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ORIGINAL ARTICLE

The Levels of Ghrelin in Children with Cyanotic and Acyanotic Congenital Heart Disease

Hassan M Al-Asy[1], Amr A. Donia[2], Doaa M. El-Amrosy[3],Enaam Rabee[4], Amal Al Bendary[5]

Department of Pediatrics[1,2,3] and Clinical Pathology[4,5], Faculty of Medicine, Tanta University, Egypt

Abstract:

The cause of growth retardation in congenital heart disease is multifactorial. The relationship between congenital heart disease (CHD), malnutrition, and growth retardation is well documented. Ghrelin has effects on nutrient intake and growth. Ghrelin exerts potent GH-releasing activity and stimulates food intake. Circulating ghrelin levels are increased in anorexia and cachexia, reduced in obesity and restored by weight recovery. The relation between ghrelin and congenital heart disease is evident in adults but it is not studied well in pediatric age. The aim of the present study is to evaluate the serum ghrelin in congenital heart disease. We measured serum ghrelin, using ELISA technique in 60 patients with congenital heart disease (20 with acyanotic congenital heart disease with no heart failure (HF), 15 with cyanotic congenital heart disease with no HF) and 25 patients with congenital heart disease (cyanotic or acyanotic) with HF, in addition to 30 age and sex matched children as a control group. All children were subjected to measurement of height, weight, body mass index (BMI). In comparison to controls, serum ghrelin levels were significantly higher in patients with congenital heart disease (acyanotic patients and cyanotic with or without HF than in the control group (p=0.01). Also ghrelin level was significantly increased in children with cyanotic congenital heart disease than in those with acyanotic congenital heart disease. Patient with congenital heart disease with evidence of HF had significant higher levels of serum ghrelin than those with congenital heart disease without HF. Weight, height and BMI were significantly lower in cyanotic and acyanotic patients compared to the control group (p=0.001), also these measures were significantly reduced in patients with congenital heart disease with HF than in those without heart failure. There was a significant negative correlation between serum ghrelin and BMI in patients with heart failure, cyanotic patients and acyanotic patients; (r = -0.608, -0.831 and -0.458) and (p = 0.007, 0.02 and 0.017) respectively. In onclusion, serum ghrelin levels is elevated in children with acyanotic and cyanotic congenital heart disease with or without HF. Increased ghrelin levels represents malnutrition and growth retardation in these patients. This may suggest that ghrelin may have an important role as a compensatory mechanism in the regulation of the metabolic balance in these patients.

Keywords: *ghrelin , congenital heart disease , cyanotic , acyanotic , heart failure*

Corresponding author: *Hassan M. Al-Asy, Tanta Faculty of Medicine, Tanta University, Pediatric Department, Egypt*
Telephone : 00201008100153; e-mail: drhassanalasy@yahoo.com

Introduction

The relationship between congenital heart disease (CHD), malnutrition, and growth retardation is well documented [1]. Infants with congenital heart disease are prone to malnutrition for several reasons including decreased energy intake, increased energy requirements, or both. Different types of cardiac malformations can affect nutrition and growth to varying degrees. Ghrelin, a 28-amino-acide peptide, has been implicated in the control of food intake and energy homeostasis in human beings and rodents [2–5]. Ghrelin is a potent stimulator of growth hormone release and it is mainly produced in the stomach but not secreted into the gastrointestinal

tract like digestive enzymes but into blood vessels to circulate throughout the body [6]. Ghrelin causes weight gain by increasing food intake and reducing fat use [7, 8]. Ghrelin has effects on nutrient intake and growth hormone (GH) release, subsequently on physical development and growth [9]. Although nutritional and growth status were investigated in children with cyanotic and acyanotic heart disease, serum ghrelin levels have not been established. The objective of this study is to investigate and compare the functional role of ghrelin on the regulation of energy balance in children with congenital cyanotic and acyanotic heart disease.

Material and Methods

The study was carried out on 20 children with acyanotic CHD with no heart failure, 15 children with cyanotic CHD with no heart failure, 25 patients with congenital heart disease either cyanotic or acyanotic and having evidence of heart failure, in addition to 30 age and sex - matched healthy children. The clinical diagnosis of all patients was made on the basis of clinical and laboratory examinations using electrocardiogram, and echocardiography. None of the patients had other associated abnormalities or pulmonary hypertension, or evidences of nutritional deficiency due to other chronic gastrointestinal or renal diseases. Body mass index (BMI) was calculated as the ratio of body weight (kg) and squared height (m). Informed consents were obtained from the parents of all subjects. Serum ghrelin levels were analyzed with ELISA kits (Ghrelin kit from Phoenix USA).

Statistical methods:

All data were analyzed by SPSS software, version for Windows. Data were presented as mean ± standard deviation. The given data were compared between groups using one-way ANOVA test. Correlation between the parameters were explored with Spearman's correlation. P values less than 0.05 were considered statistically significant.

