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The Effect of Transcatheter Ventricular Septal Defect Closure on Children's Appetite, Hormones, and Growth

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ABSTRACT

Objective: Children with congenital heart disease are at risk for malnutrition. The aim of this study is to investigate the changes in appetite, nutritional hormones, and anthropometric measurements of patients before and after the transcatheter closure of ventricular septal defect.

Materials and Methods: Twenty patients whose defect was closed percutaneously and 26 children as healthy control group were included in the study. The anthropometric evaluation, symptoms, and blood tests of patient group were enrolled at initial and follow-up (1st and 6th month visit).

Results: The median age of patient and control group was 27 and 29.5 months, respectively. Lack of appetite, inadequate weight gain, and fatigue were higher in the patient group at initial visit (p=0.027, p=0.029, and p=0.033, respectively). At 1st month after closure, the rate of decrease in lack of appetite, inadequate weight gain, and fatigue were statistically significant (p=0.016, p=0.031, and p=0.031, respectively). After closure, increasing body mass index, its z score, and mid-upper arm circumference were statistically significant at 1st month (p=0.008, p=0.018, and p=0.018, respectively). Insulin-like growth factor-1, insulin-like growth factor binding protein-3, and their z scores were increased compared to the initial values at 1st month (p=0.001, p=0.033, p=0.002, and p=0.048, respectively). Ghrelin levels showed a linear decrease; leptin levels showed a linear increase for 6 months.

Conclusion: Children with ventricular septal defect are under the risk of malnutrition. One of the goals of our treatment plan for these children should be the prevention of malnutrition; therefore, the timing of interventional therapy should be before malnutrition develops

Keywords: Children, ghrelin, growth, leptin, transcatheter, ventricular septal defect

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INTRODUCTION

Ventricular septal defect (VSD) is one of the most frequent congenital cardiac abnormalities (1). Patients with congenital heart disease (CHD) are at risk of malnutrition by the reason of inadequate calorie intake, increased energy expenditure, frequent pulmonary infections, malabsorption, and accompanying genetic diseases (2). In particular, access to the food supply in developing countries, such as in ours, may be even more difficult (3). Ghrelin and leptin hormones that affect appetite have an important contribution on growth (4–9). In cases of decreased cardiac functions, plasma ghrelin levels are increased in patients with malnutrition due to negative energy balance (10, 11). Leptin secreted from adipocyte is required for the regulation of body weight. While growth hormone (GH) and basal cortisol levels are high in children with malnutrition, insulin-like growth factor-1(IGF-1) and leptin levels are found to be lower than healthy children (12). Besides, the effects of endocrinological factors such as GH, IGF-1 and 2, insulin-like growth factor binding proteins (IGFBP) on nutrition and growth were investigated in children with CHD. Most authors found decreased levels of these parameters (13, 14).

In our clinical experience, we observed that the nutritional status of children with VSD who underwent transcatheter closure improved significantly, and their growth was well affected. We aimed to investigate the effects of percutaneous VSD closure on appetite and growth and to evaluate changes in hormone levels.

MATERIALS and METHODS

This case-control study was carried out between 2017 July and 2018 February at the outpatient clinic of Erciyes University Children Hospital. Study approval was obtained from the ethics committee of Erciyes University (2017/347). Defects of 20 patients who met the indications were closed. These indications were as follows: (1) hemodynamically significant left to right shunt (Qp/Qs >1.5), (2) failure to thrive, (3) signs of heart failure, and (4) manifestation of left ventricular volume overload by echocardiography. Patients with a mean pulmonary arterial pressure (mPAP) ≥25 mmHg during angiography were defined as pulmonary hypertension (PHT) group.

Twenty-six healthy controls were included after obtaining voluntary informed consents. Patients with chromosomal abnormalities, additional systemic disease, and systemic infections were excluded.

Anthropometric evaluation: height for age (HFA), weight for age (WFA), body mass index (BMI) and their z scores, mid-upper arm circumference (MUAC), and triceps skinfold thickness (TSF) were recorded. These measurements for the patients aged under 60 months old were evaluated in accordance with World Health Organization (WHO) Anthro program, for the patients aged 6 to 18 years old were evaluated according to WHO Anthro Plus program which was established according to WHO standards. The anthropometric measurements were repeated at follow-up (1st and 6th month visit) in patient group.

