

RESEARCH ARTICLE

Correlation of Ghrelin and Obestatin with Waist Circumference in Central Obese Men

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Abstract

BACKGROUND: Central obesity is known as the cause of many metabolic disorders called Metabolic Syndrome. Accumulation of adipocytes in central obesity increases production of cytokines proinflammation (1,2). Free fatty acid increases in obesity that drives atherogenic dyslipidemia and insulin resistance (3). IDF 2005 states that waist circumference (WC) is regarded as the simple criteria of obesity. (4). Energy imbalance lasting for a long period is a determinant factor for obesity, e.g. when energy intake is greater than energy expenditure. The brain and gastrointestinal tract work together to maintain this system. Ghrelin and Obestatin are two gut hormones that work in different ways to keep the energy balance. Ghrelin increases appetite but Obestatin decreases it. The two hormones play an important role in maintaining the dynamic equilibrium of energy balance. This study was aimed to determine correlation of Ghrelin and Obestatin with WC in central obese men.

METHODS: This was a cross sectional study involving 53 central obese men. Based on IDF 2005 central obesity is most easily measured by waist circumference using the guidelines ethnic group (not country of residence) specific. We used South Asia ethnic which including

Chinese, Malay and Asian Indian population as criteria for this study, that was WC > 90 cm, aged 20 - 60 years. Subjects who had smoking habit, any infectious disease, and ACS were excluded from the study. No restriction was applied on the kind of meals the subjects were having or activities they were doing. The correlation of waist circumference with ghrelin and obestatin was assessed with a significance level of 95% ($\alpha = 0,05$).

RESULTS: Patient's age was $40,9623 \pm 7,9080$ year, waist circumferences was $102.1981 \pm 10,2696$ cm, weight was $85,8679 \pm 16,5475$ kg, height was $168,8066 \pm 6,3535$ cm, BMI was $29.9723 \pm 2,4937$ kg/m². Concentration of Ghrelin were 0.70 - 13.72 ng/mL, and Obestatin 16.66 - 148.84 pg/mL. Pearson correlation showed that Ghrelin ($r = -0.1114$, $p = 0.4271$) and Obestatin ($r = -0.1781$, $p = 0.2020$) had no significant correlation with WC. But in patients WC ≥ 120 cm had significant negative correlation with Obestatin ($r = -0.375$, $p = 0.049$).

CONCLUSIONS: There was no significant correlation of Ghrelin and Obestatin with WC in obese men. However, there was a negative correlation tendency found in patients with greater WC (≥ 102 cm).

KEYWORDS: Obesity, Ghrelin, Obestatin, Waist Circumference (WC).

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Introduction

Obesity has become common among the world's population and it has started to replace under nutrition and infectious diseases as the most significant contributor to health problem (5, 6). Central obesity and metabolic syndrome can not be separated. Accumulation of fat in the body that occurs in central obesity leads to several diseases such as diabetes mellitus, insulin resistance, atherogenic dyslipidemia and inflammation, which are collectively known as metabolic syndrome (5, 6). Simple criteria for central obesity use WC measurement according to the criteria of IDF 2005. (4).

Body fat storage correlates with obesity, but it is not merely caused by bad diet habit, instead it is the result of the combination of genetic susceptibility, high intake of high-energy foods, and decreased requirements for physical activity in modern society (7,8). The gastrointestinal tract plays an important role in regulation of energy homeostasis in the body through ingestion, absorption and assimilation of nutrients contained in the food (7, 8, 9). The gastrointestinal tract consists of endocrine cells that produce some hormones useful for regulation of secretion of enzymes and other mechanisms of food processing. These hormones give signals to the brain to process energy homeostasis (10, 11).

