DOI: 10.59213/TP.2023.55265
Trends in Pediatrics 2023;4(1):6-13

Original Article

The effects of transcatheter atrial septal defect closure on appetite, nutritional hormones and growth in children

Onur Taşcı[1], **Özge Pamukçu**[1], **Nazmi Narin**[1], **Didem Barlak Keti**[2], **Süleyman Sunkak**[1], **Çağdaş Vural**[1], **Ali Baykan**[1]

[1]Erciyes University, School of Medicine, Department of Pediatric Cardiology, Kayseri, Türkiye
[2]Erciyes University, School of Medicine, Department of Biochemistry, Kayseri, Türkiye

Cite this article as: Taşcı O, Pamukçu Ö, Narin N, et al. The effects of transcatheter atrial septal defect closure on appetite, nutritional hormones and growth in children. Trends in Pediatrics 2023;4(1):6-13.

ABSTRACT

Objective: Children with congenital heart disease are at risk of malnutrition due to inadequate calorie intake, increased energy expenditure, pulmonary infections, and malabsorption. The aim of this study was to investigate the changes in appetite, nutritional hormones, and anthropometric measurements before and after the transcatheter closure of the atrial septal defect.

Method: The study included 27 patients whose atrial septal defect closed percutaneously and 25 children as a healthy control group. The initial symptoms, anthropometric measurements, and laboratory tests were recorded initially, and 1 month and 6 months after the closure.

Results: The mean age of patients and control group were 88.29 ± 58.25 months, 86.52 ± 55.81 months respectively. At the 1st month after the closure, all the symptoms in the patient group decreased compared to the initial visit except rapid breathing (p <0.05). The percentage of patients who had a lack of appetite decreased from 45% to 5% at the 1st month visit. After the closure, the increase in weight for age, body mass index, and z-score were statistically significant at the 1st and 6th months (p <0.05). Insulin-like growth factor-1 levels increased compared to the initial values at the 1st month (p =0.016). A linear decrease in ghrelin levels and a linear increase in leptin levels were observed in the atrial septal defect group during the 6-month follow-up after the closure.

Conclusion: Children with atrial septal defect are at the risk of malnutrition. The primary prevention of malnutrition should be the goal of our treatment plan for these children; the timing of the interventional treatment is critical and has to be before the development of malnutrition.

Keywords: Atrial septal defect, children, ghrelin, growth, leptin, nutrition

INTRODUCTION

Atrial septal defects (ASD) are among the most common congenital heart diseases (CHD).[1] ASDs with a significant left-to-right shunt may increase the risk of malnutrition by leading to more frequent respiratory infections and hospitalizations.[2]

Ghrelin and leptin hormones, which affect appetite, have an important contribution to growth.[1,3-6] Ghrelin's function is to stimulate growth hormone secretagogue activity.[3-7] Eventually, ghrelin may signal the conservation of energy to prevent further weight loss and restore usual body weight by increasing food intake and reducing the use of fat.[8-10] Leptin is a peptide encoded by the obese gene.[11] Research on leptin has shown that leptin has effects that decrease food intake and increase adipose tissue. Besides, the effects of endocrinological factors such as growth hormone, insulin-like growth factors-1/2 (IGF-1/IGF-2), and insulin-like growth factors binding proteins on

Correspondence: Onur Taşcı **E-mail:** dr_onurtasci@hotmail.com
Received: 06.07.2022 **Accepted:** 19.12.2022

growth and nutrition were investigated in children with CHD. Most authors found the levels of these parameters to be low in these children.[12,13]

ASD closure is performed by transcatheter or surgical procedures in the presence of a significant left-to-right shunt. Since it is a less invasive method, transcatheter ASD closure should be preferred in cases suitable for treatment. It is a fact that the nutritional status and the growth of children improve significantly after the transcatheter closure. In this study, we aimed to demonstrate the effects of the transcatheter ASD closure treatment on appetite and growth through the changes in hormone levels such as ghrelin, leptin, IGF-1, and insulin-like growth factor binding protein-3 (IGFBP-3).

