Serum IGF-1, IGFBP-3 and growth hormone levels in children with congenital heart disease: relationship with nutritional status, cyanosis and left ventricular functions

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Abstract

In this study we aimed to evaluate serum insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3) and growth hormone (GH) levels in children with congenital heart disease (CHD) and to determine if these parameters have any relationship to the cyanosis, nutritional status and the left ventricular systolic function.

This study is prospective-randomized study which conducted in 94 CHD patients (36 girls and 58 boys, aged between one 1–192 months, 19 cyanotic CHD and 75 acyanotic CHD) and age-sex matched 54 children (26 girls and 28 boys) with no CHD. In the study group, 37 out of the 94 CHD patients (39.4%) and 16 out of the 54 controls (29.6%) had malnutrition. The difference between the cyanotic and acyanotic patients in respect to malnutrition was significant (57.9% and 34.6%, $p<0.05$). Serum IGF-1 levels were lower (41.8±3.9 µg/L, 106.9±17.9 µg/L respectively, $p<0.001$) and GH levels were higher (6.43±0.9 ng/ml, 3.87±0.5 respectively, $p<0.05$) in CHD patient group than the controls. Serum IGF-1 levels were significantly lower in cyanotic CHD patients than the acyanotic patients (17.2±3.2 µg/L, 48.7.0±4.6 µg/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). Serum IGF-1 and GH levels were similar between the well-nourished CHD patients and CHD patients with malnutrition ($p>0.05$). In total study group, the most effective factors on serum IGF-1 levels was presence of CHD ($p<0.001$), in CHD patients, the presence of cyanosis is the most effective factor on serum IGF-1 level, the presence of malnutrition is the most effective factor on serum IGFBP-3 levels ($p<0.01$). In the acyanotic, cyanotic, and the entire CHD patient groups, we find no correlations between the serum IGF-1, IGFBP-3 levels and left ventricular systolic function

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measurements. But serum GH levels were negatively correlated with diastolic left ventricular interseptum diameter, diastolic left ventricular mass and left ventricular end-diastolic volume measurements in CHD patients.

In conclusion, we determined that the most important factor on serum IGF-1 levels is cyanosis. Reduced IGF-1 levels and decreased left ventricular mass with an elevated GH levels in CHD patients and these findings are prominent in the cases with cyanosis and malnutrition. For this reason we believe that chronic hypoxia plays a significant role in the pathogenesis of malnutrition and also we believe that IGF-1 deficiency seen in CHD patients may be responsible in the etiology of the decrease in left ventricular mass independently from GH.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital malformation which occurs in 0.8% of all live births [1]. Protein-energy malnutrition and failure to thrive are well-recognized complications of the CHD [2]. They are related with repeated respiratory infections, increased oxygen consumption rate and changes induced by chronic hypoxia. Due to hypoxia difficulties in feeding and insufficient caloric intake occur and intestinal anoxia and venous congestion may lead to malnutrition. These factors cause cellular hypoxia, hypermetabolism, reduction in nutrient ingestion and intestinal malabsorbtion of nutrients [2–4]. Varan *et al*. [5] reported that children with CHD had been shown to have different degrees of malnutrition and in certain cases failure to thrive co-existed in these subjects. They also concluded that nutrition and growth are most adversely influenced in CHD patients with cyanosis and pulmonary hypertension,

Insulin-like growth factors (IGF) are growth hormone (GH)-related peptides which play role in anabolic and mitogenic activities. The combination of decreased IGF-1 levels and increased basal GH levels is associated with malnutrition and hypermetabolic states [6–7]. IGFs are pronounced to have also effects in the pathogenesis of failure to thrive seen in CHD [4]. Recent studies reported conflicting results about IGF system in CHD. Barton *et al*. [8]. reported that children with CHD have reduced levels of serum IGF-1 and IGFBP-3 but no difference was observed between cyanotic and acyanotic patients. Because of the conflicting GH-induced stimulus to increase IGF-1 secretion as opposed to the malnutrition-induced stimulus to reduce it, serum IGF and IGF binding protein (IGFBP) system must be evaluated with other factors. In this study we aimed to evaluate serum IGF-1, IGFBP-3 and GH levels and to determine if these parameters have any relationship to the cyanosis, nutritional status and the ventricular systolic function.