Table 1. Demographic data and anthropometric measurements

	Patient with CHD (n=60)			Control (n=30)	p
	C-CHD (n=15)	AC-CHD (n=20)	HF (n=25)		
Age in months (mean ± SD)	12±4	14±3	13±5	13±4	0.09
Sex (M:F)	1.3:1	1:1.3	1:1.3	1:1	0.62
BMI [kg/m^2] (mean ± SD)	13.30 ± 2.8	16.25 ± 1.94	10.60 ± 1.58	21±4	0.001
Weight (kg)	9.25 ± 2.3	10.8 ± 1.4	8.8 ± 1.5	12.5 ± 1.1.	< 0.05
Height (cm)	76.3 ± 1.5	82.2 ± 1.7	70.1	88.6	< 0.05

C-CHD, Cyanotic Congenital Heart Disease; HF; heart failure
AC-CHD, Acyanotic Congenital Heart Disease

Results

This study included 60 children with CHD; 20 children with acyanotic CHD with no heart failure, 15 children with cyanotic CHD with no heart failure, 25 patients with CHD and heart failure, in addition to 30 control children. Age and anthropometric data of the patients and the control subjects are shown in Table (1). The mean value of BMI in patients with congenital heart diseases was significantly lower than in control subjects (p=0.001). Serum ghrelin level was significantly higher in acyanotic and cyanotic children with or without heart failure compared to those of the control group (p=0.003 and 0.001) respectively (Table 2). Cyanotic patients had significantly higher mean serum ghrelin level than acyanotic patients (p<0.001). Patients with congenital heart disease with HF had significantly higher mean serum ghrelin

Table 2. The diagnosis of the studied children with Congenital Heart Disease

	Cyanotic patients without heart failure (n= 15)	Acyanotic with heart patients (n=20)	Cyanotic and Acyanotic CHD patients with heart failure (n=25)
Tetralogy of Fallot	8/15		
Tricuspid atresia	3/15		
Transposition of great arteries	3/15		
Truncus arteriosus	1		
Ventricular septal defect		11	
Patent ductus arteriosus		4	
Atrial septal defect		5	
VSD with HF			11/25
PDA with HF			4/25
ASD with HF			3/25
TGA with HF			3/25
Ticusped Atresia with HF			3/25
Truncus Arteriosus with HF			1/25

Table 3. Serum ghrelin level in different groups

	Serum ghrelin	Control	P
All CHD patients without HF	25.4±4.2	6.200 ± 2.65	0.01
Patients with HF	41.72 ± 4.0	6.200 ± 2.65	0.02
Cyanotic patients	21.25±1.94	6.200 ± 2.65	0.001
Acyanotic patients	13.30±2.85	6.200 ± 2.65	0.003

level compared to children with congenital heart disease without heart failure ($p<0.02$). There was a significant negative correlation between ghrelin and BMI in all patients' groups including cyanotic heart disease with no HF ($r=-0.831$, $p=0.02$), patients with acyanotic congenital heart disease with no HF ($r=-0.458$, $p=0.017$); and patients with congenital heart disease and heart failure ($r=-0.608$, $p=0.007$).

Discussion:

Growth failure is evident in patients with cyanotic or acyanotic heart disease either associated with heart failure or not. The cause of growth retardation in CHD is multifactorial. Inadequate caloric intake, malabsorption, and increased energy requirements caused by increased metabolism may all contribute. However, inadequate caloric intake appears to be the most important cause of growth failure in CHD [1, 10, 11]. Although growth impairment is most pronounced in infants with cyanotic CHD, growth failure does not correlate well with the degree of hypoxia. In this study, the cyanotic children had a more pronounced retardation in both height and weight than in the acyanotic patients [12,13] and this reduction was more marked in those having evidences with heart failure. Ghrelin is accepted as a good marker of the nutritional state, mainly in situations of malnutrition, like anorexia nervosa, owing its fast recovery after weight gain [14]. The inverse correlation between ghrelin levels and BMI is well defined [9,15]. We observed the mentioned correlation, both in children with cyanotic heart disease and in children with acyanotic heart disease. We found that serum ghrelin levels were significantly elevated in the cyanotic patients than in the acyanotic patients. Growth failure in cyanotic children has not been shown to be proportional to the severity of cyanosis, suggesting that multiple factors are involved in the pathogenesis of their growth disturbance [16]. Alteration of endocrine mediators of growth has been implicated as a possible mechanism of growth failure in cyanotic patients. Cardiac cachexia describes wasting primarily due to loss of lean body mass.

