Received: 7 August 2017 | Revised: 11 October 2017 | Accepted: 31 October 2017

DOI: 10.1111/chd.12555

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Body composition, appetite-related hormones, adipocytokines, and heart failure in adult patients with congenital heart disease: A preliminary study

Yumi Shiina MD, PhD[1] | Tomoaki Murakami MD, PhD[2] | Noriko Matsumoto MSc[3] | Daisuke Okamura PT[4] | Yuta Takahashi MSc[4] | Yosuke Nishihata MD, PhD[1] | Nobuyuki Komiyama MD, PhD[1] | Koichiro Niwa MD, PhD[1]

[1]Department of Cardiology, Cardiovascular Center, St. Luke's International Hospital, Tokyo, Japan

[2]Department of Cardiology, Chiba Children's Hospital, Chiba, Japan

[3]Department of Nutrition, St. Luke's International Hospital, Tokyo, Japan

[4]Department of rehabilitation, St. Luke's International Hospital, Tokyo, Japan

Correspondence
Tomoaki Murakami, MD, PhD, Department of Cardiology, Chiba Children's Hospital, 579-1 Heta-cho, Midori-ku, Chiba 266-0007 Japan.
Email: murat@seagreen.ocn.ne.jp

Funding information
Japan Society for the Promotion of Science, Grant/Award Number: 16K19432e

Abstract

Objectives: To assess body composition and relationships among body composition, appetite-related hormones, adipocytokines, and heart failure (HF) in adult patients with congenital heart disease (CHD).

Patients: This prospective study enrolled 46 consecutive adult patients with CHD and 12 age-matched healthy controls. The patients and control subjects were divided into four groups: 13 patients with Fontan circulation (group A), 16 patients with cyanosis (group B), 17 patients who previously underwent biventricular repair (group C), and 12 age-matched healthy controls.

Design: Body composition was measured using InBody730, and levels of appetite-related hormones (ghrelin and leptin) and adipocytokines (leptin, interleukin-6, and tumor necrosis factor-α) were determined. Relationships of these measurements between severe HF, defined as New York Heart Association functional class III–IV and/or recent repeated unscheduled hospitalizations due to HF, were examined using univariate logistic analysis.

Results: Mean patient age was 32.1 ± 7.4 years. The skeletal muscle mass was significantly decreased in groups A and B compared with that in controls. Interestingly, ghrelin levels in groups A and B were also significantly lower than those in controls. Univariate logistic analysis revealed that ghrelin level, percent body fat, and pulse oximetric oxygen saturation were significantly associated with severe HF.

Conclusions: Patients with Fontan circulation and those with cyanosis might be at a risk of sarcopenia. Despite the decreased skeletal muscle mass and increased body fat, ghrelin levels in these patients were decreased. These changes might have a negative impact on HF in these patients.

KEYWORDS
body fat, congenital heart disease, ghrelin, heart failure, muscle mass

1 | INTRODUCTION

With the advent of surgical procedures and medical therapy, most patients with congenital heart disease (CHD) can now be expected to survive into adulthood[1]; this has led to the emergence of problems associated with aging. Several studies have reported that body mass index (BMI) is lower and metabolic syndrome is more common among adults with CHD than in the general population,[2,3] implicating reduced body muscle and increased body fat in such patients. Sarcopenia, which is a progressive generalized loss of skeletal muscle mass, is also one of

the most important problems associated with aging[4] that has gained considerable attention for its association with heart failure (HF) in recent years.[5] However, the role of sarcopenia in adult patients with CHD remains unclear. HF is a major cause of death in adults with CHD (42%), with more than 50% of all patients with CHD over 40-year old developing HF.[6] In its advanced stages, HF is often accompanied by the loss of muscle mass and strength, because malnutrition, systemic inflammation, endocrine imbalances, and oxidative stress link sarcopenia with HF.[5,7] Lower BMI relates to worse prognosis, particularly in symptomatic patients with CHD with complex anomalies, suggesting that cardiac cachexia plays a role.[2,3] Potential therapeutic strategies are needed to impede the progression of muscle wasting in patients with HF. Furthermore, hormonal supplementation with growth hormone, testosterone, and ghrelin is often discussed as potential treatments.[5]

