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Ghrelin and Obestatin Levels as a Novel Marker in Iraqi Obese Children

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Abstract:

Obesity is an escalating health problem in developing countries. One to ten children worldwide are overweight in a report showed by the International Obesity Task Force. Ghrelin, orexigenic peptide, has 28 amino acids, it is considered the greatest remarkable promotion in the last two decades for understanding the physiological changes of action regulating food intake and hunger. Obestatin is a 23-amino acid peptide nearly connected to ghrelin that secures from substitution splicing the alike resort molecule, pre-proghrelin. The study is designed to assess the level of ghrelin and obestatin in Iraqi obese children and its relation with other biochemical parameters. Ghrelin and obeststin levels were measured in sixty obese children; the range of their age was (5-16) years, and this group was compared to 30 children in a healthy state as a control. Serum FBS, PPBS, and also lipid profiles (TG, TC, HDL-c, and LDL-c) were determined in the studied groups. Calculation of insulin resistance was done by using (HOMA-IR) a Homeostasis Model assessment of insulin resistance. Ghrelin levels were lower in a significant way in subjects who have obesity in comparison with control group. Significantly, there was a high increase in obestatin in obese patients when compared with control. This study demonstrates that obestatin raises and ghrelin is low in obesity, these hormones are related to the resistance of insulin, and there is an association between ghrelin and oxidative stress. The scales between obestatin and ghrelin are likely disturbed in obesity.

Keywords: Ghrelin, Insulin resistance, Lipid profile, Obesity, Obestatin.

Introduction:

Obesity is an escalating health problem in developing countries. One to ten children worldwide are overweight as a report showed in the (IOTF) International Obesity Task Force, about 155 million of adolescents and children are overweight and approximately (30–45) millions are categorized as obese[1]. Throughout the world, obesity has an approach to epidemic proportions, also the people of the Gulf regions have been influenced, mostly it is available in high income and oil manufacturing countries. In the Gulf countries the range of obesity increases between adolescents and children about 3% to 18% in females and 5% to 14% in males [2, 3]. Bone and joint conundrums are the greater risks for children and adolescents who are in obesity state, some psychological problems affect obesity like stigmatization, sleep apnea, and poor self-esteem. Also, it is related to several hazard factors for later chronic and heart disease such as hypertension, atherosclerosis in the early stage, hyperlipidemia, and hyperinsulinemia [4]. This is a pathological condition that leads to important health consequences in childhood and later life. Childhood anemia is a condition where a child has abnormal and insufficient hemoglobin levels to provide adequate oxygen to the body tissues [5].

Ghrelin is an orexigenic hormone that was originally isolated from the stomachs of humans and rats in 1999. It includes 28 amino acids and is considered one of the most significant advances in our understanding of physiological processes that regulate food intake and hunger in the last two decades. The interference of peptide with melanocortinergic system affects the pleiotropic metabolic [6]. Growth hormone is stimulated by ghrelin and secrets gogue receptor a (G-protein) that is connected in receptor and this is highly expressed

in gland of pituitary also in the different brain regions, in the pancreas, also the thyroid that stimulates orexigenic neural connections in hypothalamus and activates food intake-separate lipid formation, consequently rises body weight and fat cluster. Farther from its orexigenic influence, ghrelin also controls glucose metabolism, taste, sleep-wake rhythm, and gut motility. Obestatin is defined as a peptide that causes anorexigenic and is widely associated with ghrelin that comes from alternative splicing of the identical primary molecule, called pre-proghrelin. In humans, obestatin is primarily is localized in the domain of the gastro intestine, especially in the stomach. This compound might decrease gastric emptying and food intake, these actions are yet not firmly validated[7]. Obestatin increases insulin sensitivity and glucose uptake also suppresses lipid lysis and might have a suitable, effect on the heart and the vascular process [8]. As a result of these cardiovascular and metabolic effects, obestatin is considered as a promising target for the cardiovascular state that prevents obesity in patients, particularly those with diabetes. Furthermore, in both fat and lean instances, substantial doses of these peptides are poured out [9]. Their adipose tissue of patients with high weight releases factors that raise angiogenesis. In the medical literature, data shows that the growth factor A (VEGF-A), vascular endothelial, which is produced by the intensified manufacture of hormonal compounds and cytokines released by the adipose tissue, has an important role in the production of new vessels. Interactions between this growth factor in the pancreatic beta-cells and endothelial cells, which plays a serious role in the differentiation and regeneration of this endocrine cell [10.] This study is designed to assess the level of ghrelin and obestatin in Iraqi obese children and its relation with other biochemical parameters.

