significant differences between adults with CHD and the healthy population ($p < 0.01$ in men and $p < 0.05$ in women).

Fig. 1 shows the detailed dietary intake in adults with CHD. Intake of green and yellow vegetables, fruits, fish, and milk products was increased, and intake of grains, potatoes, and meats was minimized compared to those in the National Nutritive Intake Investigation.

Comparison of body composition and dietary intake: sarcopenic vs. non-sarcopenic adults with CHD

BMI in sarcopenic men and women with CHD was lower than their non-sarcopenic counterparts ($p < 0.05$). Sarcopenic men with CHD showed lower skeletal muscle mass index ($p < 0.001$) and higher edema index ($p < 0.05$) than their non-sarcopenic

counterparts. Sarcopenic women with CHD also showed lower skeletal muscle mass index, lower BMI, and higher edema index. The difference in age and body fat percentage between sarcopenia and non-sarcopenia was not significant in both men and women (Table 2).

Regarding the dietary intake in men with CHD, intake of calories, fat, carbohydrates, and salt was higher in patients with sarcopenia than those with non-sarcopenia (Fig. 2). By contrast, the difference in intake of calories, fat, carbohydrates, and salt between sarcopenia and non-sarcopenia was not significant in women with CHD. In both men and women, there was no statistical difference in protein intake between sarcopenia and non-sarcopenia.

As for the detailed dietary intake in men with CHD, intake of grain, beans, vegetables, and mushrooms was increased in sarcopenia compared to non-sarcopenia. On the other hand, there was no statistical difference between the two in women with CHD.

Resistance training and amino acid intake in adults with CHD

Patients were divided into three groups: amino acid intake plus resistance training in CHD (group A), amino acid intake alone in CHD (group B), and age-matched healthy controls with amino acid