MATERIAL AND METHODS

Subjects

This case-control study was carried out at the outpatient clinic of Erciyes University Children's Hospital. Study approval was obtained from the ethics committee of Erciyes University (2017/347). Twenty-seven patients with ASD were included in the study. The main inclusion criteria of the patients were as follows: Secundum type ASD (diagnosed by echocardiography), $Qp/Qs \geq 1.5$ (calculated during angiography), defects larger than 8 mm with sufficient rims.

Twenty-five healthy control children without malnutrition were included in the study after obtaining voluntary informed consent. Patients with chromosomal abnormalities, systemic diseases, and systemic infections were excluded from the study. We evaluated data of 20 patients, who came for regular follow-up in the 6th month. Unfortunately, seven of the patients did not come for their 6th month visit.

Measurements

Anthropometric measurements of patients: weight for age (WFA), height for age (HFA), body mass index (BMI) and their z-scores were recorded at the initial visit before the closure treatment, and at 1st and 6th month visits. These measurements were evaluated according to the World Health Organization (WHO) Anthro program for patients aged under 60 months, and according to WHO Anthro Plus program for patients aged 6 to 18 years were evaluated, which was established according to the WHO standards (https://www.who.int/tools/child-growth-standards/software).

Questionnaires

Questions about the symptoms, inadequate weight gain, lack of appetite, frequency of infection (frequent respiratory tract infections were defined as ≥ 6 events per year requiring antimicrobial treatment), respiration rate (using accessory respiratory muscles), fatigue were asked to all parents in two groups at initial visit. These questionnaires[14] and visual analogue scale (for lack of appetite) were repeated in the patient group at the 1st and 6th month visits. When asking questions about appetite to the families of children under the age of 6, the items in the questionnaire that were appropriate for our patient group were used. For children older than 6 years, the same procedure was performed by asking the patient himself/herself. The answer to the questions was asked to be shown on the visual analogue scale. The patient's lack of appetite was determined by applying a 100 mm long visual analogue scale (0-100 mm). The values close to '0' are composed of words and images expressing a decrease in the patient's appetite, while values close to '100' represent an increase in appetite. The cut-off value for lack of appetite was determined to be less than 50 mm. Answers to other questions were recorded as 'Yes' or 'No'.

Blood sampling

During the initial evaluation, approximately 6 mL of venous blood samples were collected from the patients between 9:00 a.m. and 10:00 a.m. after an average of 10 hours of fasting before the closure treatment. Four mL of the samples were centrifuged at 4000 rpm for 10 minutes in standard biochemistry tubes and their serums were separated. On the same day, IGF-1 and IGFBP-3 were measured at the central laboratory. A portion of the 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 10 min were stored until the time of ghrelin analysis.

Ghrelin Human ELISA kit (Invitrogen, Catalog Number: BMS2192, USA) and Leptin Human ELISA kit (Invitrogen, Catalog Number: KAC2281, USA) were measured by the ELISA method. The lower limit of detection is 15.6 pg/mL for each hormone. IGF-1 was studied at cobas c 702 device at the Central Biochemistry Laboratory (Roche Diagnostics). IGFBP-3 was analyzed by IGFBP-3 Siemens kits in Immulite 2000 XPi device using the chemiluminescence method. We calculated IGF-1 and IGFBP-3 z-scores based on age- and gender-specific reference values for healthy Turkish children.[15] The laboratory tests of the patients were repeated at the 1st and 6th month visits.

Statistics

Data were analyzed using SPSS 22.0 computer software. The normality of the distribution of numerical variables was evaluated. Numerical data were compared between the groups using the Mann-Whitney U test (for not normally disturbed data) and sample t-test (for normally disturbed data). The chi-square test was used for categorical variables. We studied the correlation of the measured levels of individual hormones with anthropometric parameters, including z-scores of weight and height. For repeated measures, 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 the correlation between hormone levels and anthropometric parameters. Statistical significance was determined according to a value of $p<0.05$.

