Evaluation of the Insulin like growth factor (IGF) and thyroid function in patients with cyanotic congenital heart disease

A.M.Shaheen[1], T.M.khattab[1], E.G.Amer[1], S.M.fayed[2] and M.F.Ebrahim[1]
[1]Pediatrics, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[2]clinical pathology, Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
E-mail:mezom518@gmail.com

Abstract

Background: Children with congenital heart disease (CHD) have been reported to show significant growth retardation both prenataly and postnatally. Cyanotic CHDs in children commonly cause more pronounced growth retardation in comparison with acyanotic CHDs. Chronic hypoxemia has been suggested as the cause of poor growth in these patients. Interruption of GH / IGF-1 axis decreased appetite due to hypoxemia leading to insufficient food intake and increased energy consumption may be a cause of the increased growth failure in patients with cyanotic CHDs. The relationship between cyanotic CHDs, malnutrition and growth retardation is well documented. The aim of this study was to investigate the effects of cyanosis and chronic hypoxia on plasma level of insulin-like growth factor-1 and to examine the prevalence of elevated TSH in the patients with cyanotic congenital heart diseases. Methods: This study had two groups; Cases group: included 30 patients with cyanotic CHD, who admitted to the Pediatric Cardiology Outpatient Clinic of benha university hospital, Another 35 patients, who admitted to the Pediatric Outpatient Clinic with several complaints, including headache or abdominal discomfort or for scheduled vaccination visits were included in the control group. Results: The mean age in the studied cases was 24.1±13.8 months, ranged from 3-60 months, and consists of 18 males and 12 females, the mean age in the control group was 21.8±12.6 months, ranged from 3-60 months, and consists of 18 males and 17 females. There was no statistical difference between cases and control groups regarding age, or sex. The most frequent diagnosis in our study, was TOF (46.7%), then TGA (40%), All the studied cases had history of previous hospital admission, and 40% of cases had history of previous PICU admission.There was statistical significant difference between studied groups regarding anthropometric measures, as weight, height and BMI centiles were statistically lower in cases group, while there was no significant difference between groups regarding head circumference. There was Hb and WBCs were statistically higher in cases group, while platelets were statistically lower in cases group, compared to control group (p<0.001). Serum urea and creatinine were significantly higher in cases group compared to control group (p<0.001, and p=0.42, respectively). While there was no significant difference between groups regarding random blood sugar, serum Ca , serum K, serum Na and serum phosphorus. Insulin-Like Growth Factor (IGF-1) was statistically higher in cases group (60.4±24.3 ng/mL), compared to control group (141.2±45.6 ng/mL), p<0.001.There was no significant difference between groups regarding thyroid function tests. Seven children (23.3%) in cases group had subclinical hypothyroidism, while 4 children (11.4%) of control group had subclinical hypothyroidism, but no significant difference were found.There was a significant difference between IGF-1 regarding sex as it was significantly lower in males (48±12.95 ng/mL) compared to females (79±25.43 ng/mL), p= 0.002. And it was significantly lower in patients with previous history of PICU admission (52.33±25.13 ng/mL), compared to patients without previous history of PICU admission (72.5±17.12 ng/mL), 0.014. While there was no significant difference between different etiologies of cyanotic heart diseases regarding IGF-1, p=0.45. There was a significant positive correlation between IGF-1 and (BMI and platelets), and there was a significant negative correlation between IGF-1 and (Hb level and serum creatinine). While there was no significant correlation between IGF-1 and other parameters. Conclusion: Cyanotic CHDs in children commonly cause more pronounced growth retardation. IGF-1 was decreased in patients with cyanotic CHD, also, IGF-1 correlated with growth parameters. For this reason, we believe that chronic hypoxia plays a significant role in the pathogenesis of malnutrition through GH/IGF-I axis.

Key words: Insulin like growth factor, IGF, thyroid function, cyanotic congenital heart disease.

1. Introduction

Cyanotic congenital heart defects (CHDs), which account for approximately 25% of all CHDs, make significant contributions to infant morbidity and mortality (Galvis et al., 2021; Singampalli et al., 2021). The patients appear blue (cyanotic), due to deoxygenated blood bypassing the lungs and entering the systemic circulation. Cyanotic CHDs in children commonly cause more pronounced growth retardation in comparison with acyanotic CHDs [1].

