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Changes of serum Leptin and Ghrelin Levels in Children with Congenital Heart Disease and Correlations with growth parameters.

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ABSTRACT

Background: Children with congenital heart diseases (CHD) are prone to malnutrition because of low caloric intake, increased caloric requirements and cardiac lesions effects. Leptin and ghrelin play an important role in appetite control. Leptin is anorexiogenic while ghrelin is orexieginc. Researches done to investigate the relationship between leptin or ghrelin levels and growth of CHD patientsrevealed dissimilar & conflicting results across different countries. So, we aimed to measure and compare leptin & ghrelin levels ofchildren with cyanotic and acyanoticCHDwith those of age and sex matched controlsand to correlate them with the different growth parameters of those children. Material and Methods: This study was carried out on 110children (40 patients with acyanotic, 30 patients with cyanotic CHD and 40 healthy controls). Patients and controls were subjected to history taking, clinical examination, chest x-ray, electrocardiogram, echocardiography and measurement of serum leptin and ghrelin levels using enzyme-linked immunosorbent assay. Results: Patients with CHD had significantly lower weight, length, mid upper arm circumference and body mass index compared to controls. Serum leptin level was significantly lower and serum ghrelin level was significantly higher in CHD patients compared to controls. Leptin levels were positively correlated, while ghrelin levels were negatively correlated with body mass index, mid arm circumference and age in all groups Also leptin was negatively correlated with ghrelin levels. Multiple linear regression analysis revealed a predictable fixed relationship between BMI and both leptin and ghrelin levels. Conclusion: Children with CHD have lower leptin & higher ghrelin levels than healthy controls. Changes in leptin & ghrelin levels seem to play a role in the cachexia associated with CHD.

Key words: Leptin; ghrelin; congenital heart disease;acyanotic congenital heart disease; cyanotic congenital heart disease.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital anomalies in pediatrics, representing a major cause of morbidity and mortality. Prevalence of CHD varies widely among studies worldwide, however it was reported that 1.35 million babies are born with CHD every year [1].

Poor growth is common problem in children with congenital heart disease [2]. The prevalence being as high as 64% in developed countries of the world [3]. The problem is more severe in the developing regions, where malnutrition is common even in otherwise normal children [4,5]. Several factors may play a role, including low caloric intake, increased metabolic requirements, effects of the primary cardiac defect and associated non-cardiac and genetic diseases [6]. However, the exact mechanism underlying this growth retardation is not yet clear.

Leptin and ghrelin are hormones that have been recognized to have a major impact on energy balance. Leptin is involved in long-term regulation of energy balance, suppressing appetite and consequently stimulating weight loss. Ghrelin on the other hand is a fast-acting hormone playing a role in stimulating food intake [7].

Research on relationship between leptin or ghrelin levels and growth of patients with cyanotic and acyanotic CHD revealed dissimilar & conflicting results across different countries [8-16].

The aim of this study was to measure serum leptin and ghrelin levels in Egyptian children with cyanotic and acyanotic congenital heart disease and to evaluate their possible impact on growth of those children.

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MATERIALS AND METHODS

This study was conducted onseventy Egyptian patients with congenital heart disease (40 patients with acyanotic CHD and 30 patients with cyanotic CHD) and forty apparently normal children with comparable age, sex and socioeconomic status as a control group. Patients were collected from the Pediatric Cardiology Clinic, Menoufia University Hospital in the period from February 2015 to January 2016. Criteria for eligibility in the study included 1)patients withacyanotic or cyanotic congenital heart diseases, 2) age from 2 months up to 18 years, 3) parental consent. We exclude patients with other congenital anomalies, chromosomal abnormalities, any other chronic disease & patients with acquired heart disease. Control group were selected from general pediatric outpatient clinic in the same period. They were healthy children; non-hospitalizedwith no pathological findings had recorded in their physicalexamination.

All patients & control were subjected to the following:

- Complete history taking and thorough clinical examination.
- Anthropometric measurements including length in cm, weight in kg, mid upper arm circumference (MAC) in cm and body mass index (BMI) in kg/m^2.
- Investigations including oxygen saturation by pulse oximetry, Chest x-ray, Electrocardiograpy (ECG). Echocardiography using philips HD 11 machine and Serum leptin (ng/ml) & ghrelin (ng/dl) levels using enzyme-linked immunosorbent assay (ELISA).