Questions about the symptoms, inadequate weight gain, lack of appetite, frequency of illness (frequent respiratory tract infections were defined as ≥6 events per year requiring antimicrobial treatment), rate of breathing (using of accessory respiratory muscles), and fatigue were asked to all parents at initial in two groups. These questionnaires (15) and visual analog scale (for lack of appetite) were repeated in the patient group at 1st and 6th month visits. While asking questions about appetite to the families of children under the age of 6 years old, the items in the questionnaire that were appropriate for our patient group were used. Above 6 years old, the same procedure was performed by asking the patient himself/herself. The response of the questions was asked to be shown on the visual analog scale. The lack of appetite in patients was determined by applying a 100-mm-long visual analog scale (0–100 mm). The values close to "0" are composed of words and images expressing a decrease in the patient's appetite, and values close to "100" represent an increase in appetite. The cut off values for lack of appetite were determined based on under 50 mm. The answers to other questions were recorded as "Yes" or "No."

At initial, 6 ml of blood samples were taken after an average of 10 hours fasting. Four ml of the samples was centrifuged at 4000 rpm for 10 min in standard biochemistry tubes, and their serums were separated. On the same day, IGF-1 and IGFBP-3 were measured. A portion of separated serum was then stored at -80 °C to study leptin later. Two ml of venous blood sample was taken into tubes containing aprotinin. Plasma samples separated by centrifugation at 4000 rpm for ten min were stored until the time of ghrelin analysis.

Ghrelin and leptin were measured by ELISA method; IGF-1 was studied at cobas c 702 device at the biochemistry laboratory (Roche Diagnostics). IGFBP-3 was analyzed by IGFBP-3 Siemens kits in Immulite 2000 XPi device using chemiluminescence method. The laboratory tests were repeated at follow-up (1st and 6th month visit) in patient group.

Statistics

Data were analyzed using SPSS 22.0 computer software. Normality of distribution of numerical variables was evaluated. Numerical data were compared between the groups using Mann-Whitney U-test (not normally disturbed subjects) and sample t-test (normally disturbed subjects). Chi-square test was used for categorical variables. For repeated measures, analysis of variance (ANOVA) was used in dependent groups for numerical variables matching normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. Friedman test was used for numerical variables that did not conform to normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. We used Pearson and Spearman's rank difference correlation to examine correlation between hormone levels and anthropometric parameters. Statistical significance was determined according to value $p<0.05$.

Table 1. Baseline characteristics of ventricular septal defect group (n=20)

Age (month) median (min–max)	27 (2–171)
Gender, Female/male	13/7
VSD size (mm), Mean±SD	4.05±1.40
VSD type	
Perimembranous	19
Muscular	1
Qp/Qs, Mean±SD	2.06±0.55
PVR/SVR	0.22±0.09
Mean PAP (mmHg)	26.30±8.27
VSD occluder devices	
Amplatzer duct occluder 1	1
Amplatzer duct occluder 2	15
Oclutech duct occluder	3
Amplatzer muscular VSD occluder	1
NT-ProBNP (pg/mL) Median (min–max)	4002 (117–35000)

NT-ProBNP: N-terminal pro hormone brain natriuretic peptide; Qp/Qs: Pulmonary-systemic shunt ratio; PAP: Pulmonary arterial pressure; VSD: Ventricular septal defect; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance; Min: Minimum; Max: Maximum; SD: Standard deviation

RESULTS

Twenty (13 females and 7 males) patients with VSD, and 26 (16 females and 10 males) healthy controls were included. The age range of patients and controls were 2–171, median: 27 months; 3–187, median: 29.5 months, respectively. Defect sizes were ≤6 mm as measured by angiography (because the maximum waist diameter of the device is 6 mm). Only 1 patient had a muscular type VSD, while other patients had perimembranous type. Fourteen of these patients had a mPAP ≥25 mmHg during angiography. For closure, Amplatzer Duct Occluder (ADO) 2 device was used in 15 patients, Occlutech Duct Occluder device was used in 3 patients, ADO 1 device was used in 1 patient, and Amplatzer muscular VSD occluder device was used in 1 patient (Table 1).

The symptoms of two groups were evaluated. Lack of appetite, inadequate weight gain, and fatigue were significantly higher in the patient group at initial ($p=0.027$, $p=0.029$, and $p=0.033$, respectively). There was no statistically significant difference in the other symptoms at initial. At 1st month after closure therapy, all symptoms in the patient group decreased compared to initial. The rate of decrease in lack of appetite, inadequate weight gain, and fatigue were statistically significant ($p=0.016$, $p=0.031$, and $p=0.031$, respectively). The percentage of patients who had lack of appetite before VSD closure decreased from 45% to 10% at 1st month visit.