The etiology of growth retardation (GR) in the patients with CHD is still unclear. GR may result from decreased energy along with loss of appetite, inadequate utilization of nutrients due to hypoxia, malabsorption due to intestinal venous congestion, and relatively increased nutritional demand or increased energy demand including frequent infectious diseases and increased oxygen demand [2].

Insulin-like growth factors (IGFs) are a family of polypeptide that mediate the anabolic action of IGF-1, which is a well-known biochemical marker in the growth of mammals and is secreted in response to growth hormone to stimulate tissue growth [3].

A high prevalence of subclinical hypothyroidism (SCH) has been reported in a small cohort of cyanotic congenital heart disease patients. Subclinical hypothyroidism has a prevalence of up to 10% in the general population and is regarded as a mild thyroid failure. It can hence be interpreted as part of a

continuum between an euthyroid state and overt hypothyroidism [4].

SCH is defined as at least two consecutive measurements of elevated thyroid-stimulating hormone (TSH), with thyroid hormones within the normal range. Furthermore, SCH represents an increased risk of progression to overt hypothyroidism in the general population [5].

The aim of this study was to investigate the effects of cyanosis and chronic hypoxia on plasma level of insulin-like growth factor-1 and to examine the prevalence of elevated TSH in the patients with cyanotic congenital heart diseases.

2.Patients and Methods

This case-control study, included 30 patients with cyanotic CHD, who admitted to the Pediatric Cardiology Outpatient Clinic of benha university hospital, and another 35 patients, who admitted to the Pediatric Outpatient Clinic for scheduled vaccination visits were included in the control group, during the period from January 2021 to September 2021.

Inclusion criteria:
- All children diagnosed with cyanotic congenital heart disease, Diagnosis of cyanotic CHD was based on physical examination, echocardiography, cardiac catheterization and angiography in the cases indicated (6).
- Age less than 18 years,
- Congenital heart disease patients pre-operated or post-operated .
- Both sexes will be included.

Exclusion criteria:
- Patients with Down syndrome, Turner syndrome, additional genetic diseases
- Endocrinological disease including hypothyroidism
- Renal or hepatic failure,
- Those Who Were Born Less Than 37 Weeks Of Gestational Age, And Those With A Birth Weight Of Less Than 2500 G.

Ethical Consideration:
- Ethical permission for the study were obtained from the parents who were fully informed about all study procedures and their consent was obtained prior to the children enrollment in the study.
- This study was approved by the ethical committee of the faculty of Medicine, Benha University Hospitals.

We have two groups:
- **Group (I):** included 30 patients with cyanotic CHD
- **Group (II):** included 35 apparently healthy individuals, age and sex matched as a control group.

All patients were subjected to the following:
1-History taking:
A-Detailed history taking including:
- Personal history including: age, sex, all patients name was hidden and replaced by code number to maintain privacy of the participants.

- Past history including; Antenatal, Natal and postnatal history.
- Developmental history.
- Family history and history of consanguinity.
- Present history: age of onset, type and co-morbidities.
- History suggestive of acute complications, as (high fever, toxic manifestation, blurring of vision, Tachycardia, hypotension, and coma) for infective endocarditis or heart failure

2- Clinical Examination: (including)
- **Vital signs:** pulse, blood pressure, capillary filling time, respiratory rate and temperature.
- **Assessment of developmental milestones.**
- **Anthropometric measure:**
- Weight in Kilograms (kg), Height in Centimeters (cm). Body Mass Index (BMI).

D) System examination:
1. **Cardiovascular System**: For detection of any abnormal heart sounds or murmurs.
2. **Respiratory System**: For detection of any abnormal breath sound, adventitious sounds and respiratory distress.
3. **Gastrointestinal Tract (GIT) and Abdomen**: Presence of organomegaly.
4. **Central Nervous System (CNS) and Musculoskeletal System** Assessment of Pupillary reaction, examination of motor system including power, tone and reflexes, Presence of abnormal movement, sensory system and co-ordination were also tested

3-Laboratory investigations,
Complete blood picture (CBC)
By SysmexKX-21N, Sysmex Corporation, New York, USA to estimate hemoglobin level and blood indices (MCV, MCH, MCHC and RDW). Then blood films were prepared and stained by Leishman's stain for differential count.