Materials and Methods:

Patients and Control

National Diabetes Center, Mustansiriyah University was the place of collecting the samples during the period from September 2020 to the end of October 2021. Sixty obese children; with age range (5-16) years were enrolled, comparisons were done with 30 healthy children as a control group.

Demographic characters such as age, sex, waist, hip, WHR, height, weight, BMI, SBP, and DBP were collected. Body mass index was calculated from the subjects [11]. The percentage of body fat for the subjects can be evaluated from the BMI of a person by using the formula below:

BF%= (1.51×BMI) – [0.7×age] – (3.6×Gender) + 1.4) [12] (Gender represents 1 if male and 0 in female

Serum FBS, PPBS, and lipid profile (TG, TC, LDL-c, and HDL-c) were measured by using an automated analyzer (BIOLABO Kenza 240TX). The levels of serum insulin were evaluated by the {DRG} ELISA kit [13]. (HOMA-IR) Homeostasis model of IR = {[fast. ins. (μU/ml)] × [fast. Glu. (mg/dl)]}/405 [14]. Serum Ghrelin and Obeststin levels were measured by ELISA kit.

Results:

Table 1, shows that weight, waist, BMI, body fat (BF)% , SBP, and DBP (Mean±SD) increased significantly ($P<0.05$) in obese child when compared with the control. Table 2, shows a significant increase in FBS, fasting insulin level, HOMA-IR, total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-c), [$P<0.05$] in the children who have obesity in comparison with the control group. High significant increase was observed in ghrelin and serum obestatin levels, ($P<0.01$) in obese children when compared with the control group.

As shown in Table 3, serum ghrelin shows a negatively significant correlation in waist circumferences, weight, BMI, BF%, SBP, fasting insulin level, and L.D.L. ($P<0.05$), and a highly significant negative correlation with fasting plasma sugar, HOMA-IR and triglyceride ($P<0.01$) in obese children. While a positive correlation is shown between ghrelin level and high-density lipoprotein ($P<0.05$). Serum obestatin level shows positively significant correlation to waist circumferences, BMI, weight, BF%, SBP, fast, blood sugar, fasting insulin level, HOMA-IR, triglyceride and low-density Lipoprotein. [$P<0.05$] in obese children, while no relation is found in serum ghrelin and serum obestatin levels with age, Hip, WHR, height, DBP, PPBS, and Ghrelin/ Obestatin in obese children.

Figs. 1, 2 explain the comparison of serum ghrelin and serum obestatin levels between males and females in obese children**.**

Table 1. Anthropometric measurement of obese and control children.

Parameters	Obese Children (n=60)	Control (no.=30)	P-Value
Gender (M/F)	(33/27)	(14/16)	-
Age in Years	10.84± 3.9	10.11± 3.61	0.108
Waist(cm)	102.26± 7.3	84.38±5.62	0.05
Hip(cm)	104.72± 3.0	102.71 ± 2.3	0.106
WHR	0.98± 0.06	0.84 ±0.04	0.142
Weight(kg)	49.08± 11.21	34.46± 12.70	0.05
Height(cm)	138.45± 8.6	130.10 ±24.72	0.16
BMI(Kg/m^2)	28.00± 4.43	18.16± 2.79	0.05
Body Fat%	24.12± 2.33	19.11 ±2.20	0.05
SBP(mmHg)	120.0±5.0	110.0±5.0	0.05
DBP(mmHg)	70.0±8.5	62.0±10.0	0.05

At level {*P<0.05 }and {**P<0.01} p-value is significant.

Table 2. Characteristics parameters of the study in obese and control children.

Parameters	Obese Children (no.=60)	Control (n=30)	P Value
Gender (M/F)	(33/27)	(14/26)	-
FBS(mg/dl)	103.68± 6.18	78.33± 4.41	0.05
PPFG(mg/dl)	141.44± 18.22	131.12± 8.80	0.63
Insulin (µU/ml)	15.47± 6.06	11.98± 3.86	0.05
HOMA-IR	3.94± 1.51	2.30 0.74	0.05
TC (mg/dl)	179.44± 29.80	152.0± 26.71	0.05
TG (mg/dl)	165.41± 16.81	94.55±11. 23	0.05
HDL-C (mg/dl)	41.93± 3.93	52.26± 5.31	0.22
LDL-C (mg/dl)	122.36± 30.7	80.83± 8.30	0.05
Ghrline(pg/ml)	25.68± 8.05	46.26± 5.31	0.01
Obestatin(pg/ml)	197.15 ±97.91	101.73± 21.19	0.01
Ghrline/ Obestatin	0.15 ±0.06	0.47 ±0.10	0.11

At level {*P<0.05 }and {**P<0.01} p-value is significant.