Two groups were evaluated in terms of anthropometric measurements. Body mass index, BMI z score, and MUAC value were

Table 2. Comparison of anthropometric measurements and laboratory tests between ventricular septal defect group (before closure) and control group

	Ventricular septal defect group (n=20)	Control group (n=26)	p
Weight for age z score, Mean±SD	-0.56±1.30	0.10±0.88	0.059
Height for age z score, Mean±SD	-0.24±1.35	-0.15±0.80	0.792
BMI, Median (min–max)	15.20 (12.80–25.60)	16.20 (14.01–22.70)	**0.029***
BMI z score, Mean±SD	-0.59±1.31	0.33±0.96	**0.012***
TSF, Mean±SD	11.06±4.77	12.51±4.86	0.314
MUAC (cm), Median (min–max)	15.25 (11.00–25.30)	17.00 (10.50–26.00)	**0.016***
Ghrelin (pg/mL), Mean±SD	1103.85±582.56	769.00±593.14	0.062
Leptin (pg/mL), Median (min–max)	1981.50 (778.00–29688.00)	3619.00 (996.00–38567.00)	**0.010***
IGF-1 (ng/mL), Median (min–max)	42.50 (15.00–462.00)	81.65 (20.50–233.00)	**0.027***
IGF-1 z score, Mean±SD	-1.48±1.15	-0.64±1.96	0.075
IGFBP-3 (ng/mL), Mean±SD	2829.00±1544.68	3633.00±1317.15	**0.018***
IGFBP-3 z score, Mean±SD	0.29±1.51	1.06±1.55	0.102

IGF-1: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor binding protein-3; MUAC: Mid-upper arm circumference; SD: Standard deviation. Min: Minimum; Max: Maximum. The p* values represent the comparison between the ventricular septal defect group (at initial) and the healthy control group. Student's t-test was used in independent groups for numerical variables matching normal distribution. Nonparametric tests (Mann-Whitney U-test) were used for numerical variables that do not confirm the normal distribution. *: P<0.05 was considered statistically significant

found statistically significantly lower in the patient group (Table 2, p=0.029, p=0.012, and p=0.016, respectively). All of other anthropometric values were lower compared to the controls, but there is no statistically significance. After closure, it was found that anthropometric measurements increased at the 1st month visit compared to the initial. Unfortunately, two patients did not come to their 6th month visit. Table 3 shows the initial, 1st month, and 6th month control data of 18 patients who came to their follow-up regularly. Especially the increase in BMI, BMI z score, and MUAC value was statistically significant at 1st month follow-up (p=0.008, p=0.018, and p=0.018, respectively). At the 6th month visit, there was a statistically significant increase in all anthropometric measurements compared to initial (Table 3).

When we compared the laboratory parameters (Table 2), leptin, IGF-1, and IGFBP-3 levels were statistically significantly low in the patient group at initial compared to control (p=0.010, p=0.027, and p=0.018, respectively). Ghrelin levels were higher, and IGF-1 z score and IGFBP-3 z score values were lower at the initial visit compared to control, but it was not statistically significant. At the 1st month visit, IGF-1 and IGFBP-3 levels and their z scores were statistically significantly increased, ghrelin levels statistically significantly decreased compared to the initial values, and ghrelin levels showed a linear decrease; leptin, IGF-1, IGF-1 z score, IGFBP-3, and IGFBP-3 z score levels showed a linear increase during for 6 months (Table 3).

The correlation of initial hormone levels and anthropometric measurements of patients with VSD were also evaluated (Table 4). A moderately negative correlation was found between ghrelin and BMI (r=-527, p=0.017). There was a moderately (r=0.531, p=0.016) correlation between IGF-1 level and WFA z score, and a strong positive correlation between IGF-1 level and BMI/ BMI z scores (r=0.802 p<0.001 and r=0.763, p<0.001, respectively). Insulin-like growth factor binding protein-3 levels correlated strong with BMI and BMI z scores like IGF-1 values (r=0.788, p<0.001 and r=0.651, p=0.002, respectively).

DISCUSSION

We investigated the symptoms, anthropometric measurements, hormonal levels, and their correlation data of the children before and after transcatheter VSD closure.