Renal function tests; Serum urea and creatininene was do as described by [7]

Random blood glucose.
Serum electrolytes (sodium, potassium, calcium, phosphorus).
Serum electrolytes) using a heparinized whole blood sample (ABL 800 BASIC, Denamark) for assessment of metabolic acidosis, hypoxemia and hypercapnia**.**

TSH - Free T3 - Free T4
Serum levels of FT4, TSH, T4, and T3 were determined by chemiluminescence assays (Vitros Eci Technology, Ortho-Clinical-Diagnostics, Amersham, UK).

Insulin like growth factor (IGF-1), by ELISA
- Blood sample: two milliliters of venous blood were drawn under aseptic conditions and were taken in plain test tubes without anticoagulant (red cap) and left until coagulation. After coagulation, the samples were centrifuged at 1500 rpm for 15min. The separated serum were stored at −80°C in freezers until analysis for IGF-1.

- Serum IGF-I samples were analyzed at Esoterix Laboratory Inc. (Austin, TX). IGF-I was measured by a competitive binding radioimmunoassay that utilizes rabbit polyclonal antisera specific for IGF-I as the primary antibody and radioiodinated rHIGF-I as the tracer. Duplicate and control samples values were determined from a dose-response curve generated in each assay from purified rHIGF-I.

Sensitivity of the assay is 15 ng/mL and the CV is 5.3 %.

Statistical analysis

The data were coded, entered and processed on computer using SPSS (version 24). The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were use as descriptive statistics [8].

3. Results

Table (1) Insulin-Like Growth Factor (IGF-1) in the studied groups.

	Cases		Control		Test	P value
	N=30	%	N= 35	%		
Insulin-Like Growth FactorMean ±SD	60.4±24.3		141.2±45.6		t=8.6	<0.001**
(IGF-1) (ng/mL) Range	35-106		60-200			

t: Student t-test; **: high significance,

This table shows that Insulin-Like Growth Factor (IGF-1) was statistically higher in cases group (60.4±24.3 ng/mL), compared to control group (141.2±45.6 ng/mL), p<0.001.

Table (2) Thyroid function tests in the studied groups.

		Cases		Control		Test	P value
		N=30	%	N= 35	%		
Subclinical	**Yes**	7	23.3%	4	11.4%	X^2=1.68	0.21
hypothyroidism	**No**	23	76.7%	31	88.6%		
TSH (mIU/L)	**Mean ±SD**	4.9±2		4.4±1.8		t=1	0.32
	Range	1.1-8.5		2.1-7.8			
Free T3 (pg/mL)	**Mean ±SD**	3.5±0.7		3.6±0.6		t=0.39	0.69
	Range	2.7-4.7		2.7-4.8			
Free T4 (ng/dL)	**Mean ±SD**	1.2±0.2		1.3±0.2		t=1.3	0.21
	Range	0.9-1.7		0.8-1.8			

t: Student t-test; TSH; Thyroid stimulating hormone, T3; triiodothyronine, T4; thyroxine.

This table shows that there was no significant difference between groups regarding thyroid function tests or regarding presence of subclinical hypothyroidism. 7 children (23.3%) in cases group had subclinical hypothyroidism, while 4 children (11.4%) of control group had subclinical hypothyroidism, but no significant difference were found.

4.Discussion

The mean age in the studied cases was 24.1±13.8 months, ranged from 3-60 months, and consists of 18 males and 12 females, the mean age in the control group was 21.8±12.6 months, ranged from 3-60 months, and consists of 18 males and 17 females. There was no statistical difference between cases and control groups regarding age, or sex.

Our results were matched with Chowdhury et al. [9], who studied comparison of growth in children with cyanotic and acyanotic congenital heart disease in a tertiary care hospital, they included 30 children with cyanotic CHD, their mean age (± standard deviation) was 28.88 months (±15.12) and 66.67% patients were male and 33.33% patients were female.