Sampling:

Blood samples of 3 mL were collected by venipuncture from all participants after a fasting period of 3 hours in plain vacutainer tube.Samples were separated by fully centrifugation at 3000 rpm for 20 minutes. Clear sera were separated and kept frozen at -20°C until the time of the assay. Leptin was measured using the DRG Leptin EL1SA (DRG International, Inc., USA), while Ghrelin was measured with Invitrogen Ghrelin Human ELISA (Thermo Fisher Scientific Inc. USA) by indirect enzyme linked immunosorbent assay according to the protocol provided by the manufacturer. The intensity of color developed is proportional to the concentration of leptin and gherlin in the sample, the absorbance is measured at 450 nm and their concentrations were determined from standard curve.

Groups:

The studied population was classified into three groups:

1. Acyanotic group consisted of 40 patients with acyanotic congenital heart disease (24 boys and 16 girls; mean age = 20.2±36.1 months). They had no central cyanosis and oxygen saturation (SpO2) was > 98% measured at rest.
2. Cyanotic group consisted of 30 unrepaired & unpalliated patients with cyanotic congenital heart disease (18 boys and 12 girls; mean age= 26.3±40.1 months). They had central cyanosis &oxygensaturation(SpO2) was 75-85%measuredatrest.
3. Control group consisted of 40 healthy children (20 boys and 20 girls, mean age = 28.8±40.9 months).

All our patients had been fed orally by mouth as other healthy controls. No one of them has nasogastric tube or g-tube.

Ethical Standards:

The authors assert that all procedures contributing to this work comply with the ethical standards of the Egyptian national research committee and with the Helsinki Declaration of 1964,as revised in 2013, and has been approved by the by Ethical Committee of Menoufia faculty of medicine. Informed consent was obtained from the guardian of each participant included in the study.

Statistical analysis:

The data collected were analyzed using IBM SPSS (statistical package for the social science software) version 22 on compatible computer. Variables are presented as numbers and percentages or mean ± SD, as indicated. The distribution of qualitative variables among groups was analyzed by Chi-square test. Means were compared with ANOVA (F), Kruskal Wallis test or Mann-Whitney test as appropriate. Leptin and gherlin levels were correlated with other variables using Spearman correlation test in all groups. Multiple linear regressions were applied to detect the relationship between two variables by fitting a linear equation to observed data. A linear regression line had an equation of the form Y = a + b X, where X was the independent (explanatory) variable, Y was the dependent variable (BMI). The slope of the line is “b”, and “a” is the intercept (the value of y when x = 0). Significance of the obtained results was judged at the 5% level.

Results:

The three groups (acyanotic, cyanotic & control groups) were homogenous as regards age and gender characteristics. Patients with congenital heart disease had significantly lower weight, length, MAC & BMI compared to controls. BMI of cynotic patients was significantly lower than that of acyanotic patients (Table 1)

According to the etiological diagnosis of cardiac anomalies in patients with CHD; we found

that out of the acyanotic group 18 had ventricular septal defect, 13 had atrial septal defect, 7 had patent ductus arteriosus, 1 had coarctation of aorta and 1 had atrial and ventricular septal defect and out of cyanotic group 15 had tetralogy of Fallot, 6 had transposition of great arteries, 3 had tricuspid atresia, 3 had double outlet right ventricle with pulmonary stenosis, 1 had pulmonary atresia, 1 had double inlet single ventricle with pulmonary stenosis and 1 had ebstein anomaly (Table 2).

Leptin & ghrelin levels were significantly different between the acyanotic, cyanotic and control groups (P= 0.03 &<0.001 respectively). On post hoc test showed that leptin levels were significantly lower in acyanotic& cyanotic groups when compared with controls (P< 0.05). On the other hand, Ghrelin levels were significantly higher in patients with acyanotic& cyanotic groups compared to controls (P< 0.001) (Table 1).

Leptin levels were positively correlated with BMI, MAC & age in all groups (P<0.001), while ghrelin levels were negatively correlated with BMI, MAC & age in all groups (P<0.001) (Table 3). Also leptin levels were negatively correlated with ghrelin levels (P<0.001) (Table 4). Linear regression analysis revealed a predictable fixed relationship between BMI and both leptin & ghrelin levels, where β was 0.710 for leptin & - 0.522 for ghrelin (P<0.001) (Table 5).

