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Plasma levels of obestatin and ghrelin and obestatin/ghrelin ratio in obese patients

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Abstract

Background: Obestatin and ghrelin are two gastric hormones that have a potential role in dietary intake regulation. Obestatin/ghrelin ratio has been proposed as activity markers in obesity. The study aimed to evaluate ghrelin, obestatin and the ghrelin/obestatin ratio in obese compared to control subjects and to determine their relationship with anthropometric and metabolic parameters.

Methods: Fasting obestatin and ghrelin levels were measured using enzyme-linked immunosorbent assay ELISA in 28 obese and 24 healthy subjects. The fasting ghrelin/obestatin ratio was calculated. Anthropometric and metabolic parameters were also assessed.

Results: Obese patients had significantly lower obestatin and ghrelin blood levels compared with controls. The Ghrelin/Obestatin ratio was significantly lower in obese group 0.813±0.0417 ng/ml than in the control group 0.896±0.049 ng/ml, ($p<0.001$). In obese patients, obestatin and ghrelin were significantly and negatively correlated with BMI and positively correlated with HDL-C.

Conclusion: Circulating preprandial ghrelin to obestatin ratio is decreased obese subjects. We suggest that low preprandial ghrelin to obestatin ratio may be involved in the etiology and pathophysiology of obesity.

Keywords: Obesity; Ghrelin; Obestatin; BMI and Lipid Parameters

1. Introduction

Obesity continues to be a public health concern across the globe [1]. The number of patients affected by this epidemic and associated comorbidity, such as diabetes mellitus, cardiovascular disease and cancer, is constantly increasing, as are the associated health costs, making the management of obesity paramount importance [2,3].

Obesity is a multifactorial disease controlled by the interaction between, genes, hormones, dietary intake, physical activity and environmental factors. Ghrelin and obestatin are two gastric hormones that convey information concerning nutritional status to the central nervous [4].

Ghrelin is a 28-amino acid peptide primarily produced by the stomach and expressed in many other central and peripheral tissues [5]. In addition to potent GH release activity, ghrelin is involved in the control of central and

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peripheral food intake and energy metabolism, which affect endocrine pancreatic function, glucose and lipid metabolism [6].

Obestatin is a 23-amino acid peptide produced by the post-translational modification of a protein precursor that also generates ghrelin and is found mainly in the stomach cell. Most studies in animal models put in evidence that the effect of obestatin on food consumption is opposite to ghrelin, and it has been suggested that obestatin is a new target for the control of obesity [7,8]. Both ghrelin and obestatin have been proposed to contribute to development of obesity.

The aim of the present study was to compare ghrelin, obestatin and the ghrelin/obestatin ratio between obese and control subjects and to determine their relationship with anthropometric and metabolic parameters.

2. Material and methods

The study population was collected at the Endocrinology Department of Rabta University Hospital. It includes 28 obese patients (BMI≥30.0 kg/m^2) and 24 healthy subjects (BMI between 19-25 kg/m2). The study subjects volunteered to participate in the study and informed consent was obtained from each participant. The study was approved by the Rabta Hospital Ethics Committee and was conducted in accordance with the ethical standards set out in the 1964 Helsinki Declaration and subsequent amendments or comparable ethical standards. Weight and height were measured in each study participant and body mass index (BMI = weight / height^2) was calculated.

2.1. Blood sample collection and laboratory measurement

A fasting venous blood sample with a total volume of 10 ml was collected from each study participant. 5 ml of this was used for testing of glucose, as well as lipid profiles including cholesterol (TC), triglyceride (TG) and high-density protein of cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation [9]. The remaining 5 ml of the blood sample was collected into EDTA tubes containing for the measurement of plasma levels of ghrelin and obestatin. The samples were then centrifuged at 3000 g for 15 min, and the plasma was kept at -80 C until analysis.

2.2. Measurement of plasma obestatin and ghrelin

Plasma levels of ghrelin and obestatin were determined using enzyme-linked immunosorbent assay ELISA kits for ghrelin and obestatin (CUSABIO BIOTECH CO.LTD. CHINA) which used quantitative sandwich enzyme immunoassay technique according to the manufacturer's instructions. The range of examination sensitivity of the assays was 0.625-40 pg/ml for ghrelinand 4.69-300 pg/ml for obestatin. The concentration of ghrelin and obestatin were calculated using the typical standard curve.

2.3. Statistical analysis

The Statistical Package for the Social Sciences version 23 (SPSSv23) was used for data analysis. Descriptive statistics (mean + standard deviation) were calculated. The Mann–Whitney test was applied to compare means between obese and control groups. Correlations were tested using the Spearman correlation coefficient. A *P* value <0.05 was considered statistically significant.