And in the study by Matter et al. [10], who studied determinants of platelet count in pediatric patients with congenital cyanotic heart disease, The 46 studied patients with CCHD included 30 males and 16 females with a male to female ratio of 1.9:1. Their ages ranged from 1–192 months, with a median of 18.5 months

This wasn't in agreement with Ulfah et al. [11], who studied the effect of cyanotic and acyanotic congenital heart disease on children's growth velocity, This study was conducted in patients less than 24 months of age with CHD, 58.7% of subjects were female and 41.3% were male.

The most frequent diagnosis in our study was tetralogy of Fallot (TOF) (63.4%), then transposition of the great arteries (TGA) (23.3%). This was in the same line with Ulfah et al. [11], who reported that the most diagnoses of cyanotic CHD were TOF in 14 patients (61%), followed by TGA in 3 patients (13%). Also in the study by Chowdhury et al. [9], TOF was the most common (63.3%), then TGA (13.3%), TAPVC (13.3%), and TA (10%).

This wasn't in agreement with Abou-taleb et al. [12], who observed that the most common type of CCHD was d-transposition of great arteries (D-TGA) (66%) followed by complex CCHD (12%) and hypoplastic left heart syndrome (HLHS) (12%), whereas the less common type was hypoplastic right ventricle (2%). This difference can be because of inclusion of only neonates in Abou-taleb et al. [12] study, and the

mean age of presentation was 11.78 ± 9.4 days, and usually Tetralogy of Fallot presents after few months of life.

In the current study, all the studied cases had history of previous hospital admission, and 40% of cases had history of previous PICU admission.

Congenital heart defects (CHD) are serious and common conditions that have a significant impact on morbidity, mortality and healthcare costs in both children and adults (13). And Gundogdu et al. [14], observed in their study, that out of 566 admissions into the PICU during the study period, 76 out of 566 patients (13.4%) had cardiac abnormalities,

In the present study, there was statistical significant difference between studied groups regarding anthropometric measures, as weight, height and BMI centiles were statistically lower in cases group, while there was no significant difference between groups regarding head circumference.

This was in agreement with El-Sisi et al. [15], who studied linear growth in relation to the circulating concentration of insulin-like growth factor-I and free thyroxine in infants and children with congenital cyanotic heart disease, they showed that cases with cyanotic CHD had markedly lower BMI (15.3 ± 2.7) compared with normal controls (16.4±1.5).

Also, in the study by Sjarif et al. [16], they had a total of 95 patients, 73 patients with acyanotic and 22 patients with cyanotic lesions. Prevalence of undernutrition in CHD was 51.1%, with 22.3% severe undernutrition. FTT was found in 64.9%, short stature in 49.5% and microcephaly in 37% patients. FTT was found higher in acyanotic (72.2%) compared to cyanotic lesions (42.9%). In acyanotic, weight was affected more than length (72.2% vs 49.3%). In cyanotic, weight and length affected equally (42.9% vs 54.5%).

And in the study by Chowdhury et al. [9], In cyanotic congenital heart disease; 100% children had underweight. Among them, 23.33% had moderate and 76.67% had severe underweight. and 96.67% children with cyanotic congenital heart disease had stunting (length/height for age). Among them, 13.33% had moderate (-2 to -3 Z) and 83.33% had severe (<-3 Z) stunting.

Children with CHD can present undernutrition due to many factors, such as: type or physiopathology of the CHD, cyanosis, pulmonary hypertension or cardiac insufficiency, being small-for-gestation-age or low-birth-weight, having a genetic syndrome or another non-cardiac severe disease, frequent hospitalizations and inadequate oral intake due to anorexia, dyspnea or diminished gastric volume due to hepatomegaly that causes early satiety. Many of these factors cannot be reversed, even with the adequate medical treatment, thus, it is difficult to achieve a similar growth in healthy children. [17]

In the current study, there was Hb and WBCs were statistically higher in cases group, while platelets were statistically lower in cases group, compared to control group (p<0.001).