RESULTS

Baseline characteristics

Twenty-seven (14 females, 13 males) patients with ASD fulfilling the inclusion criteria, and 25 (14 females, 11 males) healthy controls, who don't have any chronic diseases but have normal echocardiography findings, were included in the study. The age range of patients and healthy controls were 12-197 months (mean 88.29 ± 58.25 months) and 10-187 months (mean 86.52 ± 55.81 months), respectively. The baseline characteristics of the ASD group were summarized in Table 1. The mean size of the ASDs calculated by balloon sizing during angiography was 17.63 ± 5.48 mm. The patient group and control group were evaluated in terms of anthropometric measurements and hormone levels (Table 2). Ghrelin and leptin levels were higher, IGF-1 z-score and IGFBP-3 z-score values were lower at the initial visit compared to the control group, but there was no statistical significance. The WFA z-score, BMI, and BMI z-score were lower in the ASD group compared to the control group, but there was no statistical significance. Before the treatment, there were 9 patients (out of 20 patients) with an appetite score below 50. The mean appetite score was found to be 52.15±15.83 at initial visit.

Table 1. Baseline characteristics of atrial septal defect group

n=27	(%)
Age (month)	88.29 ± 58.25
Gender (female/ male)	14 (%52)/ 13 (%48)
ASD size (mm)	17.63 ± 5.48
Qp/ Qs	2.20 ± 0.66
PVR/SVR	0.14 ± 0.09
mean PAP (mmHg)	20.77 ± 5.50
ASD occluder devices:	
-Amplatzer septal occluder	10 (%37)
-Memopart septal occluder	6 (%22)
-Occlutech septal occluder	11 (%41)

ASD: Atrial septal defect, Qp/Qs: Pulmonary-systemic shunt ratio, PAP: Pulmonary arterial pressure, PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance

First month results

At the 1st month visit after the closure, all symptoms decreased in the patient group compared to the initial visit. The percentage of patients who had a lack of appetite decreased from 45% to 5% at the 1st month visit (p= 0.002). The mean appetite score was calculated to be 68.95±11.90. Only 1 patient with an appetite score below 50 was detected at the 1st month follow-up after ASD closure. The decrease in fatigue, inadequate weight gain, and frequency of infection was statistically significant (<0.001, 0.001, and 0.008 respectively). Nevertheless, the decrease in rapid breathing was not statistically significant.

After the closure, anthropometric measurements were found to be increased at the 1st month visit with a more prominent acceleration compared to the initial values (Table 3). The increase in WFA z-score, BMI, and BMI z-score was statistically significant ($p<0.05$).

At the 1st month visit, IGF-1 levels were significantly increased compared to the initial values (Table 3, p = 0.016). Ghrelin levels were found to be decreased, and leptin, IGF-1 z-score, IGFBP-3, and IGFBP-3 z-score levels were found to be increased at the 1st month visit compared to the initial visit. However, these differences were not statistically significant.

Sixth month results

At the 6th month visit after the closure, all the symptoms in the patient group decreased compared to the initial visit ($p<0.05$). The mean appetite score was calculated to be 70.95±12.50. At the 6th month follow-up after treatment, only 1 patient with an appetite score below 50 was detected, similar to the 1st month control. We found a statistically significant increase in WFA z-score, BMI, and BMI z-score at the 6th month visit when we compared to initial visit (0.05 vs 0.31 p <0.001, 17.80 vs 18.55 p=0.001, 0.17 vs 0.33 p=0.002, respectively). Laboratory tests

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

	Atrial septal defect group (n=27)	Control group (n=25)	p value*
Weight for age z score	0.07 ± 1.37	0.10 ± 0.90	0.941
Height for age z score	-0.08 ± 1.10	-0.11 ± 0.79	0.919
Body mass index	18.94 ± 3.88	20.42 ± 2.25	0.236
Body mass index z score	0.18 ± 1.36	0.21 ± 1.29	0.158
Ghrelin (pg/mL)	636.00 (144.00-2208.00)	580.00 (212.00-2788.00)	0.603
Leptin (pg/mL)	4600.00 (441.00-55500.00)	3488.00 (996.00-38567.00)	0.862
IGF-1 (ng/mL)	95.50 (19.10-401.00)	82.00 (20.50-233.00)	0.680
IGF-1 z score	-0.98 ± 1.72	-0.59 ± 1.98	0.454
IGFBP-3 (ng/mL)	3877.77 ± 1850.70	3692.00 ± 1308.87	0.676
IGFBP-3 z score	0.42 ± 1.03	1.06 ± 1.59	0.097

IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3, Student's t-test was used in independent groups for numerical variables matching normal distribution. Non-parametric tests (Mann-Whitney U test) were used for numerical variables that do not confirm the normal distribution. p* <0.05 was considered statistically significant.

showed an increase in IGF-1 z-score at the 6th month visit when compared to the initial visit. Ghrelin levels showed a linear decrease; leptin levels showed an increase in the 6th month. These changes were not statistically significant.