Ghrelin and leptin are important appetite-related hormones that control appetite. Reportedly, plasma ghrelin levels are significantly high in infants and children with CHD.[8–13] An elevated ghrelin level, which has a favorable effect on growth, might be a compensatory mechanism for malnutrition and growth retardation in these patients.[8–11] Moreover, promising results with several ghrelin agonists have already been reported in animal models of HF-related body wasting.[5] However, there are currently no reports on the role of ghrelin in adult patients with CHD. Adults with CHD who might continually secrete high levels of ghrelin since childhood, with a positive effect on HF, may be prone to obesity due to endocrine issues. The adipokines leptin, interleukin (IL)-6, and tumor necrosis factor (TNF)-α have been reported to be elevated in patients with CHD, particularly those with cyanotic CHD.[14] Despite scarce data in adults with CHD, these inflammatory cytokines may have an effect on HF and sarcopenia.

This study aimed to determine the body composition of adult patients with CHD and to investigate associations among body composition, appetite-related hormones, adipocytokines, and HF.

2 | METHODS

In total, 46 adult patients with CHD who visited the clinic of St. Luke's International Hospital from July 2016 to December 2016 were enrolled in this study. Patients were categorized into three groups: those with Fontan circulation ($n = 13$, group A) and cyanosis ($n = 16$, group B) and those who underwent biventricular repair ($n = 17$, group C). Group A comprised two patients with a lateral tunnel-type Fontan circulation and 11 patients with an extracardiac conduit and total cavopulmonary connection. Group B included seven patients with an unrepaired ventricular septal defect (VSD), pulmonary atresia, and major aortopulmonary collateral arteries; four patients with unrepaired tetralogy of Fallot (TOF); three patients with single ventricles and central or Blalock–Taussig shunts; one patient with unrepaired congenitally corrected transposition of the great arteries who had a VSD and developed severe pulmonary hypertension; and one patient with transposition of the great arteries after the Senning procedure who had severe baffle leakage, pulmonary hypertension, and eventual severe cyanosis. Group C included nine patients who developed TOF after right ventricular outflow tract reconstruction, five patients who developed TOF after the Rastelli procedure, and three patients who developed TOF after prosthetic pulmonary valve replacement. Twelve age-matched healthy subjects, all of whom were medical staff at our hospital, were enrolled as controls.

We did not include other biventricular repair CHD except for TOF, because the sample becomes heterogeneous which is difficult to be analyzed. We divided three groups (Fontan, cyanotic CHD, and biventricular repair) because cyanosis has some influences on neurohormones. Furthermore, exercise capacity and edema are totally difference between Fontan and biventricular groups.

Patients with severe HF were classified as those in the New York Heart Association (NYHA) functional class III or IV and/or those with a recent history of repeated unscheduled hospitalizations due to HF (at least twice for a year).

BMI, percent body fat, skeletal muscle mass index, basic metabolism, and edema index of all patients were measured using bioelectrical impedance analysis (BIA). Body composition values were determined using an InBody730 device (InBody, Tokyo, Japan). InBody730 can measure percent body fat, edema index (extracellular water/total body water), skeletal muscle mass index, and BMI. InBody is widely used to assess body composition, sarcopenia, and edema in gymnasiums as well as in geriatrics, nephrology, and gastroenterology.[15–17] Many studies have also reported that this noninvasive BIA is useful to predict clinical outcomes in patients with HF.[15] Muscle mass index was expressed as muscle weight divided by the square of body height (kg/m^2).