Table 1: Demographic data, anthropometricmeasurements, leptin and ghrelin levels of studied groups.

Items	Acyanotic group *(N=40)*	Cyanotic group *(N=30)*	Control group *(N=40)*	P value	Post hoc test
Age (month)	20.2±36.1	26.3±40.1	28.8±40.9	0.16	P1=0.36 P2=0.06 P3=0.45
Male: female,*N* (%)	24:16(60/40)	18:12 (60/40)	20:20 (50/50)	0.59	P1=1.00 P2=0.37 P3=0.41
Weight (Kg)	10.2±10.2	8.1±5.9	14.8±12.8	0.002	P1=0.31 P2=0.003 P3=0.003
Length (m)	0.74±0.28	0.74±0.26	0.84±0.27	0.004	P1=0.73 P2=0.002 P3=0.01
BMI (Kg/m^2)	15.4±1.9	13.3±3.0	17.5±3.5	<0.001	P1=0.001 P2=0.002 P3<0.001
MAC (cm)	13.3±3.8	12.4±3.5	15.6±4.1	0.001	P1=0.35 P2=0.008 P3=0.001
Leptin *(ng/ml)*	2.9±1.5	2.7±2.2	3.9±2.3	0.03	P1=0.29 P2=0.04 P3=0.03
Ghrelin *(ng/dl)*	5.7±1.3	6.6±2.8	2.8±1.4	<0.001	P1=0.10 P2<0.001 P3<0.001

Data were expressed as mean ± SD except male:female ratio.
P1: Acyanotic versus cyanotic groups.
P2: Acyanotic group versus controls.
P3: Cyanotic group versus controls.

Table 2: Specific diagnoses in acyanotic& cyanotic groups.

Diagnosis	Number (%)
Acyanotic group	40 (100)
• Ventricular septal defect	18 (45)
• Atrial septal defect (ASD)	13 (32.5)
• Patent ductus arteriosus (PDA)	7 (17.5)
• Coarctation of aorta	1 (2.5)
• ASD & PDA	1 (2.5)
Cyanotic group	30 (100)
• Tetralogy of Fallot	15 (50)
• Transposition of great arteries	6 (20)
• Tricuspid atresia	3 (10)
• Double outlet right ventricle with pulmonary stenosis	3 (10)
• Pulmonary atresia	1 (3.33)
• Double inlet single ventricle with P.S.	1 (3.33)
• Ebstein anomaly	1 (3.33)

Table 3: Correlation of leptin & ghrelin level with age, BMI & MAC among studied groups.

Items	Leptin (ng/ml)		Ghrelin (ng/dl)	
	r	P value	r	P value
Age	0.672	<0.001	-0.593	<0.001
BMI	0.754	<0.001	-0.743	<0.001
MAC	0.675	<0.001	-0.731	<0.001

Table 4: Correlation between leptin and ghrelin levels among studied groups.

Item	Leptin level (ng/ml)	
	r	P value
Gherlin level (ng/dl)	-0.681	<0.001

Table 5: Multiple linear regression analysis to detect predictable factors for BMI among studied groups.

Predictors	Beta (β)	T	SE	P value
Age (month)	0.01	1.83	0.006	0.07
Leptin level (ng/ml)	0.710	5.85	0.121	<0.001
Ghrelin level (ng/dl)	-0.522	5.09	0.103	<0.001

The power of this regression model (R^2) to predict BMI was 64.7%. It was found that constant (a) was 15.66.

Discussion:

Malnutrition occurs among children with congenital heart disease, irrespective of the type of the cardiac defect [17].We found that patients with congenital heart disease had significantly lower weight, length, MAC & BMI compared to controls. BMI of cyanotic patients was significantly lower than that of acyanotic patients. Similar results were obtained by other studies [8,11,18-20].

Studies showed that growth retardation may be caused low caloric intake caused by anorexia, dyspnea & tachypnea [5], increased energy requirements caused by increased metabolism, or both [21-23]. However, the exact mechanism of this poor growth is not yet clear.