Correlations

The correlation between initial hormone levels and anthropometric measurements of ASD patients was also evaluated in Table 4. The leptin, IGF-1 and IGFBP-3 levels, and IGF-1 z-scores were positively correlated with WFA and HFA. Similarly, there was a positive relationship between the IGFBP-3 z-score and WFA. The WFA z-scores were also weakly positively correlated with IGF-1 and strongly positively correlated with leptin levels. Ghrelin levels were strongly negatively correlated with WFA and HFA, and these results were statistically significant.

DISCUSSION

In this study, we investigated the symptoms, anthropometric measurements, hormonal levels, and their correlations in children before and after transcatheter ASD closure.

1. Symptoms and anthropometric evaluation

Rapid breathing, lack of appetite, frequency of infection, inadequate weight gain, and fatigue are frequently expected symptoms in patients with ASD that are hemodynamically significant. All the symptoms except rapid breathing decreased statistically significantly at the 1st month visit after the closure. These positive effects may be explained by changes in the morphology of the right ventricle that affects the left ventricle and the cardiac output. Therefore, pulmonary arterial blood flow and pulmonary congestion are reduced. A significant increase in appetite and food intake, a decrease in the frequency of infection, and a decrease in catabolism have been observed with ASD closure. Similar to our study, Knop et al.[16] and Sharma et al.[17] observed an increase in exercise capacity, a decrease in the frequency of infection, and an improvement in weight gain after transcatheter ASD closure. Narin et al.[18] evaluated 44 infants who underwent percutaneous ASD closure treatment with symptomatic ASD indication and they reported that 17 of the patients had a WFA z-score below -2 before ASD closure, their WFA z-scores had increased significantly after 12 months of follow-up, and only 3 patients had a WFA z-score below -2. Symptoms associated with heart failure should be considered in the timing of ASD closure and symptoms should be carefully evaluated at each visit.

Growth retardation and malnutrition are expected findings in children with CHD and have been reported since 1962. Mehrizi et al.[19] were the first to report it. Most patients with CHD present with growth retardation and malnutrition due to multifactorial reasons. Many patients with CHD have nutritional difficulties with decreased energy intake and increased energy requirements, provoking growth retardation. Malnutrition is not

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

Atrial septal defect group	Initial time n=20	1st month n=20	6th month n=20	p value
Weight for age z score	0.05 ± 1.02	0.33 ± 1.34	0.31 ± 1.37	**0.008**[a] **<0.001*** 0.498† **<0.001‡**
Height for age z score	-0.11 ± 1.13	0.02 ± 1.22	0.06 ± 1.14	0.144[a] 0.068* 0.309† 0.054‡
Body mass index	17.80 ± 4.21	18.31 ± 4.00	18.55 ± 4.03	**0.015**[a] **0.013*** 0.389† **0.001‡**
Body mass index z score	0.17 ± 1.48	0.19 ± 1.33	0.33 ± 1.16	**0.012**[a] **0.009*** 0.086† **0.002‡**
Ghrelin (pg/mL)	763.00 (144.00-2208.00)	695.00 (192.00-1916.00)	436.00 (128.00-1436.00)	0.095[b] 0.102* 0.087† 0.061‡
Leptin (pg/mL)	3840.00 (441.00-55500.00)	6100.00 (690.00-59800)	9056.00 (447.00-51800.00)	0.198[b] 0.425* 0.126† 0.091‡
IGF-1 (ng/mL)	87.00 (19.10-401.00)	108.00 (15.00-429.00)	103.10 (26.20-539.00)	**0.027**[b] **0.016*** 0.258† 0.115‡
IGF-1 z score	-1.02 ± 1.66	-0.68 ± 1.53	-0.55 ± 1.47	0.225[a] 0.340* 0.668† 0.071‡
IGFBP-3 (ng/mL)	3720.48 ± 1620.30	4056.62 ± 1798.86	4040.50 ± 1845.74	0.569[a] 0.358* 0.843† 0.625‡
IGFBP-3 z score	0.40 ± 1.01	0.58 ± 0.94	0.43 ± 0.91	0.481[a] 0.287* 0.410† 0.793‡

IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3
*: p value between initial and 1st month, †: p value between 1st and 6th month, ‡: p value between initial and 6th month.
Table 3 shows the initial, 1st and 6th months control data of 20 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 atrial septal defect group

n = 27 (initial levels)	**Weight for age**	**Weight for age z score**	**Height for age**	**Height for age z score**
Ghrelin	r = -0.683 **p < 0.001†**	r = -0.336 p = 0.087†	r = -0.704 **p < 0.001†**	r = -0.091 p = 0.651†
Leptin	r = 0.809 **p < 0.001†**	r = 0.647 **p < 0.001†**	r = 0.716 **p < 0.001†**	r=0.217 p=0.277†
IGF-1	r = 0.765 **p < 0.001†**	r = 0.386 **p = 0.047†**	r = 0.766 **p < 0.001†**	r = 0.154 p = 0.443†
IGF-1 z score	r = 0.582 **p = 0.001***	r = 0.310 p = 0.115*	r = 0.402 **p = 0.038***	r = 0.071 p = 0.725*
IGFBP-3	r = 0.792 **p < 0.001***	r = 0.293 p = 0.138*	r = 0.760 **p < 0.001***	r = 0.025 p = 0.903*
IGFBP-3 z score	r = 0.975 **p = 0.006***	r = 0.025 p = 0.902*	r = -0.102 p = 0.612*	r = -0.102 p = 0.612*

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

expected in the early period of ASD. The characteristics of the acyanotic lesions such as coexisting pulmonary hypertension, failure to detect calorie intake, and use of medication due to heart failure may be an additive factor for malnutrition. Therefore, malnutrition is an expected finding in patients with hemodynamically significant ASD. Planning the most appropriate time for the defect closure is critical and it should be done before the onset of malnutrition.

Anthropometric measurements are substantial markers in investigating growth and the nutritional status.[8] Consequently, improvement in the weight status is the simple prominent data for the evaluation of growth. In our study, although not statistically significant, WFA z-score, BMI and BMI z-score values of patients were low compared to the control group. These results indicated that the time of closure in our patient group was well arranged that WFA z-score, BMI, and BMI z-score values had not been severely affected yet. Yilmaz et al.[20] found that the mean body mass index (BMI), WFA, and HFA of the control group were significantly higher compared to the CHD group in their study. This difference may be due to the variations in the study group. We observed a statistically significant increase in the WFA z-score, BMI, and BMI z-score at the 1st and 6th month follow-up compared to the initial visit measurement. This shows how effective transcatheter closure therapy is in the early phase and how it improves weight gain. This may be explained by the increased appetite of our patients after the closure. Similar to our study, Blasquez et al.[21] noted that the most important cause of insufficient growth in CHD was inadequate calorie intake. Soliman et al.[22] studied the linear growth of surgically treated children with CHD during the pre-operative and post-operative periods. They found a significant increase in HFA z-score and BMI z-score 1 year after the operation compared to the preoperative period. We also found an increase in the HFA z-score in our study, but it was not statistically significant. If we had followed-up the patients for 1 year instead of 6 months, maybe we might have obtained similar results. In our study, positive changes were observed in anthropometric measurements, especially in WFA, BMI and their z-scores at each visit. Thus, the cycle of negative metabolic balance can be considered broken.

2. Biochemical and hormonal evaluation

There are several hormones affecting growth such as growth hormone, 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 among heart failure, growth, and ghrelin was first examined in 2010 by Kitamura et al.[6] They reported high ghrelin levels in patients with heart failure. Yilmaz et al.[20] found that ghrelin levels were higher in the CHD group compared to the control group. Therefore, they concluded that ghrelin may have an important role in metabolic balance such as growth retardation and malnutrition.[8,10] In our study, no statistically significant differences were found in ghrelin compared to the control group. Nevertheless, ghrelin levels of 20 patients with ASD were found to be lower at each visit compared to the previous value. This decrease in ghrelin levels may be associated with increased appetite and food intake after ASD closure.