Similarly, Amornchaicharoensuk et al. [18], who studied comparison of renal function between cyanotic and acyanotic congenital heart disease in children and adolescent, reported that hemoglobin level were significantly higher in cyanotic CHD (17.88 ± 4.43 g/dl), compared to acyanotic CHD (12.01 ± 1.23), p<0.001. Also, Awad et al. [19], observed that hematocrit was statistically higher in children with cyanotic CHD compared to controls (p<0.001). Moreover, Maleki et al. [20], observed that hemoglobin was higher in cyanotic CHD patients (15±3.6 d/dL), compared with acyanotic CHD patients (12.5±2 g/dL), and controls (11.8±1.8 g/dL), p<0.001.

Matter et al. [10], who studied thrombocytopenia among patients with CCHD; reported that thrombocytopenia was present in 6 (13%) of the screened patients. The mean platelet count was 244.7 ± 88.6 × 109/L in patients without thrombocytopenia and 63.2 ± 21.9 × 109/L in the thrombocytopenic group. Also, Lill et al. [21] found that out of 105 patients with CCHD, 26 (25%) had thrombocytopenia; however, all these patients with thrombocytopenia had Eisenmenger syndrome and their mean platelet count was 155 ± 12 × 109/L (range, 125–332 × 109/L).

Erythrocytosis, thrombocytopenia, platelets function defects, coagulation factors deficiencies are the main hematologic disorders in patients with cyanotic congenital heart disease (CCHD). (10)

Amornchaicharoensuk et al. [18], who studied comparison of renal function between cyanotic and acyanotic congenital heart disease in children and adolescent, concluded that cyanotic CHD patients had more prevalence and higher abnormal biochemical markers for renal dysfunction than those of acyanotic CHD. Their urine protein/creatinine, FE Mg2 and urine NAG/creatinine were higher than those of acyanotic CHD. Only low correlation among biochemical markers was found.

And Agras et al. [22], found that median fractional excretion of sodium (FeNa) and urinary NAG/creatinine were significantly higher in the cyanotic group than in the control group (p = 0.022 and p = 0.002, respectively). There were no statistically significant differences among the groups with respect to urinary beta(2)-microglobulin/creatinine, urinary microalbumin/creatinine or glomerular filtration rate.

Our results came in the same line with Mohamed et al. [23], who studied assessment of renal functions in infants and children with congenital heart diseases, found that children with cyanotic CHD had higher values in all parameters (Estimated glomerular filtration rate (EGFR) and urinary albumin and creatinine ratio), and concluded that risk of renal dysfunctions increase by time especially in children with cyanotic CHD which may be due to effect of chronic hypoxia and other conditions such as polycythemia.

In addition, a previous study by krull et al. [24], children with persistent congenital cyanotic heart disease have substantial risk of developing a

glomerulopathy if the cyanosis remains unchanged for more than ten years. Patients with persistent CCHD have a substantial risk of developing glomerulopathy. Significant proteinuria may occur in as high as 70% of them in patients over 10 years of age.

In the present study; Insulin-Like Growth Factor (IGF-1) was statistically higher in cases group (60.4±24.3 ng/mL), compared to control group (141.2±45.6 ng/mL), p<0.001.

Our results were in agreement with Shiva et al. [25], who studied growth parameters and insulin like growth factor-1 on comparison between cyanotic and acyanotic congenital heart disease and normal children, IGF-1 was significantly lower in cyanotic group than other groups (both, p<0.001).

Also Dinleyici et al. [26], reported that serum IGF-1 levels were significantly lower in cyanotic CHD patients than the acyanotic patients (17.2+/-3.2 microg/L, 48.7.0+/-4.6 microg/L respectively, p<0.001) and serum IGF-1 levels were both lower in acyanotic and cyanotic CHD patients than the controls (p<0.001 for both).

In the study by Dundar et al. [27], The cyanotic CHD patients were divided into malnourished and well-nourished groups (21 and 8 patients, respectively) according to their nutritional status. Serum IGF-I concentrations were measured in the two patient groups and the controls. The malnourished group had the lowest IGF-I levels (48.14 +/- 21.8 ng/ml, p<0.05). However, the well-nourished group's IGF-I levels were significantly lower than the control subjects' despite improved nutritional status (85.5 +/- 30.2 and 107 +/- 19.7 ng/ml, respectively, p<0.05).