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Table 3. Correlations between serum ghrelin and obestatin with other parameters in obese children.

Parameters	Ghrelin	Obestatin
	r	R
Age (years)	0.133	0.166
Waist(cm)	0.232*-	0.312*
Hip(cm)	0.011	0.016
WHR	0.074	0.107
Weight(kg)	0.231*-	0.255*
Height(cm)	0.192	0.201
BMI (Kg/m^2)	0.269*-	0.252*
Body Fat%	0.211*-	0.312*

SBP(mmHg)	0.301*-	0.235*
DBP(mmHg)	0.188-	0.192
FBS (mg/dl)	0.529**-	0.358*
PPFG(mg/dl)	0.701	0.635
Ins. level (µU/ml)	0.393*-	0.234*
HoMa-IR	0.502**-	0.227*
TC [Mg/dl]	0.160	0.172
TG [Mg/dl]	0.539**-	0.349*
HDL [mg/dl]	0.247*	0.081
LDL [mg/dl]	0.343*-	0.369*
Ghrline/ Obestatin	0.125	0.094

At level *(P<0.05) and **[P<0.01] p-value is significant.

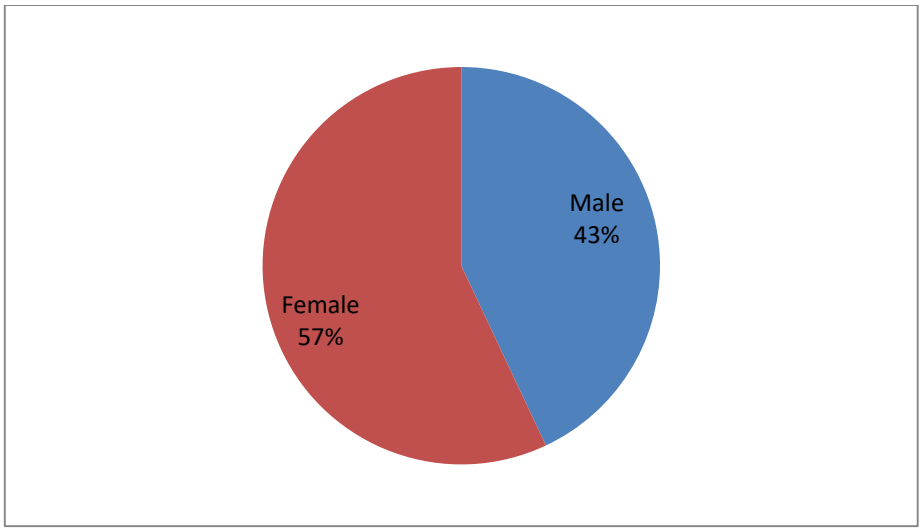

Figure 1. Comparison of ghrelin concentration between males and females in obese children.

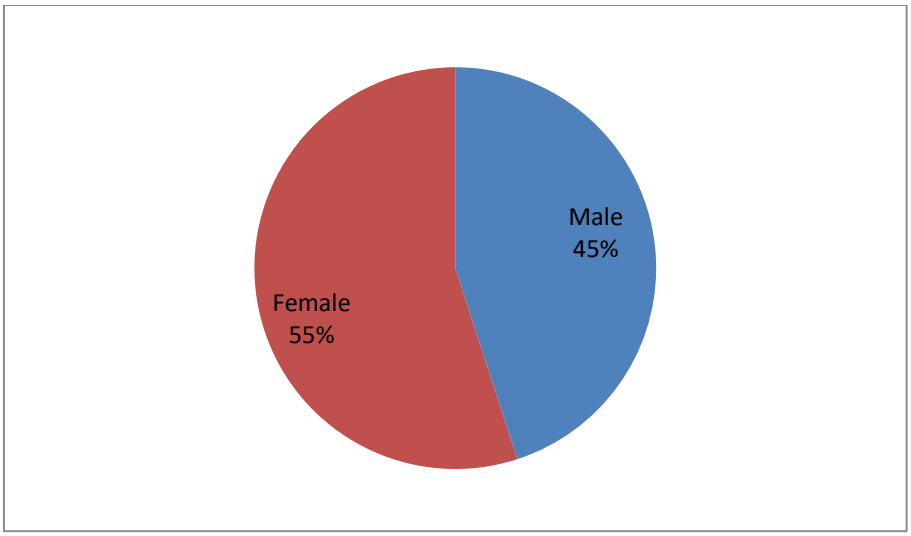

Figure. 2: Comparison of obestatin concentration between males and females in obese children.