In this study, no statistically significant differences were found in leptin levels compared to the control group at initial visit. After transcatheter closure, leptin levels were increased gradually at the 1st and 6th month visits, compared to the initial visit. However, it was not statistically significant. This increase can be explained by an increase in fat tissue as a result of weight gain.

In our study, no significant differences were found in IGF-1 and IGFBP-3 values at the initial visit. In the 1st month, IGF-1 levels significantly increased compared to the initial visit. In the study of Surmeli-Onay et al.[23], the preoperative IGF-1 and IGFBP-3 levels were found to be higher in the control group compared to the children with CHD. They noted that IGF-1 and IGFBP-3 were important markers of nutrition. Similar to our study, Soliman et al.[22] also showed a significant increase in IGF-1 and its z-score values 1 year after the operation compared to the preoperative period. These findings support the view that the attained growth spurt after treatment is mediated by increased IGF-1 synthesis. So IGF-1 and IGFBP-3 values can be largely reversible after a nutritional intervention, these values are on an increasing trend in patients with weight gain after ASD closure. In our study, it is noteworthy that the rate of increase in IGF-1 and IGFBP-3 levels and related anthropometric measurements are more significant in the early period of the treatment, becoming evident by the 1st month. Parallel to this, the accompanying symptoms seemed to be resolved in a short time. These results may be explained by the increase in appetite and weight after ASD closure.

3. The correlations

We observed that ghrelin levels were low; leptin and IGF-1 levels and IGF-1 z-score were high in the patients whose weight and height for the age group were high. In a study[8], a negative correlation was found between ghrelin level and WFA z-score. Yilmaz et al.[20] found that ghrelin levels were negatively correlated with BMI. These results suggest that ghrelin is one of the most potent orexigenic and adipogenic agents that increase to compensate for weight loss. In a study by Hallioglu et al.[24] a significant positive correlation was found between the BMI and leptin levels of the patients. This correlation is explained by the positive relationship between leptin and the adipose tissue mass.

CONCLUSION

In summary, children with CHD are often at risk of malnutrition. The primary prevention of malnutrition should be the goal of our treatment plan for these children; the timing of the interventional treatment is critical and has to be before the development of malnutrition, which has a positive effect on hormonal status. Briefly, transcatheter ASD closure is important because it improves the symptoms, has positive effects on hormones that affect appetite and growth, and as a result, it contributes to somatic growth.

LIMITATIONS

The most important limitation of our study is that the study has the data from a single center with a relatively limited number of patients which restricts the generalizability of our results. The second limitation was the wide age range of the patients. It was so wide that some patients were infants and some were adolescents. Therefore, calculating the calorie intake specifically for those who are breastfed was impossible. The third limitation was that the symptoms of the patients were asked to their parents, which relied on their observations and can be subjective. The last limitation was that seven of the patients did not come to their 6th month visit.

Ethical approval

This study has been approved by the Erciyes University Clinical Research Ethics Committee (approval date 16/06/2017, number 2017/347). Informed consent forms were obtained from parents.

Author contribution

Surgical and Medical Practices: OT, ÖP, NN, AB; Concept: OT, ÖP; Design: NN, DBK; Data Collection or Processing: OT, DBK, SS, ÇV; Analysis or Interpretation: OT, SS, ÇV; Literature Search: OT, ÖP, NN; Writing: OT, ÖP. All authors reviewed the results and approved the final version of the article.

Source of funding

This study was funded by the Scientific Research Projects Unit of Erciyes University (Project no: 7645).