3. Results

Characteristics of the populations are presented in Table 1. The results of lipid profile components showed significantly higher levels of serum TG and considerably lower levels of HDL-C in the obese group as compared with the control group. There was no significant change in serum Cholesterol and LDL-C between the groups.

Fasting plasma levels of ghrelin and obestatin and the ghrelin/obestatin ratio in obese and control groups are given in Figure 1. Plasma ghrelin and obestatin concentrations were significantly lower in the obese group than the control group. The mean ghrelin level in obese and control group were 198.066±70.258 ng/ml and 261.600±65.240 ng/ml, (p=0.002) respectively. The mean obestatin level in obese and control group were 242.986±83.075 ng/ml and 294.286±79.783 ng/ml, (p=0.028) respectively. The Ghrelin/Obestatin ratio was significantly lower in obese group 0.813±0.0417 ng/ml than in the control group 0.896±0.049 ng/ml, (p<0.001) (Figure 1).

Table 2 shows the correlations between BMI, biochemical parameters and fasting plasma ghrelin and obestatin levels. A positive and significative correlation between obestatin and ghrelin was observed r=0.980; p=0.0001. In obese group, a negative correlation between obestatin and BMI r=-0.545; p=0.003.

Table 1 Characteristics of the population

	Control (n=24)	**Obese (n=28)**	***p***
Age (years)	45,63±6,573	46,39±5,915	0,659
Total cholesterol (mmol/l)	1,883±0,419	1,84±0,374	0,371
Triglycerides (mmol/l)	0,837±0,135	1,19±0,636	0,009
HDL-C (mmol/l)	1,177±0,104	0,69±0,199	0,000
LDL-C (mmol/l)	1,432±0,888	1,19±0,270	0,184
Obestatin (ng/ml)	294,28±79,78	242,98±83,07	0,028
Ghrelin (ng/ml)	261,60±65,24	198,06±70,25	0,002
Ratio Ghrelin/Obestatin	0,896±0,049	0,813±0,041	0,000

HDL = High-Density Lipoprotein, LDL = low-density lipoprotein

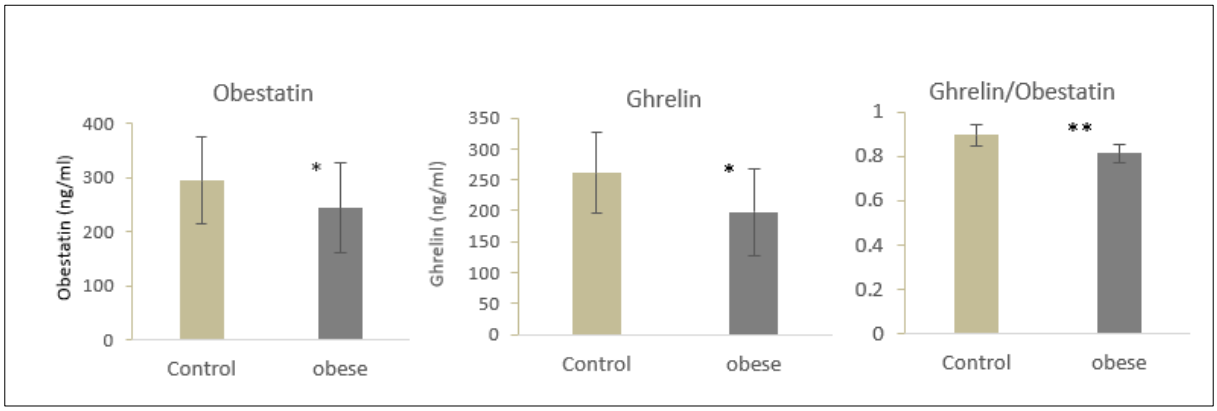

Figure 1 Plasma levels of ghrelin and obestatin and the ghrelin/obestatin ratio in control and obese groups

A positive correlation between obestatin and HDL-C in obese group r=0.410; p=0.031. Table 2 shows a negative correlation between ghrelin and BMI in obese group r=-0.543; p=0.003. A positive correlation between ghrelin and HDL-C in obese group r=0.421 p=0.025.

Table 2 Correlations between BMI, biochemical parameters and plasma ghrelin and obestatin levels in obese group

Parameters	**r**	**p**
Obestatin and ghrelin	0.980	0.0001
Obestatin and BMI	-0.545	0.003
Obestatin and HDL-C	0.410	0.031
Ghrelin and BMI	-0.543	0.003
Ghrelin and HDL-C	0.421	0.025

Spearman's correlation coefficient

4. Discussion

In this study, obese patients displayed significantly decreased circulating levels of obestatin and ghrelin and decreased ghrelin/obestatin ratio. In agreement with our result previous study by Vicennati et al. indicates women had a decreased ghrelin/obestatin ratio that in the presence of obesity [10].