Discussion:

Obesity in childhood is a general disease that acts as an epidemiological condition [15, 16]. It is considered one of the risk factors for cardiovascular that is related to morbidity, hypertension, and hyperlipidemia. Furthermore, it has been shown that obese children's overweight is more likely to appear again in adulthood and to cause cardiovascular diseases at an early age compared to their peers that have normal weight. Both hyperlipidemia and hypertension can also happen in children and are related to cardiovascular outcomes in adulthood [17]. Many studies revealed that cardiovascular mortality and morbidity raise with BMI [18]. Although BMI is useful for determining obesity, it is not, precise enough to detect early fat

gathering and early cardiovascular hazard[19]. Although, the most important aim of protective pediatrics is to check children with higher cardiovascular risk as soon as possible [18]. Studies are directed towards finding early parameters of cardiovascular risk, including potential biological markers like obestatin and ghrelin.

The results of complex interactions between genes, environment, physical activity, dietary intake and, obesity are considered as critical hazard factors to the evolution of resistance of insulin in children [20]. Adolescent and also obese childhood was leading to the developing of type 2 diabetes and metabolic syndrome [21]. Obestatin and ghrelin are two peptides secreting that play a valuable role that regulate body weight and dietary intake [22]. Many studies have focused on the character of ghrelin in obese subjects. In the administration of ghrelin, ghrelin is considered one of the causes of obesity because it has shown to enhance fat deposition and food intake in some previous researches [23]. Once, a study on the ghrelin, metabolism, and balance of energy was performed by total ghrelin test. The circulation of ghrelin is in two pathways, it is different in the acyl formation, the greatest plentiful of which is non-acylated ghrelin; however, the acylated version is more active [24]. In this work, plasma ghrelin in the fasting state and obestatin levels were measured in obese children and compared with control. In agreement with other past studies in adults [25] and children [26], this study found that the fasting plasma obestatin levels in obese children increased while ghrelin was lower than the control group.

The action of which ghrelin concentration is diminished in obesity has not been illustrated, these results are in agreement with other studies that found low levels of ghrelin in type T2DM and obesity [27,28].

In this research, we demonstrate that ghrelin is associated in negatively way with LDL-C, TG, HOMA-IR, and insulin as factors of insulin resistance and metabolic syndrome. The two hormones ghrelin and insulin that play a pertinent role in the regulation of the weight of the body [29]. Many studies in vivo and in vitro have shown that insulin and glucose metabolism regulate ghrelin[30]. Ghrelin mechanism is shown to repress secretion of insulin from islet cells in the pancreas [31]. The secretion of ghrelin could be influenced by deposition via insulin or metabolism of glucose [32]. Even though some experts disagree with these findings, studies have shown that intravenous insulin treatment causes a decrease in ghrelin levels in people [33, 34]. Ghrelin has an important role as a protective marker against oxidative stress by reducing peroxidation of lipids [35] and normalizing the tissue red-ox state in high-fat-fed conditions[36]. Also, studies have shown that adolescents and obese children are connected by decreased antioxidant potential and elevated levels of Reactive Oxygen Specie (ROS) that are combined with atherosclerosis and hypertension. Oxidative stress and ghrelin relationship have not been in the past studied in adolescents and obese children. The reliable marker for the assessment of oxidative stress was MDA, that is producing the peroxidation of lipids as a result. Decreasing levels of ghrelin diminishes its protective role as an antioxidant in obese subjects. Obestatin levels were measured in this study in fasting state in obese children as well as in control and the finding was high levels of fasting plasma obestatin concentrations in obese patients compared with controls, which agrees with former studies in adults[25]. Also, we noticed a positive correlation in a significant way between BMI and obestatin. Many studies on the animal design showed that obestatin has an adverse influence on ghrelin, suggesting that it may give a new aim for testing obesity [36]. It has been shown that obestatin and ghrelin have a contrary glucose-induced dynamic designs in obese individuals in pediatrics. The obestatin function in the mechanical way of obesity is yet not fully underlying. Although obestatin has antagonistic efficaciously to ghrelin on weight gain and appetite, raised levels of obestatin might be an adaptive reaction to obesity in a trial to low food intake. Significantly, obestatin was associated with both HOMA-IR and insulin concentrations, but not FBG, indicating a relation between insulin and obestatin. Certainty, it has been shown that obestatin conceivable –induced glucose to the insulin excretion at normal glucose concentrations, but none of great glucose levels[37] confirm the beholder relation and the part of insulin resistance with obestatin. As obestatin and ghrelin are consequences of a single gene, their concentrations might be under the specified ordinance, and the equilibrium between obestatin and ghrelin might play a significant part in obesity [38]. Thus, the ratio of ghrelin-to-obestatin was as well examined in obese children and began to decrease in obese children in comparison to control groups, a signalizing disorder in the balance between them. The ratio of ghrelin to obestatin has been before that time determined in obesity and shown to be low in obese patients [39].