Leptin is a hormone produced mainly by adipose tissue, released into blood stream, crosses the blood brain barrier and binds to hypothalamic leptin receptors [24]. It transfers information about the triglyceride content of adipocyte, as well as the macronutrient and energy composition of recent food intake, [25–27]. Low circulating leptin levels have been found to increase activity of hypothalamic neurons that secret orexigenic peptides and decrease activity of in neurons that secret anorexigenic peptides, thereby increasing appetite & stimulate weight gain [28].

On the other hand, ghrelin "hunger hormone" is secreted mainly by the stomach. Its effects on energy balance are also mediated by the hypothalamus. It stimulates food intake and adiposity through stimulation of hypothalamic orexigenic neuropeptides [29].Ghrelin also stimulates the expression and secretion of growth hormone (GH) and thus indirectly triggers expression and secretion of hepatic insulin-like growth factor-1 (IGF-1) [29,30-32]. Both, GH and IGF-1 are anabolic hormones known to increase lean body mass [33-35]. Ghrelin levels increase before & decrease after meal [36-38] and it has been demonstrated that the preprandial increase in ghrelin levels correlates with hunger scores in healthy adults, initiating food intake voluntarily in the absence of time and food-related stimulus [39].

Our study showed that serum leptin level was significantly lower & serum ghrelin level was significantly higher in CHD patients compared with controls. No significant differences in leptin or ghrelin levels were found between acyanotic and cyanotic groups. Previous studies investigated the level of leptin or ghrelin in children with CHD are summarized in tables 6 and 7.

Table 6: Previous studies investigated leptin levels* in pediatric patients with acyanotic& cyanotic congenital heart diseases

Author	CHD patients		Controls	Significance (p value)
	Acyanotic	Cyanotic		
Rao et al. [20]	(n= 25) 6.20 ± 4.23		(n= 59) 7.97 ± 2.79	S(< 0.05)
Hallioglu et al. [11]	(n=20) 3.41 ± 3.39	(n=28) 2.55 ± 1.69	---------	NS(> 0.05)
Aydin et al. [18]	(n=20) 6.89 ± 1.43	(n=18) 7.55 ± 1.46	---------	NS(> 0.05)
Shahramian et al. [13]	(n=21) 2.18 ± 2.07	(n=24) 1.86 ± 1.53	(n= 19) 1.39 ± 1.45	NS(> 0.05)
El-Melegy& Mohamed [10]	(n=30) 32.93 ±9.53	(n=30) 41.96± 11.05	(n=25) 8.88 ± 2.03	S (<0.01) S (<0.001)#
Zhang et al. [19]	(n =48) -With HF (n=20) 8.45 ± 1.73 -Without HF (n=28) 6.33 ±1.46	(n=20) 9.87 ± 2.51	(n= 20) 3.24 ± 0.94	S (<0.01)

* measured by ng/ml.
#Acyanotic versus cyanotic groups.
Data were expressed as mean ± SD.
S: statistically significant difference.
NS: no statistically significant difference.

Table 7: Previous studies investigated ghrelin levels in pediatric patients with acyanotic& cyanotic congenital heart diseases

Author	CHD patients		Controls	Significance (p value)
	ACCHD	CCHD		
Yilmaz et al.* [15]	(n= 47) 41.9 ± 11.6		(n= 21) 19.2 ± 5.9	S(< 0.001)
Al-Asy et al.* [9]	(n=33) 13.30 ± 2.85	(n=27) 21.25 ± 1.94	(n=30) 6.20 ± 2.65	S(0.001)
Kandil et al.* [12]	(n=22) 69.04 ± 38.97	(n=18) 99.72 ± 22.52	(n=18) 13.32 ± 6.87	S (<0.001)
Afify et al.* [8]	(n=40) 44.2 ± 13.9	(n=20) 19.7 ± 6.5	(n= 20) 9.5 ± 1.0	S(<0.001)
Yadav et al.# [40]	(n=67) Preclosure: 38.64 ± 2.67		(n=20) 20.73 ± 4.16	S (<0.05)
Wang et al.* [14]	(n =36) 40.76 ± 8.42	(n=27) 19.19 ± 5.37	(n= 28) 8.82 ± 1.34	S (<0.001)
Shahramian et al.# [13]	(n=21) 5.346 ± 2.347	(n=24) 7.625 ± 8.586	(n= 19) 6.026 ± 4.473	NS(> 0.05)

*measured by ng/ml.
measured by pg/ml.
Data were expressed as mean ± SD.
S: statistically significant difference.
NS: no statistically significant difference.