MATERIAL AND METHODS

This study is prospective-randomized study which conducted in 94 CHD patients (36 girls and 58 boys) aged between one month and 192 months who have been followed in Pediatric Cardiology Unit of Eskisehir Osmangazi University. Age and sex matched 54 children (26 girls and 28 boys) without CHD were included as the control group. None of the patients had any major anomalies other than CHD and they were not operated on curative or palliative purposes. Body weight and height measurements, detailed physical examination were performed and cases with malnutrition or cyanosis were noted. CHD patients were initially grouped as cyanotic and acyanotic cases and each subgroup were further divided into two according to presence of malnutrition. By using the body weight for height charts, subjects under 90^{th} percentile were accepted to have malnutrition.

From all cases 5 cc venous blood samples were obtained for IGF, IGFBP-3 and GH assays. Serum IGF-1 and IGFBP-3 levels were measured by ELISA method (IBL/Immuno-biological laboratories, Hamburg, Germany) and GH levels by immunometric assay (Immulite, DPC, USA).

All patients and control cases underwent echocardiographic assessment (in the Pediatric Cardiology Unit with Hewlett Packard SONOS 5500) and standard telecardiography examination for the measurement of cardio-thoracic ratio (CTR). A 64 CHD patients aged between 24 months and 120 months and age and sex matched 24 children between 24 months and 120 months of age with no underlying as the control group were evaluated also ejection fraction (EF), fractional shortening (FS), diastolic left ventricular interseptum diameter (LVIDd), left ventricular diastolic mass (LVmass(d), left ventricular systolic mass (LVmass(d), left ventricular end diastolic volume (LVEDV) measurements were recorded.

Statistical analysis was performed with SPSS for Windows 10.0 (Chicago, IL, USA). The comparisons were performed with independent sample test. And Pearson correlation test was used for correlations between parameters. A stepwise model was used for multipl regression analysis. A p value <0.05 was accepted statistically significant.

RESULTS

Ninety-four children with CHD (19 cyanotic CHD and 75 acyanotic CHD) were enrolled in the study. In the acyanotic CHD patient, the most common cardiac lesions in decreasing order were atrial septal defect as 36%, ventricular septal defect (VSD) as 26.6 and patent ductus arteriosus as 10.6%. In the cyanotic group the most common lesions were transposition of the great arteries and Tetralogy of Fallot.

Mean age, body weight and height were similar between study group and controls (Table 1). In the study group, 37 out of the 94 CHD patients (39.4%) and 16 out

of the 54 controls (29.6%) had malnutrition. 19 out of 94 CHD patients had cyanosis (20.2%) and 11 of them had malnutrition (57.9%). The malnutrition prevalence is 34.6% in acyanotic patients. The difference between the cyanotic and acyanotic patients in respect to malnutrition was significant (57.9% and 34.6%, p<0.05).

When the CHD patients and control group (with or without malnutrition) were compared serum IGF-1 levels were lower (41.8±3.9 μg/L, 106.9±17.9 μg/L respectively, p<0.001) and GH levels were higher (6.43±0.9 ng/ml, 3.87±0.5 respectively, p<0.05) in CHD patient group than the controls. Serum IGFBP-3 levels were lower in CHD patients than the controls without statistical difference (2412±128 ng/ml, 2704±149 ng/ml, p>0.05) (Table 1). However when the CHD patients were compared with the well-nourished controls, serum IGF-1 levels were still significantly lower (41.8±3.9 μg/L, 109.0±16.7 μg/L respectively, p<0.001), serum IGFBP-3 and GH levels similar between the groups (p>0.05) (Table 2).

Serum IGF-1 levels were significantly lower in cyanotic CHD patients than the acyanotic patients (17.2±3.2 μg/L, 48.1±4.6 μg/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) (Table 1).

Serum IGFBP-3 levels were significantly higher in well-nourished CHD patients than the CHD patients with malnutrition (p<0.01). Well nourished-acyanotic patients had also higher IGFBP-3 levels than the acyanotic CHD patients with malnutrition (p<0.05) however serum IGF-1 and GH levels were similar. Serum IGF-1, IGFBP-3 and GH levels were similar between the CHD patients with malnutrition and the control patients with malnutrition and also similar between the control patients with or without malnutrition (Table 2).

While the number of patients is limited for statistical evaluation in cyanotic CHD patients, serum IGF-1, IGFBP-3 and GH levels were similar between the well-nourished patients and patients with malnutrition.