Fasting venous blood samples were collected from all subjects to measure levels of ghrelin, leptin, IL-6, TNF-α, NT-pro brain natriuretic peptide (NT-pro BNP), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and hemoglobin (Hb)A1c. For ghrelin measurements, 3 mL of venous blood was collected to a tube containing 10% edetate disodium and aprotinin. After centrifugation at 1500*g* at 4°C for 15 min, plasma was separated and hydrochloric acid (1 mol/L) at 1/10 volume was added. Active ghrelin levels were measured using enzyme-linked immunosorbent assay (SRL, Tokyo, Japan). Serum leptin, IL-6, and TNF-α levels were determined using radioimmunoassay, chemiluminescence enzyme immunoassay, and enzyme-linked immunosorbent assay, respectively (SRL, Tokyo, Japan). NT-pro BNP levels and other laboratory data, including HbA1c and cholesterol levels, were assessed on the same day as the InBody measurements.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institutional Human Research Committee. The ethical committee at St. Luke's International Hospital also approved this study, and informed consent was obtained from all participants.

Statistical analysis was performed using SPSS 19.0 (IBM, Somers, New York) and MedCalc Version 17.9 (MedCalc Software, Mariakerke, Belgium). Continuous data were presented as means ± standard deviation. One-way analysis of variance with post hoc Tukey–Kramer or the Kruskal–Wallis test was utilized to compare means among the four groups. The chi-square test or Fisher's exact test was performed for comparing categorical data. A univariate logistic analysis was used to evaluate factors associated with severe HF.

TABLE 1 Patient characteristics

	Group A (13)	Group B(16)	Group C (17)	Controls (12)
Age (years)	29.0 ± 5.9	33.8 ± 7.9	32.9 ± 8.2	31.5 ± 7.2
Male	6 (46.2%)	7 (43.8%)	8 (47.1%)	5 (41.7%)
NYHA-FC	1 0, II 11, III 2, IV 0	1 0, II 11, III 5, IV 0	1 7, II 8, III 2,. IV 0	1 12, II 0, III 0, IV 0
SpO_2 (%)	93.5 ± 2.1[a]	82.8 ± 5.2[b]	97.7 ± .6	98.4 ± .5
Hypertension	0	0	0	0
Hyperlipidemia	1	3	3	0
Diabetes mellitus	0	1	1	0
Medication				
Diuretics	3	5	3	0
ACE-I, ARB	6	7	6	0
Beta-blocker	3	4	4	0

Data were expressed as mean ± SD.
[a]$P < .05$ versus Group B, C, and controls.
[b]<.05 versus Group A, C and controls (Kruskal–Wallis test).
Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NYHA-FC, New York Heart Association functional class; SpO_2, pulse oximetry oxygen saturation.

3 | RESULTS

Table 1 shows the characteristics of all participants included this study. The mean age of 46 adults with CHD was 32.1 ± 7.4 years, and 21 patients were males. No significant differences were observed in age, sex, or prevalence of hypertension, hyperlipidemia, or diabetes mellitus among the four groups. The pulse oximetry oxygen saturation (SpO_2) was lower in group A than in group C and controls ($P < .05$). Moreover, SpO_2 was lower in group B than in groups A, C, and controls ($P < .05$).

Table 2 shows the body composition data determined by InBody. The skeletal muscle mass index and basic metabolism were lower in groups A and B than in controls ($P < .05$). The edema index was higher in groups A, B, and C than in the healthy controls ($P < .05$). The percent body fat, which was higher in group B than in controls ($P < .05$), tended to be higher in group A than in controls, albeit without statistical significance. Groups A and B tended to have low BMI.

Table 3 shows the laboratory data. In groups A and B, plasma ghrelin levels were lower and IL-6 levels were higher than those in controls ($P < .05$), whereas no significant difference was observed in leptin levels among the groups. IL-6 levels were higher in groups A and B, whereas no statistically significant difference was observed in TNF-α levels among the groups. NT-pro BNP level was higher in group B than in other groups ($P < .05$). No difference was observed in the lipid profiles among the four groups. HbA1c levels were significantly higher in groups A and B than in groups C and controls ($P < .05$).