Our results go with*Rao et al.*who found that children with congenital heart disease had lower leptin levels than healthy controls [20]. Also *Hallioglu et al. and Aydin et al.* found there was no significant difference in plasma leptin levels between cyanotic and acyanotic patients despite lower BMI in cyanotic patients. These two studies did not include healthy children to compare with [11,18]. In contrary to our results**,** *Shahramian et al.*found no statistically significant difference between acyanotic, cyanotic patients and healthy controlsregarding serum leptin orghrelin level, although in his study no significant differences were observed between groups regarding weight, height and BMI [13].

Furthermore, Yadav et al. showed that serum ghrelin levels are significantly elevated in patients with CHD compared to controls and gradually return towards the baseline levels at the end of 3 months post percutaneous management of the lesions, indicating that CHD is the cause of such elevation [40]. Our results go with Wang et al. (14)who came to aconclusive evidence that serum ghrelin is elevated in children with CHD.

In our study BMI, MAC & age in all groups were correlated positively with leptin levels & negatively with ghrelin levels**.** Previous studies support these findings [9, 11,12.15,16,20]**.**

Contrarily Shahramian et al. showed that BMI is positively correlated with leptin but not with ghrelin in CHD patients [13] Also we found that leptin levels were negatively correlated with ghrelin levels (P <0.001).

To obtain more accurate & conclusive data, multiple Linear regression analysis was done which revealed a predictable fixed relationship between BMI and both leptin & ghrelin levels in our patients where β was 0.710 for leptin & - 0.522 for ghrelin (P<0.001)**.**

This study has limitations. First, it was a single-center study. Second, is the variability in the anatomy and hemodynamics between various types of CHD within the studied groups.

Conclusions:

Children with congenital heart disease are at increased risk for poor growth. Elevated leptin & reduced gherlin levels were found in children with CHD, whether cyanotic or acyanotic, suggesting a role for both hormones in regulation of nutrient intake, energy balance & maintenance of body weight in those children. Further studies are needed to clarify the impact of correcting leptin & ghrelin changes in children with CHF on growth of those children.

REFERENCES

1. Reller, M.D., M.J. Strickland, T. Riehle-Colarusso, W.T. Mahle and A. Correa, 2008. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. The Journal of pediatrics, 153(6): 807-813. doi: 10.1016/j.jpeds.2008.05.059
2. Day, M., 1989. Growth and nutritional intake of infants with congenital heart disease. Pediatr Ann, 7: 35-57.
3. Cameron, J.W., A. Rosenthal and A.D. Olson, 1995. Malnutrition in hospitalized children with congenital heart disease. Archives of pediatrics & adolescent medicine, 149(10): 1098-1102. doi: 10.1001/archpedi.1995.02170230052007
4. Thompson, O.C., N.T. Reyes, O.B. Rabiela, A.H. Buendía, I.C. Miranda and R.Q. Carrasco, 1998. The nutritional status of the child with congenital cardiopathy. Archivos del Instituto de Cardiologia de Mexico, 68(2): 119-123 .
5. Varan, B., K. Tokel and G. Yilmaz, 1999. Malnutrition and growth failure in cyanotic and acyanotic congenital heart disease with and without pulmonary hypertension .Archives of Disease in Childhood, 81(1): 49-52. doi: 10.1136/adc.81.1.49
6. Daymont, C., A. Neal, A. Prosnitz and M.S. Cohen, 2013. Growth in children with congenital heart disease. Pediatrics, 131(1): 236-242. doi: 10.1542/peds.2012-1157