In the CHD patients group, serum GH levels were negatively correlated with age (r=–0.665, p<0.001), body weight (r=–0.659, p<0.001), and positively correlated with cardio-thoracic index (r=0.290, p<0.05). While in control group we found negative correlation between the serum IGF-1 and GH levels, we found no correlation in CHD patients group. In the cyanotic patients group, serum IGF-1 levels were negatively correlated with CTR (r=–0.489, p<0.05) and positively correlated serum IGFBP-3 levels (r=–0.502, p<0.05).

In total study group, with stepwise multipl regression analysis including presence of CHD, presence of malnutrition, weight, height, age, we determined the most effective factors on serum IGF-1 levels was presence of CHD (p<0.001). Same model in CHD patients (presence of cyanosis added), the presence of cyanosis is the most effective factor on serum IGF-1 level, the presence of malnutrition is the most effective factor on serum IGFBP-3 levels (p<0.01).

A 64 CHD patients (24–120 months) and age and sex matched 24 healthy children (24–120 months) were evaluated also left ventricular systolic functions. No statistical difference was observed for left ventricular systolic functions between the CHD patients with or without cyanosis and also between the CHD patients with or without malnutrition. LVIDd was lower in CHD patients with malnutrition than control subjects (p<0.01). Other recorded left ventricular systolic functions were similar between the CHD group and control subjects.

In the acyanotic, cyanotic, and the entire CHD patient groups, we find no correlations between the serum IGF-I, IGFBP-3 levels and left ventricular systolic function measurements. But serum GH levels were negatively correlated with LVIDd, LVmass(d) and LVEDV measurements in CHD patients group especially in acyanotic CHD. In the CHD patients with malnutrition, serum IGF-1 levels positively correlated and serum GH levels were negatively correlated with LVIDd and LVEDV measurements. We found no correlations between the serum IGFBP-3 levels and left ventricular systolic measurements. In CHD patients without malnutrition, we found no correlations between serum IGF-1 or serum IGFBP-3 levels and left ventricular systolic function measurements but serum GH levels negatively correlated with LVIDd, LVmass(d) and LVEDV measurements.

Table 1. Serum IGF-1, IGFBP-3 and GH levels in CHD patients and controls.

	CHD			CONTROL		
	Cyanotic CHD (n=19)	**Acyanotic CHD** (n=75)	**Total** (n=94)	**Without MN** (n=38)	**With MN** (n=16)	**Total** (n=54)
IGF-1 (μg/L)	17.2±3.2 [d, e]	48.1±4.6 [e]	41.8±3.9 [a, c]	109.0±16.7	99.1±27.7	106.9±17.9
IGFBP-3 (ng/ml)	2265±285	2456±153.2	2412±128	2704±230.9	2662±189.6	2704±149
GH (ng/ml)	10.5±2.8	5.4±0.8	6.43±0.9 [b]	3.79±0.7	4.08±0.7	3.87±0.5

[a] p<0.001, CHD patients (total) vs Control (total)
[b] p<0.05, CHD patients (total) vs Control (total)
[c] p<0.001, CHD patients (total) vs Control patients without malnutririton
[d] p<0.001, cyanotic CHD vs acyanotic CHD
[e] p<0.0001, cyanotic CHD vs control (total) and acyanotic CHD vs control (total)

Table 2. Serum IGF-1, IGFBP-3 and GH levels according to presence of malnutrition in CHD patients and controls.

	CHD						CONTROL		
	Cyanotic CHD (n=19)		Acyanotic CHD (n=75)		Total (n=94)				
	(–)	(+)	(–)	(+)	(–)	(+)	(–) (n=38)	(+) (n=16)	Total (n=54)
IGF-1 (µg/L)	18.4±4.8	15.4 ±4.3	54.8±8.6	44.5±5.3	44.0±6.7	40.4±4.8	109.0±16.7	99.1±27.7	106.9±17.9
IGFBP-3 (ng/ml)	2882±304	2628±368	2699±281 [b]	2621±173	2772±212 [a]	2703±159	2704±230.9	2662±189.6	2704±149
GH (ng/ml)	11.2±3.6	9.4±4.7	4.42±0.8	5.93±1.2	6.46±1.3	6.42±1.2	3.79±0.7	4.08±0.7	3.87±0.5

(–); children without malnutrition, (+); children with malnutrition
[a] p<0.05; CHD patients with malnutrition vs CHD patients without malnutrition
[b] p<0.05; acyanotic CHD patients with malnutrition vs acyanotic CHD patients without malnutrition.