Table 4 shows the results of univariate logistic analysis in the determination of factors associated with severe HF. Among the three groups with HF, seven patients were defined as having severe HF according to the study criteria (one, four, and two patients in groups A, B, and C, respectively). Univariate logistic analysis revealed that plasma ghrelin levels, percent body fat, and SpO_2 were significantly associated with severe HF (odds ratios: .82, 1.13, and .87, respectively; 95%

TABLE 2 Body composition data

	Group A (13)	Group B(16)	Group C (17)	Controls (12)
Body mass index (kg/m^2)	19.7 ± 4.7	20.4 ± 2.5	22.1 ± 2.5	21.6 ± 2.1
Percent body fat (%)	24.0 ± 9.9	27.8 ± 10.2[a]	21.9 ± 5.8	20.1 ± 4.0
Skeletal muscle mass index (kg/m^2)	34.7 ± 4.4[a,b]	36.5 ± 6.1 [a,b]	43.5 ± 8.0	43.8 ± 4.4
Basal metabolism (kcal)	1165.4 ±100.5 [a,b]	1208.8 ± 139.7[a]	1366.9 ±182.3	1413.2 ± 149.1
Edema index	.38 ± .09 [a,c]	.39 ± .05 [a,b]	.37 ± .06[a]	.36 ± .02

Data are expressed as mean ± SD.
[a]$P < .05$ versus controls.
[b]$P < .05$ versus Group C.
[c]$P < .05$ versus Group B.
Statistics: body mass index, percent body fat, skeletal muscle mass index, basal metabolism: One-way ANOVA (Tukey–Kramer), Edema index: Kruskal–Wallis test.

TABLE 3 Blood test data

	Group A (13)	Group B (16)	Group C (17)	Group D (12)
Ghrelin (pg/mL)	18.1 ± 7.6[a]	19.9 ± 11.0[b]	28.1 ± 21.2	40.3 ± 19.1
Leptin (ng/mL)	9.3 ± 9.3	11.5 ± 8.8	9.4 ± 6.8	10.3 ± 3.5
IL-6 (pg/mL)	1.83 ± .9[c]	2.65 ± 2.1[b]	1.05 ± .48	.90 ± .41
TNF-α (pg/mL)	.91 ± .35	1.29 ± .61	1.14 ± .41	1.09 ± .48
NT-pro BNP (pg/mL)	122.7 ± 108.2	533.7 ± 431.9[a]	170.0 ± 183.7	85.2 ± 29.5
LDL cholesterol (mg/dL)	98.8 ± 22.1	93.2 ± 36.1	106.8 ± 27.8	107.4 ± 39.5
HDL cholesterol (mg/dL)	56.4 ± 12.2	58.7 ± 14.4	55.8 ± 12.3	56.7 ± 13.9
Triglyceride (mg/dL)	95.0 ± 70.2	94.4 ± 59.4	119.2 ± 72.1	117.1 ± 89.5
HbA1c (%)	5.9 ± .38[c]	5.9 ± .35[c]	5.8 ± 1.3	5.6 ± .12

Data are expressed as mean ± SD.
[a]<.001 versus Group D. HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IL-6, interleukin-6; LDL, low-density lipoprotein; NT-pro BNP, NT-pro brain natriuretic peptide; TNF-α, tumor necrosis factor-α.
[b]$P < .01$ versus Group D.
[c]$P < .05$ versus Group D.

confidence intervals: .67–.99, 1.007–1.26, and .77–.98, respectively; *P* values: .04, .04, and .02; respectively).