In the current study, there was no significant difference between groups regarding thyroid function tests or regarding presence of subclinical hypothyroidism. 7 children (23.3%) in cases group had subclinical hypothyroidism, while 4 children (11.4%) of control group had subclinical hypothyroidism, but no significant difference were found.

Our results were agreed with Passeri et al. [28], who studied risk for non-autoimmune hypothyroidism in young patients with congenital heart defects, Hypothyroidism was diagnosed in 39 of 324 patients (12%). Two patients were diagnosed at neonatal screening (TSH 29.0 and 35 μU/ml; estimated CH incidence in CHD one in 162) and were replaced with L-T4. At reevaluation at 3 yr of age, one patient showed a TSH level of 13 μU/ml, whereas the other had normal thyroid function and discontinued L-T4 treatment. Normal iodine thyroid uptake and normal thyroid pattern, volume, and morphology at US were diagnosed in both children. In the remaining 37 patients (11.5%), who resulted normal at neonatal screening, serum TSH levels higher than 4.0 μU/ml were detected. The raised TSH levels were confirmed at the 6-month interval. All these CHD patients had serum FT4 and FT3 levels in the normal range, and FT4 levels did not differ significantly from euthyroid CHD patients.

And in the study by Bak et al. [4], who studied subclinical hypothyroidism in adult patients with cyanotic congenital heart disease, they observed that elevated thyroid-stimulating hormone was present in 24% of the 90 screened patients. During follow-up (6.5 ± 1.0 years), SCH (defined as ≥2 consecutive elevated thyroid-stimulating hormone values) was present in 26%. Three patients progressed to overt hypothyroidism. Patients with SCH were younger (34 ± 12 vs 42 ± 16 years; P = .01) and had a lower oxygen saturation (80 ± 5 vs 84 ± 6%; P = .03).

However, in the study by El-Sisi et al. [15], circulating FT4 & TSH concentration were within normal levels, and No significant difference was detected in circulating FT4 or TSH concentration after vs. before surgery.

Subclinical hypothyroidism (SCH) is a commonly encountered laboratory finding in clinical practice, characterised by elevated levels of thyroid-stimulating hormone (TSH) in serum in the presence of normal serum levels of free thyroxine (FT4), as compared with population-based reference ranges for these values [29]. Hennessey and Espaillat, [29], Estimates for the prevalence of SCH varied by sex, age, race/ethnicity, and geographic location (range, 0.4–16.9%).

In the present study, there was a significant difference between IGF-1 regarding sex as it was significantly lower in males (48±12.95 ng/mL) compared to females (79±25.43 ng/mL), p= 0.002. And it was significantly lower in patients with previous history of PICU admission (52.33±25.13 ng/mL), compared to patients without previous history of PICU admission (72.5±17.12 ng/mL), 0.014. While there was no significant difference between different etiologies of cyanotic heart diseases regarding IGF-1, p=0.45. And, there was a significant positive correlation between IGF-1 and (BMI and platelets), and there was a significant negative correlation between IGF-1 and (Hb level and serum creatinine). While there was no significant correlation between IGF-1 and other parameters.

Shiva et al. [25], reported that there was significant positive correlation between IGF-1 and blood oxygen saturation (r=0.45, p<0.001), IGF-1 and age (r=0.63, p<0.001), IGF-1 and BMI (r=0.40, p<0.001), IGF-1 and height (r=0.37, p<0.001) and IGF-1 and head circumference (r=0.44, p<0.001).

Many factors can contribute to impaired linear growth in children with cyanotic CHD including: (i) hypoxia and defective perfusion to the growing tissues including the epiphyseal growth plate, (ii) increased metabolic rate inducing a hyper-metabolic state, (iii) decreased appetite and (iv) possible effect on GH/IGF-I axis (15).

El-Sisi et al. [15], reported that in patients with cyanotic CHD, circulating IGF-I concentrations increased significantly after vs. before surgical intervention. After surgery, the percentage change in IGF-I was correlated significantly with growth velocity (r = 0.589, p < 0.01) and BMI (r = 0.82, p < 0.001). These findings supported the view that the attained growth spurt after treatment is mediated through

increased IGF-I synthesis (stimulation of GH-IGF-I axis).