Symptoms and Anthropometric Evaluation

Rapid breathing, lack of appetite, frequency of illness, inadequate weight gain, and fatigue are frequently expected symptoms in patients with VSD who are hemodynamically significant such as having PHT. The frequency of lack of appetite, inadequate weight gain, and fatigue were statistically high in VSD group when compared to the control group. All the symptoms especially lack of appetite, fatigue, and inadequate weight gain decreased significantly at the 1st month visit after closure. Lack of appetite was described in 45% of our patients before the treatment. It was observed that this symptom gradually decreased (10%) in the follow-up after VSD closure. Decreasing inadequate weight gain could possibly be explained by reduced energy losses and increased appetite. Knop et al. (16) and Sharma et al. (17) observed an increase in exercise capacity, a decrease in the frequency of illness, and an improvement in weight gain after transcatheter atrial septal defect (ASD) closure. Similarly, we observed a significant increase in weight gain at the 12th month control in patients under 10 kg for whom we performed transcatheter ASD closure before (18). Symptoms associated with heart failure should be considered in the timing of VSD closure, and symptoms should be carefully questioned at each visit.

Growth retardation and malnutrition are expected findings in the children with CHD. We found that all of anthropometric values were lower in patient group compared to the healthy controls at initial time. Similar to our study, Vaidyanathan et al. (19) found that the preoperative anthropometric measurements of patients with VSD who underwent surgical repair were lower than the control. These findings can be explained by the hypermetabolic

Table 3. Comparison of anthropometric measurements and hormone levels of the ventricular septal defect group before and after closure†

Ventricular septal defect group (n=18)	Initial time	1st month	6th month	p
Weight for age z score, Mean±SD	-0.53±1.28	-0.05±1.30	0.22±1.18	**0.014**[a]
				0.284[*]
				0.832[**]
				<0.001[***]
Height for age z score, Mean±SD	-0.23±1.31	-0.22±1.18	-0.20±1.18	**0.022**[a]
				0.396[*]
				0.014[**]
				0.005[***]
BMI, Median (min–max)	14.95 (14.20–26.02)	15.55 (14.20–26.02)	16.38 (14.20–26.02)	**0.009**[b]
				0.008[*]
				<0.001[**]
				<0.001[***]
BMI z score, Mean±SD	-0.57±1.29	-0.29±1.24	0.04±1.14	**0.015**[a]
				0.018[*]
				0.006[**]
				<0.001[***]
TSF, Mean±SD	10.99±4.52	11.72±4.83	12.43±4.93	0.028[a]
				0.083[*]
				0.002[**]
				<0.001[***]
MUAC (cm), Median (min–max)	15.00 (13.00–26.75)	16.50 (13.00–26.75)	17.25 (13.00–26.75)	**0.003**[b]
				0.018[*]
				0.016[**]
				<0.001[***]
Ghrelin (pg/mL), Mean±SD	1108.76±581.35	870.64±488.42	654.00±243.55	**0.012**[a]
				0.029[*]
				0.066[**]
				0.003[***]
Leptin (pg/mL), Median (min–max)	1965.25 (966.00–31348.00)	2645.00 (966.00–31348.00)	3268.00 (966.00–31348.00)	0.105[b]
				0.102[*]
				0.198[**]
				0.063[***]
IGF-1 (ng/mL), Median (min–max)	36.75 (15.00–392.00)	55.50 (15.00–392.00)	68.85 (15.00–392.00)	**0.032**[b]
				0.001[*]
				0.237[**]
				<0.001[***]
IGF-1 z score, Mean±SD	-1.45±1.11	-0.73±1.09	-0.26±0.60	**0.011**[a]
				0.002[*]
				0.642[**]
				<0.001[***]
IGFBP-3 (ng/mL), Mean±SD	2812.00±1542.46	3115.87±1625.72	3299.50±1848.67	**0.037**[a]
				0.033[*]
				0.725[**]
				0.018[***]
IGFBP-3 z score, Mean±SD	0.28±1.47	0.81±1.21	1.18±1.37	**0.027**[a]
				0.048[*]
				0.267[**]
				0.009[***]

BMI: Body mass index; IGF-1: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor binding protein-3; MUAC: Mid-upper arm circumference; SD: Standard deviation; Min: Minimum; Max: Maximum; TSF: Triceps skinfold thickness; *: P value between initial and 1st month; **: P value between 1st and 6th month; ***: P value between initial and 6th month. †: The initial, 1st month, and 6th month control data of 18 patients who came to their follow-up regularly. For repeated measures, ANOVA[a] was used in dependent groups for numerical variables matching normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. Friedman[b] test was used for numerical variables that did not conform to normal distribution. After Bonferroni correction, pairwise comparisons were evaluated. P<0.05 was considered statistically significant