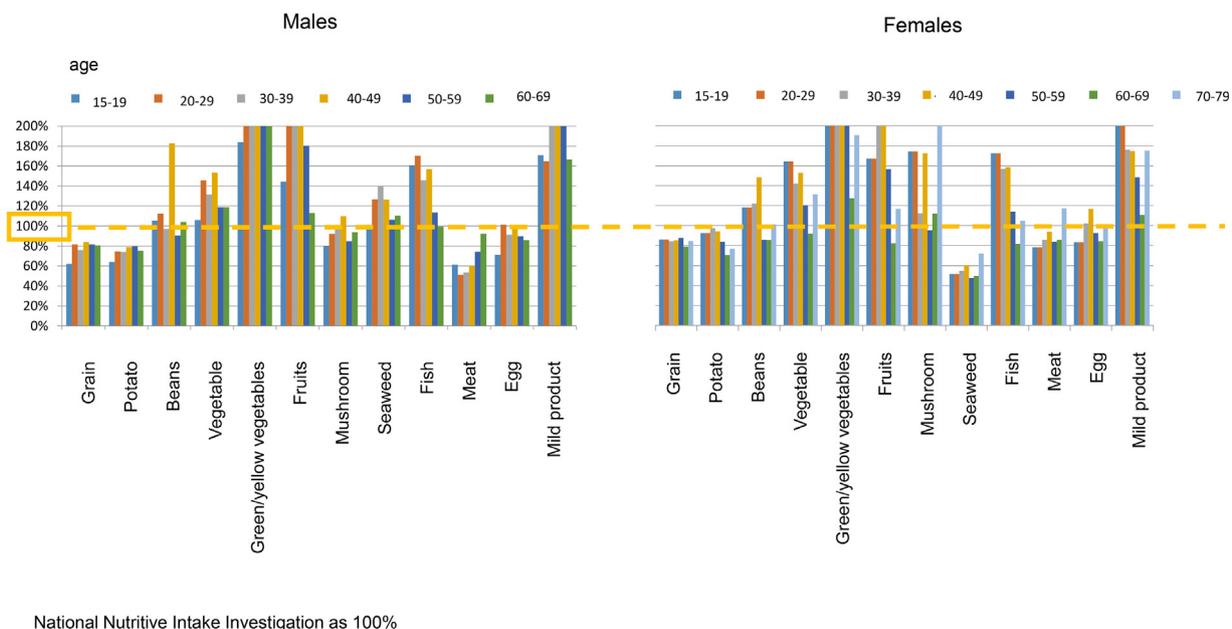


Fig. 1. Detailed dietary intake in patients with congenital heart disease (CHD). Intake of green and yellow vegetables, fruits, fish, and milk products was increased, and intake of grains, potatoes, and meats was minimized in adults with CHD compared to those in the National Nutritive Intake Investigation.

Table 2
Body composition analysis and nutritional intake sarcopenia vs. non-sarcopenia in CHD.

	Males with CHD 50 patients		p Value	Females with CHD 67 patients		p Value
	Sarcopenia 7 patients (14%)	Non-sarcopenia 43 patients		Sarcopenia 12 patients (18%)	Non-sarcopenia 55 patients	
Age (yrs)	33.3 ± 14.4	39.8 ± 14.8	ns	38.3 ± 19.8	37.6 ± 12.8	ns
Skeletal muscle mass index (kg/m ²)	6.4 ± 0.5	7.9 ± 7.9	<0.01	5.1 ± 0.5	6.5 ± 0.5	<0.01
Body height (cm)	161.3 ± 6.4	170.0 ± 7.0	<0.05	153.2 ± 5.7	159.5 ± 6.9	<0.05
Body weight (kg)	51.7 ± 9.8	65.3 ± 9.8	<0.05	40.7 ± 3.1	55.0 ± 7.1	<0.01
BMI (kg/m ²)	20.0 ± 4.3	22.7 ± 3.1	<0.05	17.4 ± 1.8	21.6 ± 2.9	<0.01
Body fat (%)	20.7 ± 9.7	17.5 ± 7.4	ns	21.7 ± 6.9	25.2 ± 8.1	ns
Edema index (%)	0.382 ± 0.018	0.374 ± 0.007	<0.05	0.385 ± 0.08	0.380 ± 0.07	<0.05
Calories (kcal)	2419 ± 309	2152 ± 152	<0.05	1853 ± 179	1836 ± 85	ns
Protein (g)	90.1 ± 4.1	86.1 ± 4.4	ns	74.2 ± 6.6	74.3 ± 5.8	ns
Fat (g)	69.9 ± 7.1	63.4 ± 3.4	<0.05	58.0 ± 3.6	58.3 ± 4.3	ns
Carbohydrate (g)	325.3 ± 59.9	279.6 ± 33.1	<0.05	248.1 ± 38.3	242.1 ± 12	ns
Salt (g)	13.6 ± 4.8	9.9 ± 1.5	<0.01	9.6 ± 0.4	9.8 ± 0.8	ns

Abbreviations. CHD: congenital heart disease, BMI: body mass index.