The neurotransmitters that are responsible for increasing the appetite are neuropeptide Y (NPY) and Agouti Related Peptide (AgRP), while the neurotransmitter responsible for reducing the appetite is proopiomelanocortin (POMC) that produces melanocyte stimulating hormone (α -MSH) (12,13). Insulin and Leptin inhibit NPY and AgRP and stimulate POMC to produce α -MSH, in order to decrease the appetite (12,13). Other hormone, named Ghrelin increases the appetite by stimulating NPY and AgRP through growth hormone secretagogue receptor (GHSR) (14, 15, 16). Obestatin is expressed from the same gene as Ghrelin. It binds to a G protein-coupled receptor (GPR39) against Ghrelin to suppress the appetite (8,17).

In 1999, Ghrelin was found as a gastrointestinal hormone that stimulated production of growth factor in mice. On the other hand, the mice studied became fat due to the continuous injection of Ghrelin. In fact, Ghrelin increased appetite of the mice and decreased energy expenditure. So the samples became obese (18). This finding has attracted many other studies done on the correlation of Ghrelin with obesity and some other conditions such as diabetes mellitus, inflammation and metabolic syndrome.

Ghrelin has some biological functions mainly in stimulation of growth hormone and appetite and carbohydrate metabolism (19). Secretion of Ghrelin increases with the decrease of body weight, restriction of calorie intake, and increase of insulin that causes hypoglycemic effect (20, 21). In *in vitro* studies, Zhang *et al.* in 2005 showed that Ghrelin inhibited adipogenesis through PPAR (peroxisome proliferator-activator receptor) (21).

Tschoop and Zhang found that Obestatin has the opposite effect as Ghrelin in normal condition. In normal condition Ghrelin and Obestatin are on a dynamic equilibrium. So, if the role of Ghrelin is disclosed, we can predict the role of Obestatin (8, 21). Our hypothesis is there is correlation between Ghrelin and Obestatin with waist circumference in the obese men.

Methods

SUBJECTS

This was a cross-sectional study involving 53 central obese men, defined by waist circumference > 90 cm. Based on IDF 2005, central obesity is most easily measured by waist circumference using the guidelines ethnic group specific, but not country of residence. We used South Asia ethnic which including Chinese, Malay and Asian Indian population as criteria for this study. WC was used to define central obesity because it's simple, reliable, and correlated well with abdominal fat content irrespective of BMI (Body Mass Index). Subjects recruitment and data collection were done in 2007 in Surabaya, and all subjects were required to state their willingness to follow the study protocol by signing an informed consent. The study protocol has been approved by The Health Research Ethics Committee of The Faculty of Medicine, Hasanuddin University of Makassar. Subjects with smoking habit, infectious disease, and Acute Coronary Syndrome (ACS) were excluded from the study. This study did not make any restriction on the meals or activities of the study subjects.

ASSAY OF BIOCHEMICAL MARKERS

Biochemical markers were measured using Ghrelin (human) EIA kit (Phoenix Pharmaceuticals, Inc., Saint Joseph, USA) and Obestatin (Human, Monkey) RIA kit (Phoenix Pharmaceuticals, Inc., Saint Joseph, USA). Briefly, fasting blood samples were collected in the morning between 07.00 until 10.00 am. Serum was separated from the whole blood after centrifugation and immediately kept at -70°C.

STATISTICAL ANALYSIS

SPSS for Windows ver. 11.5 was used for all statistical and graphical analyses. General analysis of data was done by univariate analysis to determine the minimum and maximum value, average, and standard deviation. Independent and dependent variables were analyzed by bivariate and partial Pearson Correlation. One Way Annova was used to analyze the difference between Ghrelin and Obestatin in the obese subjects.

Results

Characteristic of samples examined show in table 1 and 2. Result of Ghrelin and Obestatin were in the wide range, because this study was not use any stricted food intake to the

patients. The patients were fasting before blood sampling, but there were no rules in the food variation intake for patient in the several days before blood sampling. Ghrelin and Obestatin were gastrointestinal hormones that might be different amount in every person depends on their food intake. They were Indonesian men average 20-60 years old. Group ethics population of the patients were Chinese and Malay only. Data of subject characteristics were distributed normally so we used Mean datas, but Ghrelin and Obestatin didn't distributed normally that's why we use median in the statistics.