Table 4. Correlation of nutritional and growth hormones with anthropometric measurements in the ventricular septal defect group

n=20 (at initial)	Weight	Weight for age z score	Height	Height for age z score	BMI	BMI z score
Ghrelin	r=-0.385	r=-0.179	r=-0.393	r=0.089	r=-0.527	r=-0.320
	p=0.094**	p=0.450*	p=0.087*	p=0.709*	p=**0.017****	p=0.170*
Leptin	r=0.253	r=-0.086	r=0.281	r=-0.176	r=0.455	r=0.272
	p=0.283**	p=0.719**	p=0.229**	p=0.458**	p=**0.044****	p=0.246**
IGF-1	r=0.853	r=0.531	r=0.849	r=-0.110	r=0.802	r=0.763
	p<**0.001****	p=**0.016****	p<**0.001****	p=0.645**	p<**0.001****	p<**0.001****
IGF-1 z score	r=0.500	r=0.225	r=0.567	r=0.029	r=0.438	r=0.265
	p=**0.025****	p=0.341*	p=**0.009***	p=0.903*	p=0.053**	p=0.259*
IGFBP-3	r=0.600	r=0.335	r=0.593	r=-0.238	r=0.788	r=0.651
	p=**0.005****	p=0.148**	p=**0.006****	p=0.313**	p<**0.001****	p=**0.002****
IGFBP-3 z score	r=-0.096	r=-0.110	r=-0.082	r=-0.280	r=0.195	r=0.093
	p=0.686**	p=0.643*	p=0.730*	p=0.232*	p=0.410**	p=0.698*

BMI: Body mass index; IGF-1: Insulin-like growth factor-1; IGFBP-3: Insulin-like growth factor binding protein-3; *: Pearson correlation test; **: Spearman correlation test p<0.05 was considered statistically significant

state in lesions with left to right shunt. Lack of appetite and insufficient calorie intake seem to be the most important causes of growth retardation. The most common symptom in our patients was lack of appetite. This finding suggests that our patients consume insufficient calories, similar to the study of Varan et al. (20) Seventy percent of our patients had PHT. It is a known fact that PHT contributes to insufficient calorie intake. In the study of Blasquez et al. (21), it has been shown that insufficient calorie intake is higher especially in acyanotic patients with PHT compared to patients without PHT. It was observed that all anthropometric measurements of the patients increased at the 1st month visit. The increase in MUAC, BMI, and BMI z scores were statistically significant. This situation shows that the increase in weight gain is more positively affected in the early period compared to height recovery. However, a statistically significant increase was observed in all anthropometric measurements in the midterm period during 6th month follow-up. Similar to our study, Zhang et al. (2) and Vaidyanathan et al. (22) found more significant increase in weight gain in the first year compared to height in the patients who were operated for CHD. After the first year, height gain gets ahead weight gain. If we had followed our patients for a longer time, we might found similar results. In another study (19), they found that WFA z score and HFA z score showed improvement in 1-year follow-up in patients with VSD, but there was a significant improvement particularly mean WFA z score. The reasons of the improvement in anthropometric measurements may be the termination of the hypermetabolic process after transcatheter closure, the enhancing in food intake by increasing appetite, the stopping of anti-congestive treatments, and the disappearance of related symptoms due to the regression of PHT.