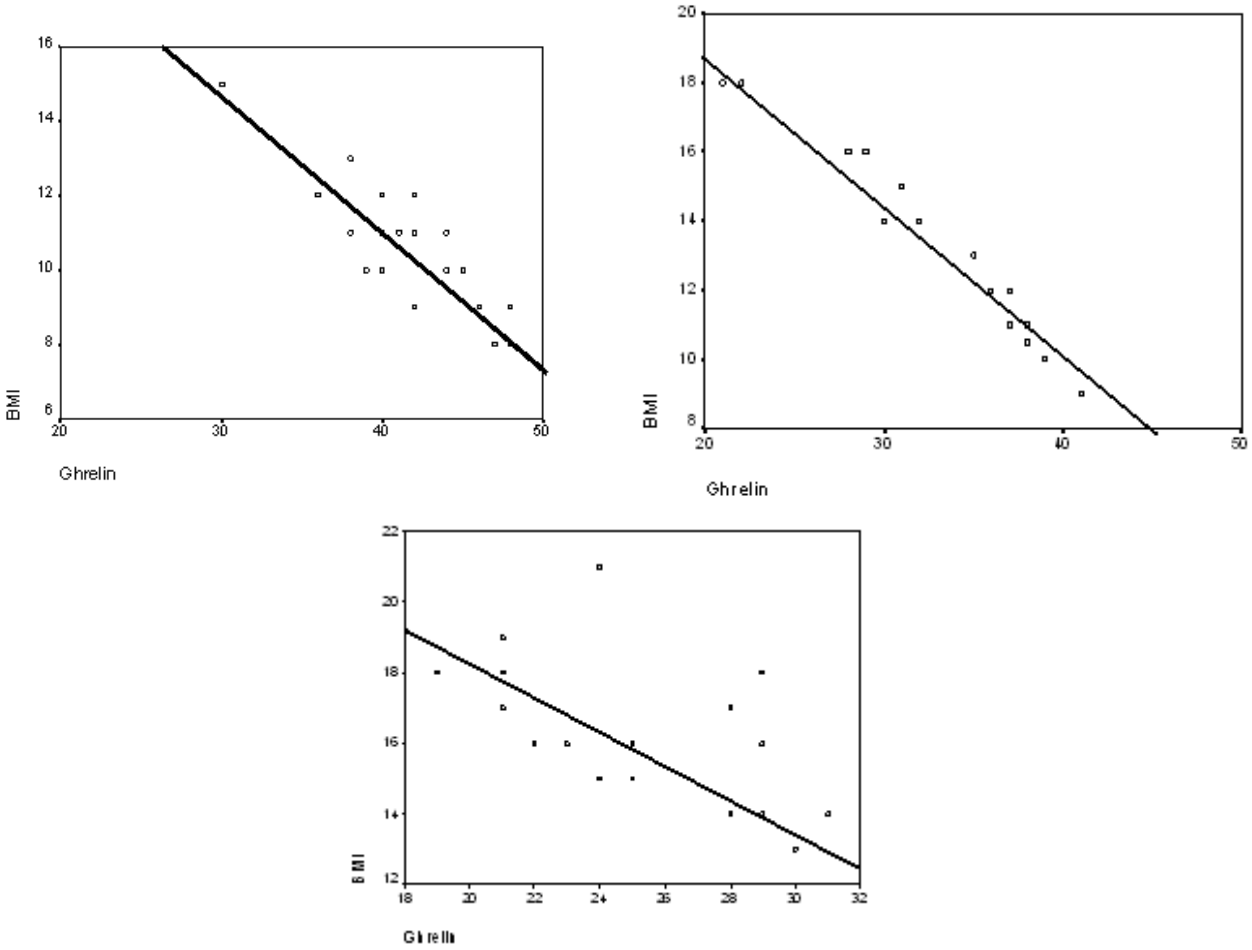

Figure 1. Correlations of ghrelins. (A) correlation between BMI and serum Ghrelin in patients with heart failure. There is significant negative correlation with r = -0.608, p = 0.007; (B) correlation between BMI and serum Ghrelin in patients with cyanotic heart disease. There is significant negative correlation with r = -0.831, p = 0.02; (C) correlation between BMI and serum Ghrelin in patients with acyanotic heart disease. There is significant negative correlation with r = -0.458, p = 0.017.

Cachexia results in decreased muscle strength and function and compromised immune function [17,18]. This syndrome is likely to occur in children who have chronic congestive heart failure, chronic hypoxemia [19]. In addition to inadequate calorie and protein intake, there is evidence that this syndrome may be caused by other chachecting factors as circulating tumor necrosis factor, which stimulates catabolism [20]. In the present study, ghrelin was significantly higher in children with CHD than in the control subjects. This finding raises the possibility of the direct effect of ghrelin or the impact of heart failure severity upon ghrelin.

Nagaya et al. [21] have shown that plasma ghrelin level is increased in cachectic patients with congestive heart failure as a compensatory mechanism in response to anabolic-catabolic imbalance. In conclusion, serum ghrelin level is elevated in cyanotic and acyanotic patients with CHD. Increased ghrelin levels represents malnutrition and growth retardation in these patients and this may be explained by the possible effect of congestive heart failure and chronic hypoxemia on ghrelin and its relation with the release of some cytokines as IL6 and TNF alpha. Also there is a limitation of the number of our cases so more studies are needed

with large sample size to clear the role of ghrelin in reflecting the nutritional status in children with congenital heart disease.

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