This result support the hypothesis that obese individuals would present with an imbalance of ghrelin and obestatin levels and suggest that changed preprandial ghrelin to obestatin ratio may have a role in the etiology and pathophysiology of obesity [11].

The presence of a positive correlation between plasma ghrelin and obestatin levels in the group of obese supports the hypothesis of simultaneous secretion of these two hormones from the common precursor. This might result in a mutual balance in the appetite regulation activities of ghrelin and obestatin [12].

Our data shows that serum levels of ghrelin are significantly reduced in obese compared to healthy subjects. These suggest that ghrelin expression is down-regulated in human obesity. We suggest that the decreased plasma ghrelin concentrations observed in obesity are a physiological adaptation to positive energy balance associated with obesity. Our finding is in accordance with several studies that fasting plasma ghrelin is reduced in obese subjects compared to controls [13- 15]. The lack of a ghrelin reduction in obese subjects may result in a decrease in the suppression of eating motivation after a meal in obese subjects, which would lead to increased food consumption and weight gain. Obestatin acts as an anorectic hormone which decreases food consumption, slows gastrointestinal motility and therefore reduces weight gain [16]. Previous studies in humans have shown that plasma levels of obestatin are significantly lower in obese than those of lean subjects [17]. We found similar results in our obese subjects. These findings are in accordance with a study by Zhang et al. who suggested that obestatin levels were significantly reduced in obese rodents [18]. In the study of Szentpéteri, they concluded that a reduction of obestatin could contribute to the development of the metabolic syndrome and impaired rate of lipoprotein metabolism in obese patients [19].

Similar to our findings, other studies in humans have shown that plasma obestatin levels are significantly lower in obese subjects, as compared to controls, indicating a role for obestatin in long-term body weight regulation [20, 17, 21].

In this study, BMI were negatively correlated with fasting plasma ghrelin levels in obese patients. This confirmed the view that low ghrelin is closely associated with obesity. These findings are consistent with previous studies where ghrelin level was found to be lowest [22- 24]. Ghrelin has been considered a cause of obesity in some studies because ghrelin has orexigenic effects in rats and humans [25, 26]. However, the results of most studies in humans, similar to ours, have shown that ghrelin levels are negatively correlated with BMI [27- 29]. Therefore, decreased ghrelin may reflect a possible physiological adaptation to positive energy balance [30].
Moreover, our results demonstrated that plasma obestatin was negatively correlated with BMI, but positively with ghrelin in humans suffering from obesity, two opposite ends of the continuum of body weight. Our findings are in accordance with other researchers who showed a negative correlation of obestatin with BMI in obese rodents and human [31,32]. This suggests that the basal secretion of ghrelin and obestatin occur in the same way and are influenced by adiposity in humans.

Ghrelin and obestatin are negatively correlated with TG and positively correlated with HDL-C in an obese subject. The study of Azar et al., concordant with our results, demonstrates that ghrelin correlated negatively with TG [30]. Obesity plays an essential role in modulating the expression of ghrelin and obestatin. It is, therefore, necessary to know how ghrelin and obestatin intervene in the metabolism regulation of adipocyte. Different studies have suggested that ghrelin may play a crucial role in adipogenesis and energystorage in adipose tissue [5,33]. Zang et al. have shown that ghrelin suppresses adipogenesis by stimulating cell proliferation in the mouse adipocyte cell line [34] . Ghrelin also inhibits the expression of adiponectin. All these results support the idea that ghrelin may have an "energy saving" effect on adipose tissue [35]. Regarding to obestatin, our study showed that low levels of obestatin are associated with high TG and low HDL-C which corroborates with the study of Gutierre-Grobe et al. that showed that lower levels of obestatin are associated with overweight, TG and TC levels [36]. The present study suggests that obestatin may be a useful marker of the nutritional status, since, similarly to ghrelin, it reflects adiposity in humans.

5. Conclusion

In conclusion, our study showed that plasma ghrelin and obestatin levels are significantly lower in obese subjects as compared to healthy subjects, indicating a role for both obestatin and ghrelin in long-term body weight regulation. Further studies are required to evaluate how specific hormonal and metabolic abnormalities associated with obesity may be related to different ratios of each ghrelin gene product.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Written and informed consent was signed by each participant included in the study.

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