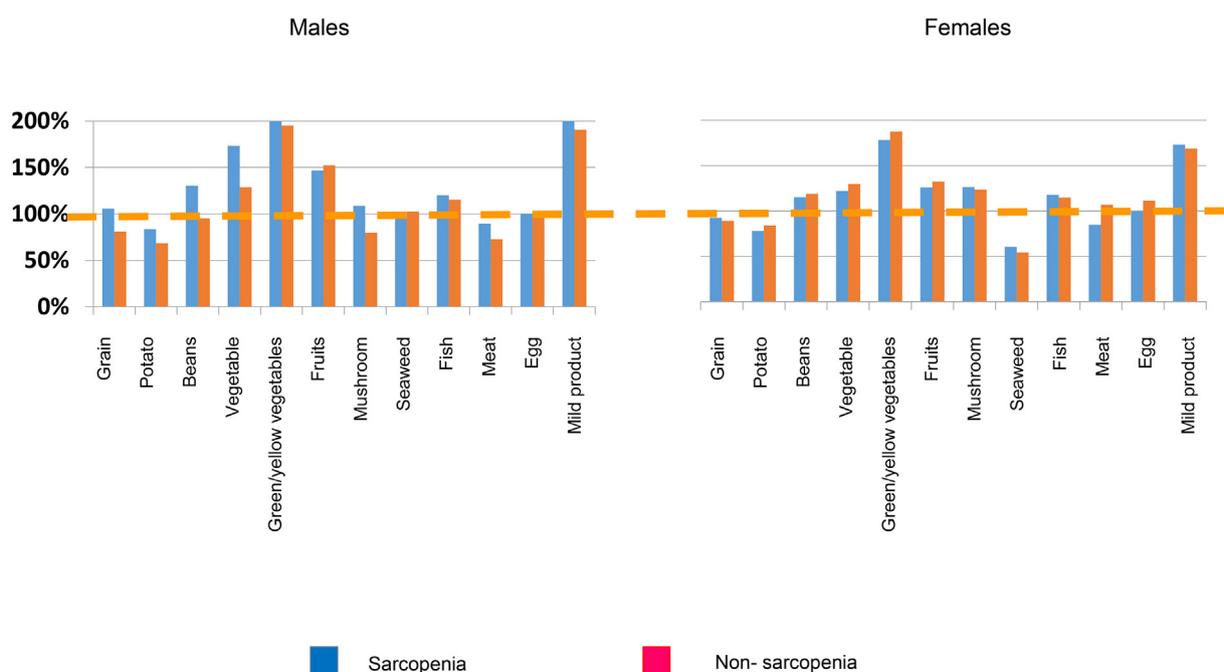


Fig. 2. Detailed dietary intake sarcopenia vs non-sarcopenia in congenital heart disease (CHD). As for the detailed dietary intake in men with CHD, intake of grain, beans, vegetables, and mushrooms was increased in sarcopenia compared to non-sarcopenia. On the other hand, there was no statistical difference between the two in women with CHD.

intake plus resistance training (group C). Group A and B had a tendency of higher body fat percentage and lower skeletal muscle mass index compared to those in group C, and there was no significant difference in them between group A and B. The difference in age, sex, BMI, basic metabolism, and edema index between the three groups was not significant (Table 3).

We compared adults with CHD before and after amino acid intake ± resistance training. In adults with CHD who took amino acid supplements plus resistance training (group A), body fat percentage, edema index, and NT-proBNP decreased, and body weight, skeletal muscle mass index, and basic metabolism increased. By contrast, in adults with CHD who took amino acid alone (group B), the difference in BMI, body weight, body fat percentage, skeletal muscle mass index, basic metabolism, edema index, or NT-proBNP before and after amino acid intake was not significant. In age-matched controls (group C), body fat percentage decreased and skeletal muscle mass index and basic

metabolism increased after amino acid intake plus resistance training.

Discussion

Adult patients with CHD are known to have lower skeletal muscle mass and relatively higher body fat percentage, suggesting both sarcopenia and paradoxical obesity, even in the younger population [4,16]. Generally, sarcopenia is strongly associated with HF and obesity (metabolic syndrome) is related to cardiovascular diseases [17], and both pathologies should be prevented, particularly in adults with complex CHD. Possible causes of sarcopenia in these populations are as follows: (1) inappropriate nutritional intake and unhealthy lifestyle, (2) no regular exercise habits since their childhood, (3) poor absorption due to gastrointestinal edema, (4) hypercatabolism, (5) hormonal imbalances, (6) inflammatory processes, (6) oxidative stress, and (7) cellular proteolysis [1,6,18].

Table 3

Before and after resistance training and amino acid intake in CHD.