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402:656-60. **[Crossref]**
2. Kimura D, McNamara IF, Wang J, Fowke JH, West AN, Philip R. Pulmonary hypertension during respiratory syncytial virus bronchiolitis: a risk factor for severity of illness. Cardiol Young. 2019;29:615-9. **[Crossref]**
3. Date Y, Kojima M, Hosoda H, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology. 2000;141:4255-61. **[Crossref]**

4. Wren AM, Small CJ, Ward HL, et al. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. Endocrinology. 2000;141:4325-8. [Crossref]

5. Mondal MS, Date Y, Yamaguchi H, et al. Identification of ghrelin and its receptor in neurons of the rat arcuate nucleus. Regul Pept. 2005;126:55-9. [Crossref]

6. 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;52:358-61. [Crossref]

7. Toshinai K, Date Y, Murakami N, et al. Ghrelin-induced food intake is mediated via the orexin pathway. Endocrinology. 2003;144:1506-12. [Crossref]

8. Kandil ME, Elwan A, Hussein Y, Kandeel W, Rasheed M. Ghrelin levels in children with congenital heart disease. J Trop Pediatr. 2009;55:307-12. [Crossref]

9. Nagaya N, Kojima M, Uematsu M, et al. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. Am J Physiol Regul Integr Comp Physiol. 2001;280:R1483-7. [Crossref]

10. Nagaya N, Uematsu M, Kojima M, et al. Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. Circulation. 2001;104:2034-8. [Crossref]

11. Toth MJ, Gottlieb SS, Fisher ML, Ryan AS, Nicklas BJ, Poehlman ET. Plasma leptin concentrations and energy expenditure in heart failure patients. Metabolism. 1997;46:450-3. [Crossref]

12. Barton JS, Hindmarsh PC, Preece MA. Serum insulin-like growth factor 1 in congenital heart disease. Arch Dis Child. 1996;75:162-3. [Crossref]

13. Kerpel-Fronius E, Kiss S, Kardos G, Gács G. Somatomedin and growth hormone in patients with retarded growth and atrophy due to congenital heart disease or malabsorption. Monatsschr Kinderheilkd (1902). 1977;125:783-6.

14. Yılmaz R, Esmeray H, Erkorkmaz Ü. Adaptation study of the Turkish Children's Eating Behavior Questionnaire. Alpha Psychiatry. 2011;12:287-94.

15. Guven B, Can M, Mungan G, Acikgoz S. Reference values for serum levels of insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) in the West Black Sea region of Turkey. Scand J Clin Lab Invest. 2013;73:135-40. [Crossref]

16. Knop MT, Białkowski J, Szkutnik M, et al. Transcatheter closure of atrial septal defects type 2 in children under three years of age. Kardiol Pol. 2018;76:1257-62. [Crossref]

17. Sharma B, Pinto R, Dalvi B. Transcatheter closure of atrial septal defect in symptomatic children weighing ≤10 kg: Addressing unanswered issues from a decade of experience. Ann Pediatr Cardiol. 2020;13:4-10. [Crossref]

18. Narin N, Baspinar O, Pamukcu O, et al. Percutaneous ASD closure of children weighing less than 10 kg. Acta Cardiol. 2020;75:631-6. [Crossref]

19. Mehrizi A, Drash A. Growth disturbance in congenital heart disease. J Pediatr. 1962;61:418-29. [Crossref]

20. Yilmaz E, Ustundag B, Sen Y, Akarsu S, Citak 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. [Crossref]

21. Blasquez A, Clouzeau H, Fayon M, et al. Evaluation of nutritional status and support in children with congenital heart disease. Eur J Clin Nutr. 2016;70:528-31. [Crossref]

22. Soliman AT, Elawwa A, Khella A, Saeed S, Yassin H. Linear growth in relation to the circulating concentration of insulin-like growth factor-I in young children with acyanotic congenital heart disease with left to right shunts before versus after surgical intervention. Indian J Endocrinol Metab. 2012;16:791-5. [Crossref]

23. Surmeli-Onay O, Cindik N, Tulgar Kinik S, Ozkan S, Bayraktar N, Tokel K. The effect of corrective surgery on serum IGF-1, IGFBP-3 levels and growth in children with congenital heart disease. J Pediatr Endocrinol Metab. 2011;24:483-7. [Crossref]

24. Hallioglu O, Alehan D, Kandemir N. Plasma leptin levels in children with cyanotic and acyanotic congenital heart disease and correlations with growth parameters. Int J Cardiol. 2003;92:93-7. [Crossref]