4 | DISCUSSION

The patients in the current study were categorized into three groups: patients with Fontan circulation with high central venous pressure, cyanotic patients, and patients who underwent biventricular repair previously. The body composition and levels of appetite-related hormones in patients after biventricular repair were similar to those in controls. However, the Fontan and cyanotic groups had similar characteristics, including those that were different from the controls. Among the data related to body composition, the skeletal muscle mass index was significantly lower, and the percent body fat was relatively higher in the Fontan and cyanotic groups than in controls, indicating that the patients in these two groups were sarcopenic. Among the laboratory data analyzed in the current study, ghrelin, IL-6, and HbA1c levels were elevated in patients with Fontan circulation and those with cyanosis.

TABLE 4 Factors associated with severe heart failure

	Univariate logistic analysis		
	Odds ratio	95%CI	*P*
Age (years)	1.28	.93-1.77	.13
Percent body fat (%)	1.13	1.007-1.26	.04
Skeletal muscle mass index (kg/m^2)	1.03	.91-1.16	.63
SpO_2 (%)	.87	.77-.98	.02
Ghrelin (pg/mL)	.82	.67-.99	.04
IL-6 (pg/mL)	1.85	.87-3.94	.11
TNF-α (pg/mL)	1.76	.37-8.30	.47
HbA1c (%)	1.31	.53-3.23	.55

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; IL-6, interleukin-6; NT-pro BNP, NT-pro brain natriuretic peptide; SpO_2, pulse oximetry oxygen saturation; TNF-α, tumor necrosis factor-α.

4.1 | Body composition: Sarcopenia and increased body fat in adult patients with CHD

The current study revealed low skeletal muscle mass index, low basal metabolism, and high percent body fat in patients with Fontan circulation and those with cyanosis. Although sarcopenia is well recognized in geriatrics, the patients in this study were young adults. However, in previous studies, highest mortality rates were observed among young adults with severe and complex CHD, Fontan physiology, and Eisenmenger syndrome.[18] For example, an average 40-year-old patient with Fontan physiology has a mortality rate comparable with that expected in a 75-year-old healthy individual.[18] This perspective indicates that these adult patients are faced with problems associated with aging.

Although loss of body weight is a defining component of cachexia, the definition of sarcopenia includes loss of muscle mass and strength/function.[5,7] Importantly, sarcopenia is not necessarily associated with changes in body weight because declining muscle mass can be masked by proportional increases in the adipose tissue.[5,7] Muscle mass loss occurs before adipose tissue loss during HF progression, which may hinder the early detection of sarcopenia. Thus, patients develop sarcopenia before becoming cachectic by progressing along a theoretical "wasting continuum." Cardiac cachexia in CHD is evident as low BMI, and adult patients with CHD with low BMI have poor prognosis[2]; therefore, cachexia should be prevented during early-stage sarcopenia. Most patients with CHD exercise safely; however, medical providers as well as their parents often impose additional unwarranted exercise restrictions,[19,20] which can hinder the formation of regular exercise habits. The exercise capacity should be carefully evaluated, and appropriate activities should be encouraged from childhood in these patients.

Although BMI is lower in adults with CHD than in the general population, the prevalence of metabolic syndrome is higher in this patient

population[3] due to the reduction in body muscle and the increase in body fat to replace this loss. Our results are compatible with this mechanism. Moreover, the risk of metabolic disorders in adults with CHD in the current study was increased, consistent with decreased insulin sensitivity. Abnormal glucose regulation (AGR) and insulin resistance are well known in patients with complex CHD,[21] even in young patients, and AGR is one of the major risk factors for poor prognosis in this population.[21] The current study also revealed that a high HgA1C level was an important factor associated with severe HF, which is in agreement with the results of previous study.