Conclusion:

The conclusion of this study is that both obestatin and ghrelin are dilapidated in obesity and related to insulin resistance, insulin levels and that may be a condition of a favorable target for the direction of

insulin resistance. Ghrelin has been linked to metabolic syndrome and oxidative stress. The ratio of obestatin to ghrelin is an important determinant in obesity and its complications.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at the Mustansiriyah University and University of Technology, Applied Science Department.
- Ethical approval of this study was obtained from:

National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.

- All patients and their families were informed about the aim and suspected benefits of the study before obtaining their agreements for participation according to the medical research and ethical regulation. Oral consent was taken from all enrolled participant and their families.

Authors' Contributions Statement:

NTT contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. WA AJ and WRA contributed to the revision and proofreading of the research.

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مستويات جريلين وأوبستاتين كمؤشر جديد لدى الأطفال العراقيين الذين يعانون من السمنة المفرطة

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الخلاصة:
السمنة مشكلة صحية متفاقمة في البلدان النامية. يعاني طفل إلى عشرة أطفال في جميع أنحاء العالم من زيادة الوزن كما أظهر التقرير في منظمة العمل الدولية المعنية بالسمنة. يحتوي جريلين ، أو الببتيد الخارجي ، على 28 من الأحماض الأمينية ، وهو يعتبر أعظم عامل محفز في العقدين الماضيين لفهم التغيرات الفسيولوجية في تنظيم تناول الطعام والشعور بالجوع. الاوبيستاتين هو عبارة عن ببتيد يتكون من 23 حامض اميني مرتبط تقريبًا بالجريلين من حيث الية العمل وهو يبدا تكوينه من جزيء الاولي البروكيرلين . صممت الدراسة لتقييم مستوى الكيريلين والأوبستاتين في الأطفال العراقيين الذين يعانون من السمنة المفرطة ومدى ارتباطه بمعايير كيميائية حيوية أخرى. تم قياس مستوى مصل كيريلين وأوبيستاتين في ستين طفلاً يعانون من السمنة المفرطة. تراوحت اعمارهم بين (5-12) سنة وهذه المجموعة مقابل 30 طفلا في حالة صحية كمجموعة ضابطة. تم تحديد مصل FBS و PPBS وأيضًا قياس الدهون (TG و TC و HDL-c و LDL-c) في المجموعات المدروسة. تم حساب مقاومة الأنسولين باستخدام (HOMA-IR) لتقييم نموذج التوازن لمقاومة الأنسولين. كانت مستويات كيريلين أقل بشكل ملحوظ في الأشخاص المصابين بالسمنة مقارنة بمجموعة السيطرة. وكذلك كانت هناك زيادة عالية في الاوبيستاتين في المرضى الذين يعانون من السمنة المفرطة بالمقارنة مع السيطرة. توضح هذه الدراسة أن زيادة الأوبيستاتين وانخفاض هرمون الكيريلين في السمنة وهذه الهرمونات لها علاقة بمقاومة الأنسولين كما ان هناك ارتباط بين هرمون الجريلين والإجهاد التأكسدي. من المحتمل أن تكون المقاييس بين الاوبيستاتين والكيرلين مضطربة في الاطفال الذين لديهم سمنة.
الكلمات المفتاحية : الكيرلين، مقاومة الانسولين، الدهون، السمنة، الاوبيستاتين.