	CHD Resistance Training and Amino Acid Intake 15 pts		CHD Only Amino Acid Intake 15 pts		Controls Resistance Training and Amino Acid Intake 10 pts	
	Before	After	Before	After	Before	After
Age (yrs)	41.3 ± 8.4		40.8 ± 11.3		38.0 ± 8.8	
NYHA I/II/III/IV	4/11/0/0		3/12/0/0		10/0/0/0	
Males	6		7		4	
SPO2 (%)	95.1 ± 2.3		94.8 ± 3.6		98.8 ± 1.1	
Diseases	TOF/DORV 11, Fontan 2, Cyanosis 2		TOF/DORV 9, Fontan 3, Cyanosis 3			
Sarcopenia	4 pts (26.7%)		4 pts (26.7%)		0 pts (0%)	
BMI	21.2 ± 3.5	21.4 ± 3.1	22.1 ± 3.0	22.3 ± 3.4	20.4 ± 1.9	20.4 ± 1.9
Body weight (kg)	55.2 ± 10.7	56.2 ± 10.6*	56.2 ± 9.1	56.7 ± 10.1	54.6 ± 10.7	54.5 ± 10.7
Body fat (%)	22.5 ± 8.7	20.0 ± 8.4 [†]	23.9 ± 8.3	23.8 ± 7.5	19.7 ± 8.1	14.8 ± 9.8**
Skeletal muscle mass index (kg/m ²)	7.4 ± 1.7	7.9 ± 1.8 [†]	7.5 ± 1.2	7.4 ± 0.9	8.1 ± 1.4	8.6 ± 1.6 [†]
Basic metabolism (Kcal)	1287.5 ± 181.4	1309.9 ± 192.6 [†]	1291.4 ± 125.4	1242.1 ± 108.3	1324.6 ± 253.6	1382.3 ± 280.5**
Edema index	0.38 ± 0.007	0.37 ± 0.008*	0.38 ± 0.01	0.38 ± 0.01	0.37 ± 0.01	0.37 ± 0.01
NT-proBNP (pg/ml)	333.0 ± 378.4	228.2 ± 403.9 [†]	468.9 ± 600.5	533.1 ± 723.4	35.3 ± 20.2	30.9 ± 16.4

Abbreviation. CHD: congenital heart disease, pts: patients, NYHA: New York Heart Association, SPO2: Blood oxygen saturation, TOF:tetralogy of Fallot, DORV: double outlet right ventricle, BMI: body mass index, NT-proBNP: N-terminal pro b-type natriuretic peptide.

* < 0.05
[†] < 0.01

Is nutritional intake appropriate in adult patients with CHD?

Our study showed that intake of calories, protein, and fat in patients with CHD was higher than those in the National Nutritive Intake Investigation; therefore, shortage of nutritional intake was not observed. This fact is inconsistent from that of the primary sarcopenia in elderly people without appetite, and our study population consists of relatively younger people with secondary sarcopenia; therefore, they still have sufficient appetite. Adult patients with CHD tended to (1) increase their intake of vegetables, fruits, fish, and milk products and (2) decrease intake of grains and meats. They tend to eat more vegetables than normal people. These healthy dietary habits should be kept in order to prevent cardiovascular diseases; however, in order to increase the skeletal muscle mass, intake of animal protein should be increased by using CHD nutritional education programs.

The possibility of poor absorption and hypercatabolism remains in patients with CHD. Potential right-sided HF is common in CHD, leading to gastrointestinal edema and poor absorption. Cardiac cachexia is also reported to be commonly observed in right-sided HF and elevated right heart pressure is associated with malnutrition [19]. Generally, PLE is strongly associated with poor absorption, but there was no patient who had active PLE with low serum albumin level and/or who was treated with steroids or intravenous infusion of albumin. Therefore, PLE was not a main issue in this study. Congestive hepatic failure is also identified in right-sided HF in CHD, which inhibits albumin synthesis. Furthermore, patients with complex CHD and HF, particularly cyanotic CHD, have chronic inflammation [4,18,20], and some cytokines, such as tumor necrosis factor- α and interleukin-6, are elevated [4,20,21]. Data on nutritional guidelines in chronic liver and renal dysfunction were easily accessible; however, data on CHD are limited. These factors should also be considered when nutritional guidelines are provided for patients with CHD; therefore, further studies are required.