4.2 | Ghrelin and heart failure

Ghrelin is an orexigenic hormone of gastric origin[22] and is a natural endogenous ligand of the growth hormone (GH) secretagogue receptor that was identified as a stimulant for GH release.[22] Ghrelin and its receptors are ubiquitously expressed in heart and vessels[23–28] and are considered to regulate appetite, energy, body weight, and metabolism of glucose and fat as well as to modulate gastrointestinal, cardiovascular, pulmonary, immune functions, and cell proliferation/apoptosis by its direct effects and via its role in GH release.[22–28] In some animal studies, exogenous administration of ghrelin led to the dilatation of peripheral blood vessels, regulation of atherosclerosis, improved endothelial function, and inhibition of myocardial cell apoptos.[24] Even in healthy human volunteers, ghrelin reportedly decreased vascular resistance and increased cardiac index and stroke volume.[24] These results are considered to relate to its vasodilator effects as well as its inhibition of sympathetic activity.[23–28]

Given that ghrelin has a favorable effect on cardiovascular function and is considered as a potentially therapeutic hormone, we examined the relationship between HF and various parameters related to ghrelin. As observed in the current study, lower ghrelin levels might have a negative impact on severe HF. Non-CHD adults with HF reportedly have much lower ghrelin levels than those without HF.[24,29] Moreover, plasma ghrelin levels are significantly high in children with CHD.[8–13] Elevated ghrelin levels in these children might be related to malnutrition, growth retardation, and chronic shunt-induced hypoxemia, wherein increased ghrelin might be a compensatory mechanism.[8–13] In contrast, the mechanism underlying low ghrelin levels in adult patients with Fontan circulation and those with cyanosis is likely distinct. Ghrelin also has direct metabolic effects in the periphery, such as endopancreatic function and altered glucose metabolism.[30] Intravenous ghrelin administration in humans has been demonstrated to promote a favorable effect on glucose metabolism, insulin sensitivity, and lipolysis inhibition.[30–32] Decreased ghrelin levels in patients with type 2 diabetes mellitus are associated with an increase in abdominal adiposity and insulin resistance.[30–32] Overall, ghrelin as an AGR-conscious therapeutic strategy might also be associated with a significant reduction in cardiovascular events.

4.3 | Adipocytokines

IL-6 and TNF-α are pleiotropic adipocytokines with numerous immunologic actions, including critical roles in catabolism. These pro-inflammatory mediators were reported to be overexpressed in patients with HF, and increases in their levels were shown to be associated with poor survival.[14,33] Several studies have reported that compared with healthy controls, IL-6 and TNF-α levels were elevated in children with CHD independently of the presence of cyanosis.[8–11] These adipocytokines are typically elevated in patients with HF and/or sarcopenia and are associated with declines in muscle mass and strength.[27] Therefore, the current study showing elevated IL-6 levels in patients with Fontan circulation and those with cyanosis who exhibited low skeletal muscle mass is in agreement with the results of the earlier studies. Conversely, albeit not statistically significant, TNF-α levels tended to increase in patients with CHD with Fontan circulation or cyanosis. This result might be partially explained by the relatively small number of patients.

Finally, HF in patients with cyanotic CHD is not necessarily caused by low cardiac function. For example, hypoxemia can induce neurohumoral factors and activate sympathetic nerves, resulting in worsened NYHA score.[14] The negative association of SpO_2 with severe HF observed in the current study is reasonable.

5 | LIMITATIONS

The current study enrolled a small number of patients with complex CHD; however, the prevalence of middle-aged cyanotic adults with unrepaired CHD is low as well. Moreover, patients came from heterogeneous backgrounds, with various initial diagnoses. Although this was a preliminary study, our findings suggest that patients with Fontan circulation as well as those with cyanosis might be at risk for sarcopenia. Future studies are necessary to elucidate the relationship between factors associated with sarcopenia and their hemodynamics. Furthermore, the amount of exercise that should be recommended to this challenging population with sarcopenia, which remains unknown, should also be addressed in future studies.