Hormonal Evaluation

There are various hormones effective on appetite and growth (GH, IGF-1, ghrelin, leptin, etc). The role of ghrelin in CHD and its effects on growth have always been an interesting subject of research in the field of cardiology. The relationship between the heart failure, growth, and ghrelin was firstly examined in 2010 by Kitamura et al (23). They reported high ghrelin levels in patients with heart failure. Yilmaz et al. (24) found that ghrelin levels were higher in the CHD group compared to control group. Therefore, they concluded that ghrelin might have an important role in metabolic balance such as growth retardation and malnutrition (11, 25). The orexigenic and cardioprotective effects of ghrelin and its positive effects on somatic growth have been shown in previous studies (26). In patients with CHD, especially with heart failure and PHT, ghrelin contributes to the reduction of mean pulmonary arterial pressure, improvement of left ventricular functions, and increasing cardiac output. The higher levels of ghrelin in our patients before treatment compared to the control can be explained by this compensatory mechanism. The effects of leptin on satiety and energy expenditure and the increase in adipose tissue mass by the hypothalamic pathway are well defined. Although low leptin levels have been shown in patient groups with protein energy malnutrition, there are different opinions in the literature on its contribution on malnutrition due to chronic heart failure (9). When we compare the other laboratory parameters, leptin, IGF-1, and IGFBP-3 levels were significantly low in the patient group at initial compared to control group. Similar to our results, Soliman et al. (27) found that basal IGF-1 levels in patients with VSD were statistically significantly lower than in the control group. In the study conducted by Surmeli-Onay et al. (28), IGF-1 and IGFBP-3 levels were found to be lower in the in patients with preoperative CHD group compared to the control group. This can be explained by the fact that the GH/IGF-1 axis, which is affected by the nutritional status, causes a decrease in fasting IGF-1 levels. Therefore, low food intake and decreased adipose tissue mass in the patient group may explain the low level of IGF-1/IGFBP-3 levels and leptin. In our study, the decrease of ghrelin level and the increase in IGF-1 and IGFBP-3 levels at the postinterventional 1st month visit may be due to the increment in appetite of the patients and related increase in food intake.

Similar to our study, Surmeli-Onay et al. (28) found that nutritional status improved after the operation, and there was a statistically significant increase in IGF levels and anthropometric measurements.

It was observed that these changes continued at the 6th month. These results may indicate that anabolism precedes catabolism. The linear increase in leptin levels can also be explained by the increase in adipose tissue. An increase in MUAC was also observed as an objective indicator of the adipose tissue mass.

The Correlations

We have observed that the ones whose BMI and BMI z score values were low, ghrelin levels were found significantly high; leptin, IGF-1, and IGFBP-3 levels were found significantly low ($p<0.05$). Yilmaz et al. (24) found that ghrelin levels were inversely correlated with BMI in children with CHD. In another study (25), an inverse correlation was shown between ghrelin and WFA z score. In particular, Li et al. (26) have described a marked increase in ghrelin levels depending on the degree of PHT and heart failure. According to these results, ghrelin seems to be a biomarker that can be used for the prognosis and timing of interventional treatment of patients with CHD at risk of malnutrition. IGF-1 levels were also significantly lower in patients with low WFA and BMI z scores. It has been described in previous studies (29) that insufficient food intake and fasting increase the GH level and cause IGF-1 suppression. In the post-treatment follow-up, we detected an increase in the appetite and IGF-1 levels of the patients and therefore an increase in anthropometric measurements. Initially, IGF-1 appears to be a variable that is affected by nutritional status rather than the cause of malnutrition. In a study by Hallioglu et al. (9), a significant positive correlation was found between BMI and leptin levels of the patients, which is similar to our study. This correlation is explained by the positive relation of leptin with the adipose tissue mass. Briefly, transcatheter VSD closure is important because of its improvement in symptoms, positive effects on hormones that affect appetite and growth, as a result of its contribution to somatic growth.

Limitations of the Study

First limitation is that the data of a single center with a relatively limited number of patients restricting the generalizability of our results. Second limitation is the broad age range of the patients. It was so wide that some patients were infants and some were adolescents. Therefore, calculating the calorie intake, especially the ones who have breast feeding, was impossible. Third limitation is symptoms of patients were asked to parents which relied on their observations which sometimes can be especially subjective.

CONCLUSION

In summary, children with CHD are under the risk for malnutrition. The primary prevention of malnutrition should be the goal of our treatment plan of these children; the timing of the interventional treatment is therefore critical and has to be before the development of malnutrition. There are many studies on the relationship between CHD, malnutrition, and growth. However, this study is the most comprehensive one in the literature including the evaluation of the appetite, growth, appetite-related hormones, and anthropometric measurements all together.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 16.06.2017, number: 2017/347).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NN, AB, ÖP, NH, OT; Design – NN, ÖP, OT; Supervision – NN, ÖP, AB, NH; Resource – OT, ÇV, DBK, SS; Materials – OT, ÇV, DBK, NH; Data Collection and/or Processing – OT, ÇV, DBK, SS; Analysis and/or Interpretation – OT, SS; Literature Search – OT, ÖP; Writing – OT, ÖP; Critical Reviews – NN, ÖP, AB, NH.

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