7. Klok, M.D., S. Jakobsdottir and M.L. Drent, 2007. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obesity reviews, 8: 21-34. DOI:10.1111/j.1467-789X.2006.00270.x
8. Afify, M.F., G.B. Mohamed, M.A. El-Maboud and E.A. Abdel-Latif, 2009. Serum Levels of Ghrelin, Tumor Necrosis Factor-α and Interleukin-6 in Infants and Children with Congenital Heart Disease. Journal of tropical pediatrics, 55(6): 388-392. doi: 10/1093.tropej/fmp036
9. Al-Asy, H.M., A.A. Donia, D.M. El-Amrosy, E. Rabee and A. Al Bendary, 2014. The levels of ghrelin in children with cyanotic and acyanotic congenital heart disease. Journal of Pediatric Sciences, 6. doi: 10.17334/jps.46761
10. El-Melegy, N.T. and N.A. Mohamed, 2010. Angiogenic biomarkers in children with congenital heart disease: possible implications. Italian journal of pediatrics, 36(1): 32. doi:10.1186/1824-7288-36-32
11. Hallioglu, O., D. Alehan and N. Kandemir, 2003. Plasma leptin levels in children with cyanotic and acyanotic congenital heart disease and correlations with growth parameters. International journal of cardiology, 92: 97-93. doi: 10.1016/S0167-5273(03)00044-5
12. Kandil, M.E., A. Elwan, Y. Hussein, W. Kandeel and M. Rasheed, 2009. Ghrelin levels in children with congenital heart disease. Journal of tropical pediatrics, 55(5): 307-312. doi: 10.1093/tropej/fmp012
13. Shahramian, I., N.M. Noori, M. Hashemi, E. Sharafi and A. Baghbanian, 2013. A study of serum levels of leptin, ghrelin and tumour necrosis factor-alpha in child patients with cyanotic and acyanotic, congenital heart disease. J Pak Med Assoc, 11(63): 1332-1337.
14. Wang, D., J. Fang, R. Wang, D. Sun, K. Xia, W. Yin, L. Sun, 2016. Elevated serum ghrelin, tumor necrosis factor-α and interleukin-6 in congenital heart disease. Pediatrics International., 58(4): 259-264. doi: 10.1111/ped.12773
15. Yilmaz, E., B. Ustundag, Y. Sen, S. Akarsu, A. Kurt and Y. Dogan, 2007. The levels of ghrelin, TNF-α, and IL-6 in children with cyanotic and acyanotic congenital heart disease. Mediators of inflammation, doi: 10.1155/2007/32403
16. Zhang, G., X. Yin, Y. Qi, L. Pendyala, J. Chen, D. Hou and C. Tang, 2010. Ghrelin and cardiovascular diseases. Current cardiology reviews, 6(1): 62-70. doi: 10.2174/157340310790231662
17. Gilger, M., C. Jensen, B. Kessler, P. Nanjundiah and W. Klish, 1990. Nutrition, growth, and the gastrointestinal system: basic knowledge for the pediatric cardiologist. The science and practice of pediatric cardiology. Philadelphia: Lea &Febiger, 2354-2370.
18. Aydin, H.I., Y. Yozgat, E.D emirkaya, A. Olgun, V. Okutan, M.K. Lenk and O. Özcan, 2007. Correlation between vascular endothelial growth factor and leptin in children with cyanotic congenital heart disease. The Turkish journal of pediatrics, 49(4): 360.
19. Zhang, Y., R. Xiang, X. Hu, H. Wen, M. Zhu, Y. Ren, Q. Chen, 2009. Changes of serum leptin and vascular endothelial growth factor in children with congenital heart disease. Chinese journal of contemporary pediatrics, 11(10): 802-804.
20. Rao, S.N., G.P. Gurumurthy, P. Gururajan, S.B. Arumugam, V. Kirthivasan and K. Cherian, 2010. Clinical and biochemical parameters in relation to serum leptin levels in South Indian children and adolescents. The Indian Journal of Pediatrics, 77(5): 555-559. doi: 10.1007/s12098-010-0061-x
21. Schuurmans, F., C. Pulles-Heintzberger, W. Gerver, A. Kester and P.P. Forget, 1998. Long-term growth of children with congenital heart disease :a retrospective study. Acta Paediatrica, 87(12): 1250-1255. doi: 10.1111/j.1651-2227.1998.tb00947.x
22. Leitch, C.A., C.A. Karn, R.J. Peppard, D. Granger, E.A. Liechty, G.J. Ensing and S.C. Denne, 1998. Increased energy expenditure in infants with cyanotic congenital heart disease. The Journal ofpediatrics, 133(6): 755-760. doi: 10.1016/S0022-3476(98)70146-5
23. Menon, G. and E. Poskitt, 1985. Why does congenital heart disease cause failure to thrive? Archives of Disease in Childhood, 60(12): 1134-1139. doi: 10.1136/adc.60.12.1134
24. Zhang, Y., R. Proenca, M. Maffei, M. Barone, L. Leopold and J.M. Friedman, 1994. Positional cloning of the mouse obese gene and its human homologue. Nature, 372(6505): 425-432. doi: 10.1038/372425a0
25. Havel, P.J., 2002. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. Current opinion in lipidology, 13(1): 51-59. doi: 10.1097/00041−433 00008−200202000
26. Havel, P.J., R. Townsend, L. Chaump and K. Teff, 1999. High-fat meals reduce 24-h circulating leptin concentrations in women. Diabetes, 48(2): 334-341. doi: 10.2337/diabetes.48.2.334
27. Weigle, D.S., D.E. Cummings, P.D. Newby, P.A. Breen, R.S. Frayo, C.C. Matthys, J.Q. Purnell, 2003. Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet. The Journal of Clinical