6 | CONCLUSIONS

Patients with Fontan circulation and those with cyanosis might be at a risk of sarcopenia. Despite the decreased skeletal muscle mass and increased body fat, ghrelin levels in these patients were decreased. These changes might have a negative impact on HF in these patients.

CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Concept/Design: Shiina
Data analysis/interpretation: Shiina, Nishihata, Matsumoto
Drafting article: Shiina, Murakami
Critical revision of article Murakami, Komiyama, Niwa
Data collection: Matsumoto, Okamura, Takahashi

ORCID

Yumi Shiina MD, PhD http://orcid.org/0000-0003-3726-3034

Tomoaki Murakami MD, PhD http://orcid.org/0000-0003-3604-151X

REFERENCES

[1] Shiina Y, Toyoda T, Kawasoe Y, et al. Prevalence of adult patients with congenital heart disease in Japan. *Int J Cardiol.* 2011;146(1):13–16.

[2] Brida M, Dimopoulos K, Kempny A, et al. Body mass index in adult congenital heart disease. *Heart.* 2017;103(16):1250–1257.

[3] Deen JF, Krieger EV, Slee AE, et al. Metabolic syndrome in adults with congenital heart disease. *J Am Heart Assoc.* 2016;5:e001132

[4] Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol.* 1998;147(8):755–763.

[5] Collamati A, Marzetti E, Calvani R, et al. Sarcopenia in heart failure: mechanisms and therapeutic strategies. *J Geriatr Cardiol.* 2016;13(7):615–624.

[6] Rodriguez FH III, Marelli AJ. The epidemiology of heart failure in adults with congenital heart disease. *Heart Fail Clin.* 2014;10(1):1–7.

[7] von Haehling S. The wasting continuum in heart failure: from sarcopenia to cachexia. *Proc Nutr Soc.* 2015;74(4):367–377.

[8] Wang D, Fang J, Wang R, et al. Elevated serum ghrelin, tumor necrosis factor-α and interleukin-6 in congenital heart disease. *Pediatr Int.* 2016;58(4):259–264.

[9] Afify MF, Mohamed GB, El-Maboud MA, Abdel-Latif EA. Serum levels of ghrelin, tumor necrosis factor-alpha and interleukin-6 in infants and children with congenital heart disease. *J Trop Pediatr.* 2009;55(6):388–392.

[10] Yilmaz E, Ustundag B, Sen Y, Akarsu S, Kurt AN, Dogan Y. The levels of Ghrelin, TNF-alpha, and IL-6 in children with cyanotic and acyanotic congenital heart disease. *Mediators Inflamm.* 2007;2007:32403

[11] Li G, Xia J, Jia P, et al. Plasma levels of acylated ghrelin in children with pulmonary hypertension associated with congenital heart disease. *Pediatr Cardiol.* 2015;36(7):1423–1428.

[12] Kitamura T, Shimizu T, Ohkawa N, Oda H, Ohtsuki M, Kishiro M. Effects of ghrelin on growth and cardiac function in infants with congenital heart disease. *Pediatr Int.* 2010;52(3):358–361.

[13] Zhang S, Guo GL, Yang LL, Sun LQ. Elevated serum levels of ghrelin and TNF-α in patients with cyanotic and acyanotic congenital heart disease. *World J Pediatr.* 2017;13(2):122–128.

[14] Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation.* 2002;106(1):92–99.

[15] Lyons KJ, Bischoff MK, Fonarow GC, Horwich TB. Noninvasive bioelectrical impedance for predicting clinical outcomes in outpatients with heart failure. *Crit Pathw Cardiol.* 2017;16(1):32–36.

[16] Thanakitcharu P, Jirajan B. Early detection of subclinical edema in chronic kidney disease patients by bioelectrical impedance analysis. *J Med Assoc Thai.* 2014;97(Suppl 11):S1–S10.

[17] Gonzalez MC, Heymsfield SB. Bioelectrical impedance analysis for diagnosing sarcopenia and cachexia: what are we really estimating? *J Cachexia Sarcopenia Muscle.* 2017;8(2):187–189.