Our results showed that IGF-1 was decreased in patients with cyanotic CHD, also, IGF-1 correlated with growth parameters. For this reason, we believe that chronic hypoxia plays a significant role in the pathogenesis of malnutrition through GH/IGF-I axis. Also. Our results showed no significant difference between groups regarding thyroid function tests or regarding presence of subclinical hypothyroidism

5. Conclusion

Cyanotic CHDs in children commonly cause more pronounced growth retardation. IGF-1 was decreased in patients with cyanotic CHD, also, IGF-1 correlated with growth parameters. For this reason, we believe that chronic hypoxia plays a significant role in the pathogenesis of malnutrition through GH/IGF-I axis. Our results showed no significant difference between groups regarding thyroid function tests or regarding presence of subclinical hypothyroidism.

References

[1] M.M.O.Galvis, R.T.Bhakta, A.Tarmahomed ."Cyanotic Heart Disease", StatPearls [Internet], StatPearls Publishing.vol.15,pp.155-200,2021.

[2] A.D.Spearman, R.S.Loomba, M.Danduran. "Intrauterine growth restriction is not associated with decreased exercise capacity in adolescents with congenital heart disease", Congenital Heart Disease, Wiley Online Library.vol. 13 , pp. 369–376,2018.

[3] S.Wrigley, D.Arafa, and D.Tropea. "Insulin-like growth factor 1: at the crossroads of brain development and aging", Frontiers in Cellular Neuroscience, Frontiers.vol. 11,pp. 14,2017.

[4] P.Bak, C.S.Hjortshøj, P.Gæde. "Subclinical hypothyroidism: a common finding in adult patients with cyanotic congenital heart disease", Congenital Heart Disease, Wiley Online Library. Vol.13,pp.263–270,2018.

[5] W.S. Yoo, and H.K. Chung, "Subclinical Hypothyroidism: Prevalence, Health Impact, and Treatment Landscape", Journal of Korean Endocrine Society, Korean Endocrine Society.vol.52,pp.140-189,2021.

[6] R.O.Bonow, D.L.Mann, D.P.Zipes. Braunwald's Heart Disease e-Book: A Textbook of Cardiovascular Medicine, Elsevier Health Sciences.vol.25,pp.350-360,2011.

[7] D.Jung, H.Biggs, J.Erikson. "New colorimetric reaction for end-point, continuous-flow, and kinetic measurement of urea", Clinical Chemistry, Oxford University Press.vol. 21,pp.1136–1140,1975.

[8] R.LevesqueSPSS Programming and Data Management: A Guide for SPSS and SAS Users, Spss.vol.24,pp.410-450,2005.

[9] F.Chowdhury, M.Hoque, M.M. Ali. "Comparison of growth in children with cyanotic and acyanotic congenital heart disease in a tertiary care hospital", Journal of Bangladesh College of Physicians and Surgeons.vol. 36 ,pp. 64–69,2018.

[10] R.M.Matter, I.A.Ragab, A.M.Roushdy. "Determinants of platelet count in pediatric patients with congenital cyanotic heart disease: role of immature platelet fraction", Congenital Heart Disease, Wiley Online Library.vol.13,pp.118–123,2018.

[11] D.A.Ulfah, E.D.Lestari, H.Salimo. "The effect of cyanotic and acyanotic congenital heart disease on children's growth velocity", Paediatrica Indonesiana.vol. 57,pp.160–163,2017.

[12] A.Abou-Taleb, M.A. Abdelhamid, and Bahkeet. "Clinical profile of cyanotic congenital heart disease in neonatal intensive care unit at Sohag University Hospital, Upper Egypt", Egyptian Journal of Medical Human Genetics.vol. 18,pp.47–51,2017.

[13] V.L.Roger, A.S.G o, D.M.Lloyd-Jones. "Heart disease and stroke statistics—2011 update: a report from the American Heart Association", Circulation, Am Heart Assoc.vol. 123,pp18–209, 2011.