DISCUSSION

Like other previous studies, the malnutrition prevalence is of the CHD patients in our study, was higher than the children without CHD and also greater in cyanotics than acyanotic children. Increased prevalence of malnutrition in cyanotic CHD could be explained with increased daily energy expenditure and increased metabolic rates [4,9]. IGF-1 is an important parameter in demonstrating normal growth and growth disturbances. Barton *et al.* [8] were reported that the serum IGF-1 levels were reduced in CHD and it was stressed that the disturbed nutritional status was responsible for these decrease. Soliman *et al.* [4] reported that the hypermetabolic status of patients with VSD compromise nutrition and this decreases IGF-1 synthesis with subsequent slowing of linear growth and weight gain and they also suggest that the size of the shunt and pulmonary flow are the main determinants of the growth failure seen in children with VSD. In our study we detected significantly reduced serum IGF-1 levels in children with CHD than the control groups and that serum IGF-1 levels increase with age in both CHD and the control groups. Also serum IGF-1 levels were lower in CHD patients with malnutrition than the CHD patients without malnutrition.

Cyanotic CHD causes more prominent impaired nutritional status than acyanotic CHD in children. Chronic hypoxemia as well as nutritional factors has been hypothesized to be responsible. Our another study which was performed in asphyxiated newborns for the determination of acute hypoxia on the cord IGF-1 levels, cord blood IGF-1 levels were significantly lower in term asphyxiated newborns and was positively correlated with umbilical cord pH, HCO_3, 5^{th} minute apgar score [10]. Bernstein *et al.* [11] reported that serum IGF-1 levels were decreased as a result of chronic hypoxia in lambs with experimentally created PS and ASD. Dündar *et al.* [12] found that children with cyanotic CHD had reduced serum IGF-1 values compared to the normal individuals. In the same study cyanotic cases with malnutrition had the lowest serum IGF-1 values and it was emphasized that nutritional factors were effective on serum IGF-1 concentrations. In our study we also observed that cyanotic patients had reduced serum IGF-1 values than the controls and acyanotic patients. But the values did not differ between the well-nourished patients and patients with malnutrition.

It was reported that children with CHD and growth failure had increased GH levels [13]. Fahrer *et al.* [14] reported that growth hormone levels are as much as sixfold greater in children with cyanotic CHD compared to controls and acyanotic CHD. This finding was interpreted as the consequence of the peripheral unresponsiveness to the GH due to the IGF-1 deficiencies. In our study we found significantly higher GH values in the CHD group, being more prominent in the cyanotic subjects. Cyanotic patients group were found to have lowest serum IGF-1 and highest GH values.

Barton *et al.* [8] reported that children with CHD had reduced serum IGFBP-3 levels but no difference was found between acyanotic and cyanotic CHD patients. In our study, serum IGFBP-3 levels were lower in CHD patients than the controls but we found no statistical differences. Argente *et al.* [15] reported that serum IGFBP-3 levels were detected to be lower in children with malnutrition and it was stressed that IGFBP-3 concentrations were reduced in circumstances like growth failure or malnutrition. But some authors reported that serum IGFBP-3 level is not much affected by chronical illness or malnutrition as IGF-1 like our study [16].

Our CHD patients had higher GH levels while their serum IGF-1 levels were lower than the controls. Patients with primary GH resistance, have no GH signal transmission and thus no generation of circulating IGF-1 [17]. Feinberg *et al.* [17] reported that these patients have significantly reduced cardiac dimensions including LV septum, LV posterior wall and end-diastolic diameter.

In our study, serum IGF-1 levels were lower in this group and positively correlated with LVDD, LVmass(d) and LVEDV. Decreased serum IGF-1 levels in CHD patients with malnutrition, especially cyanotics, may also be related with disturbed left ventricular dysfunction. These findings may be related with direct trophic effect of IGF-1 to myocardium.

In conclusion, we determined that the most important factor on serum IGF-1 levels is cyanosis. For this reason we believe that chronic hypoxia plays a significant role in the pathogenesis of malnutrition and growth failure. Cyanotic CHD patients had decreased IGF-1 levels in the face of normal or elevated GH levels. However these findings suggest peripheral GH unresponsiveness and are similar to observed in patients with malnutrition, Bernstein *et al*. [11] suggested that the mechanism of the decrease in IGF-1 may be secondary to alterations in signal transduction distal to the growth hormone receptor binding site.

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