[18] Diller GP, Kempny A, Alonso-Gonzalez R, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation.* 2015;132(22):2118–2125.

[19] Pelliccia A, Zipes DP, Maron BJ. Bethesda Conference #36 and the European Society of Cardiology Consensus Recommendations revisited a comparison of U.S. and European criteria for eligibility and disqualification of competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol.* 2008;52:1990–1996.

[20] Longmuir PE, Brothers JA, de Ferranti SD, et al. Promotion of physical activity for children and adults with congenital heart disease: a scientific statement from the American Heart Association. *Circulation.* 2013;127(21):2147–2159.

[21] Ohuchi H, Miyamoto Y, Yamamoto M, et al. High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease. *Am Heart J.* 2009;158(1):30–39.

[22] Verhulst PJ, Depoortere I. Ghrelin's second life: from appetite stimulator to glucose regulator. *World J Gastroenterol.* 2012;18(25):3183–3195.

[23] Mao Y, Tokudome T, Kishimoto I. Ghrelin and blood pressure regulation. *Curr Hypertens Rep.* 2016;18(2):15.

[24] Khatib MN, Shankar A, Kirubakaran R, et al. Effect of ghrelin on mortality and cardiovascular outcomes in experimental rat and mice models of heart failure: a systematic review and meta-analysis. *PLoS One.* 2015;10(5):e0126697.

[25] Lilleness BM, Frishman WH. Ghrelin and the cardiovascular system. *Cardiol Rev.* 2016;24(6):288–297.

[26] Virdis A, Lerman LO, Regoli F, Ghiadoni L, Lerman A, Taddei S. Human ghrelin: a gastric hormone with cardiovascular properties. *Curr Pharm Des.* 2016;22(1):52–58.

[27] Balivada S, Pawar HN, Montgomery S, Kenney MJ. Effect of ghrelin on regulation of splenic sympathetic nerve discharge. *Auton Neurosci.* 2016;201:68–71.

[28] Zhang G, Yin X, Qi Y, et al. Ghrelin and cardiovascular diseases. *Curr Cardiol Rev.* 2010;6(1):62–70.

[29] Jamar G, Caranti DA, de Cassia Cesar H, Masquio DC, Bandoni DH, Pisani LP. Leptin as a cardiovascular risk marker in metabolically healthy obese: Hyperleptinemia in metabolically healthy obese. *Appetite.* 2017;108:477–482.

[30] Kaplan RC, Strizich G, Aneke-Nash C, et al. Insulinlike growth factor binding protein-1 and ghrelin predict health outcomes among older adults: Cardiovascular Health Study Cohort. *J Clin Endocrinol Metab.* 2017;102(1):267–278.

[31] Churm R, Davies JS, Stephens JW, Prior SL. Ghrelin function in human obesity and type 2 diabetes: a concise review. *Obes Rev.* 2017;18(2):140–148.

[32] Razzaghy-Azar M, Nourbakhsh M, Pourmoteabed A, Nourbakhsh M, Ilbeigi D, Khosravi M. An evaluation of acylated ghrelin and obestatin levels in childhood obesity and their association with insulin resistance, metabolic syndrome, and oxidative stress. *J Clin Med.* 2016;5(7):61.

[33] Jug B, Salobir BG, Vene N, Sebestjen M, Sabovic M, Keber I. Interleukin-6 is a stronger prognostic predictor than high-sensitive C-reactive protein in patients with chronic stable heart failure. *Heart Vessels.* 2009;24:271–276.

How to cite this article: Shiina Y, Murakami T, Matsumoto N, et al. Body composition, appetite-related hormones, adipocytokines, and heart failure in adult patients with congenital heart disease: A preliminary study. *Congenital Heart Disease.* 2018;13:79–84. https://doi.org/10.1111/chd.12555