[14] Z.Gundogdu, K.Babaoglu, M.Deveci. "A Study of Mortality in Cardiac Patients in a Pediatric Intensive Care Unit", Cureus, Cureus Inc.vol.11,pp.11-20,2019.

[15] A.El-Sisi, A.Khella, M.Numan. "Linear growth in relation to the circulating concentration of insulin-like growth factor-I and free thyroxine in infants and children with congenital cyanotic heart disease before vs. after surgical intervention", Journal of Tropical Pediatrics, Oxford University Press.vol. 55,pp. 302–306,2009.

[16] D.R.Sjarif, S.L.Anggriawan, S.T. Putra. "Anthropometric profiles of children with congenital heart disease", Medical Journal of Indonesia.vol. 20,pp.40–45,2011.

[17] C.Le Roy, G.Larios, D. Springmüller. "Nutritional assessment in infants with congenital heart disease: comparison of two anthropometric classifications", Rev Chil Pediatr.vol. 88 , pp. 744–750,2017.

[18] Y.Amornchaicharoensuk, T.Werawatganon, P.Tohsukhowong, Boonla. "Comparison of renal function between cyanotic and acyanotic congenital heart disease in children and adolescent", J Med Assoc Thai.vol. 95 , pp. 1501–1508,2012.

[19] H.Awad, S.El-Said, I.El-Safty. "Glomerular and tubular dysfunction in children with congenital cyanotic heart disease: effect of palliative surgery", The American Journal of the Medical Sciences, Elsevier.vol. 325 , pp. 110–114,2003.

[20] M.Maleki, S.Ghaffari, M.R.Ghaffari. "Proteinuria in Congenital Heart Disease: is it a real problem?", Journal of Cardiovascular and Thoracic Research, Tabriz University of Medical Sciences.vol. 3 , pp.17–21, 2013.

[21] M.C.Lill, J.K. Perloff, and J.S. Child "Pathogenesis of thrombocytopenia in cyanotic congenital heart disease", The American Journal of Cardiology, Elsevier.vol. 98 ,pp.254–258. ,2006.

[22] P.I.Agras, M.Derbent, F.Ozcay. "Effect of congenital heart disease on renal function in childhood", Nephron Physiology, Karger Publishers.vol. 99 , pp10–15,2005.

[23] M.S.Mohamed, M.M.Rabeea, H.S. Abu Saif. "Assessment of Renal Functions in Infants and Children with Congenital Heart Diseases", The Egyptian Journal of Hospital Medicine, Ain Shams University, Faculty of Medicine, Pan Arab League of Continuous .vol. 74,pp.219–225, 2019.

[24] F.Krull, J.H.H.Ehrich, U.Wurster. "Renal involvement in patients with congenital cyanotic heart disease", Acta Pædiatrica, Wiley Online Library.vol,80,pp.1214–1219,1991.

[25] S.Shiva, M.Samadi, M.Mohammadpour Shateri. "Growth parameters and insulin like growth factor-1: Comparison between cyanotic and acyanotic congenital heart disease and normal children", Life Science Journal.vol.10, pp.577–580,2013.

[26] E.C.Dinleyici, Z.Kilic, B.Buyukkaragoz. "Serum IGF-1, IGFBP-3 and growth hormone levels in children with congenital heart disease: relationship with nutritional status, cyanosis and left ventricular functions", Neuroendocrinology Letters, [Weinheim, Ger.] Edition Medizin.vol.28 , pp.279–283,2007.

[27] B.Dündar, A.A.G.Saylam, N.Ünal. "Chronic hypoxemia leads to reduced serum IGF-I levels in cyanotic congenital heart disease", Journal of Pediatric Endocrinology and Metabolism, De Gruyter.vol.13,pp. 431–436,2000.

[28] E.Passeri, M.Frigerio, T.De Filippis. "Increased risk for non-autoimmune hypothyroidism in young patients with congenital heart defects", The Journal of Clinical Endocrinology & Metabolism, Oxford University Press.vol. 96,pp. 1115–1119,2011.

[29] J. V Hennessey, and R.Espaillat. "Subclinical hypothyroidism: a historical view and shifting prevalence", International Journal of Clinical Practice, Wiley Online Library.vol.69,pp.771–782,2015.