Endocrinology & Metabolism, 88(4): 1577-1586. doi: 10.1210/jc.2002-021262
28. Schwartz, M.W., 2001. Brain pathways controlling food intake and body weight. Experimental Biology and Medicine, 226(11): 978-981. doi: 10.1177/153537020122601103
29. Korbonits, M., A.P. Goldstone, M. Gueorguiev and A.B. Grossman, 2004. Ghrelin—a hormone with multiple functions. Frontiers in neuroendocrinology, 25(1): 27-68. doi: 10.1016/j.yfrne.2004.03.002
30. Kojima, M., H. Hosoda, Y. Date, M. Nakazato, H. Matsuo and K. Kangawa, 1999. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature, 402(6762): 656-660. doi: 10.1038/45230
31. Cheung, W.W., W. Ding, S.S. Gunta, Y. Gu, R. Tabakman, L.N. Klapper, R.H. Mak, 2013. A pegylated leptin antagonist ameliorates CKD-associated cachexia in mice. Journal of the American Society of Nephrology, ASN. 2013040432.
32. Peino, R., R. Baldelli, J. Rodriguez-Garcia, S. Rodriguez-Segade, M. Kojima, K. Kangawa, F.F. Casanueva, 2000. Ghrelin-induced growth hormone secretion in humans. European Journal of Endocrinology, 143(6): R11-R14. doi: 10.1530/eje.0.143R011
33. Amato, G., C. Carella, S. Fazio, G. La Montagna, A. Cittadini, D. Sabatini, A. Bellastella, 1993. Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy atlow doses. The Journal of Clinical Endocrinology & Metabolism, 77(6): 1671-1676.
34. Fuller, S.J., J.R. Mynett and P.H. Sugden, 1992. Stimulation of cardiac protein synthesis by insulin-like growth factors. Biochemical Journal, 282(1): 85-90. doi: 10.1042/bj2820085
35. Moller, N., M.H. Vendelbo, U. Kampmann, B. Christensen, M. Madsen, H. Norrelund and J.O. Jorgensen, 2009. Growth hormone and protein metabolism. Clinical Nutrition, 28(6), 597-603. doi: 10.1016/j.clnu.2009.08.015
36. Cummings, D.E., J.Q. Purnell, R.S. Frayo, K. Schmidova, B.E. Wise and D.S. Weigle, 2001. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes, 50(8): 1714-1719. doi: 10.2337/diabetes.50.8.1714
37. Ariyasu, H., K. Takaya, T. Tagami, Y. Ogawa, K. Hosoda, T. Akamizu, S. Toyooka, 2001. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. The Journal of Clinical Endocrinology & Metabolism, 86(10): 4753-4758. doi: 10.1210/jcem.86.10.7885
38. Tschöp, M., R. Wawarta, R. Riepl, S. Friedrich, M. Bidlingmaier, R. Landgraf and C. Folwaczny, 2001. Post-prandialdecrease of circulating human ghrelin levels. Journal of endocrinological investigation, 24(6): 19-21. doi: 10.1007/BF03351037
39. Cummings, D.E., R.S. Frayo, C. Marmonier, R. Aubert and D. Chapelot, 2004. Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time-and food-related cues. American Journal of Physiology-Endocrinology and Metabolism, 2(87): 297-304.
40. Yadav, S.K., 2015. Changes in serum level of ghrelin, tumor necrosis factor-alpha and interleukin-6 in children with congenital heart disease. Asian Journal of Medical Sciences, 6(5): 12-16. doi: 10.3126/ajms.v6i5.12129

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