Sarcopenia vs. non-sarcopenia in men and women with CHD

In male sarcopenic patients with CHD, intake of carbohydrates, fat, and salt was higher than those without sarcopenia, whereas the protein intake was not different between the two.

Theoretically, sarcopenic patients should take more protein than their non-sarcopenic counterparts. Increased intake of carbohydrates and fats can effectively prevent cachexia in sarcopenic patients; however, excessive intake of salt results in HF. The daily amount of salt intake is higher than the Japanese Ministry of Health, Labour, and Welfare's recommended value [14]; therefore, appropriate nutritional education programs are needed.

In female sarcopenic patients with CHD, BMI was lower compared to non-sarcopenia, because of the relatively lower intake of calories and proteins. Lower BMI is strongly associated with poor prognosis in HF [19]; therefore, appropriate nutritional education programs are needed for women with CHD.

Effects of resistance training and amino acid intake

There are two options to manage sarcopenia: pharmaceutical therapies (testosterone, dehydroepiandrosterone, estrogen, growth hormone, ghrelin, vitamin D, angiotensin-converting enzyme inhibitor, and eicosapentaenoic acid) and non-pharmaceutical therapies (resistance training, protein and amino acid supplementation, and non-smoking) [22]. Generally, resistance training combined with supplements containing amino acids are considered as the most effective in preventing and treating age-related muscle wasting and weakness [22,23]. Current criteria for cardiac rehabilitation of HF are (1) left ventricular ejection fraction of <40%, (2) BNP of >80 pg/ml, and (3) maximal oxygen consumption (peak VO₂) of <80% on cardiopulmonary test [23]; however, there are no criteria for right-sided HF such as CHD. In this study, previous reports and protocols of home resistance training in non-CHD patients with HF were reviewed [23–28]. The major findings were that exercises with bands, mainly at home, were effective in increasing walking distance and quality of life in patients with HF [23–28]. A previous study also reported that home exercise walking distance increased by 11% after 8 weeks (two sets and 25 repetitions/day, three times per week) [23]. This is a pilot study; therefore, appropriate exercise load and amount of amino acid intake remain unknown, and further studies are required. We believe that this study provides significant information on cardiac rehabilitation and can encourage patients with CHD to work out, especially those who have had no exercise habits since childhood.

Limitations

First, FFQ and resistance training at home were a self-reporting system. Next, in order to analyze body composition using InBody, patients with pacemaker, ICD, and CRT were excluded. Therefore, patients with severe HF were possibly excluded. However, we believe that this study is still informative to encourage those who have CHD to consume sufficient amounts of protein and undergo resistance training. Next, the number of patients who were enrolled in Study 2 was small. Patients with mental retardation were excluded because of their inability to continuously perform exercise regularly for 2 months and to provide consent. Adult patients with CHD who are reluctant to do resistance training or take amino acid supplements were also excluded, because motivation is crucial to continue working out at home. To maintain good adherence, patients were contacted through e-mails; however, this is also a self-reporting system. Lastly, this is a pilot study and treatment guidelines for CHD with sarcopenia were unavailable; therefore, appropriate exercise load and amount of amino acid intake remain unknown. Further studies are required.

Conclusions

Adult patients with CHD consume more calories, protein, and fat compared to those in a national survey, whereas sarcopenia is an important issue even in the younger population. Amino acid intake plus resistance training positively improves body fat percentage, skeletal muscle mass, and edema in adults with CHD. Appropriate nutritional education and resistance training guidelines should be provided.

Author contributions

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Conflict of interest

There are no conflicts of interest to declare.

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