The data of WC and BMI separate in two group based on mean value. WC cut point was 102 cm There were 28 men with WC < 102 cm and there were 23 men with WC \geq 102 cm. BMI cut point was 30 kg/m². There were 34 men with BMI < 30 kg/m² and there were 19 men with BMI \geq 30 kg/m². In this study used WC as criteria of central obesity but BMI was still analyze to compare the result.

Table 1. Subjects' characteristics

Variabel	Mean \pm SD	Min	Max
N	53		
Age	40.9623 \pm 7.9080	29	59
WC (cm)	102.1981 \pm 10.2696	90	132
Weight (kg)	85.8679 \pm 16.5475	64	140
Height (cm)	168.8066 \pm 6.3535	158	184
BMI (kg/m ²)	29.9723 \pm 2.4937	23.78	41.35

WC = Waist Circumference (cm), BMI = Body Mass Index (Kg/m²).

**Table 2. Ghrelin and Obestatin Level
in Central Obese Men**

Variabel	Median	Min	Max
Ghrelin(ng/mL)	1.95	0.70	13.72
Obestatin (pg/mL)	38.86	16.66	148.84

Table 3 shows that Ghrelin ($r = -0.1114$, $p = 0.4271$) and Obestatin ($r = -0.1781$, $p = 0.2020$) had no significant correlation with WC. But in patients $WC \geq 120$ cm had significant negative correlation with Obestatin ($r = -0.375$,

$p = 0.049$). There were significant negative correlation between BMI and Ghrelin, but neither Obestatin. Ghrelin and Obestatin had negative tendency correlation with BMI.

Table 3. Correlation between Ghrelin and Obestatin with WC and BMI in central obese patients

Variabel	Ghrelin		Obestatin	
	r	p	r	p
Waist circumference	-0.1114	0.4271	-0.1781	0.202
WC < 102	0.005	0.98	-0.375	0.049*
WC ≥ 102	-0.087	0.68	-0.125	0.551
Body Mass Index	-0.283	0.04*	-0.126	0.369
BMI < 30	-0.225	0.201	-0.077	0.667
BMI ≥ 30	-0.16	0.95	-0.135	0.58

Correlation is significant at the 0.05 level

Discussion

Although this study showed no significant correlation between Ghrelin and Obestatin, the negative tendency found in this study had confirmed the results of some studies done earlier. Rosicka *et al.* proved a significantly lower serum Ghrelin level in the group of central obese patients in comparison with the control group (22). In this study there was no food intake restriction, so we found the different result with study before. This study has confirmed that Ghrelin in subjects with $WC \geq 100$ cm had a negative correlation. It means that the level of Ghrelin gets lower when a subject has become more obese. The tendency of Obestatin in this study agrees with results of a recent study on Obestatin in overweight and obese patients, in which concentrations of obestatin was found decreased in overweight and obese patients (23).

Zhang *et al.* (2007) mentioned that Ghrelin and Obestatin had an inverse relationship with BMI and WC (24). Energy imbalance in the body will trigger the occurrence of obesity, including appetite regulation, controlled by Ghrelin and Obestatin. Ghrelin secretion will increase with the decrease of body weight, caloric

intake restriction, and the increase of insulin level that causes hypoglycemic effect. Another further study is recommended to carry out with restriction made on nutrition and activities of the subjects to compare with the present results (22, 24). Recent studies have indicated that ghrelin levels in systemic circulation reflect mainly nutritional status and are predominantly involved in the regulation of energy homeostasis. Thus the states associated with malnutrition are accompanied by an increase of serum ghrelin levels (25), whereas overfeeding is accompanied by decrease of serum ghrelin levels (26).

A study by Levin *et al.* has found that the decrease in body fat content caused an increase in the level of Ghrelin. As it is expressed from the same gene, it is suggested that Obestatin might have the similar pattern (27). Obesity correlates with increased body weight and accumulation of adipose tissues (7). It means that obesity may decrease secretion of Ghrelin and Obestatin. This study suggested that Ghrelin and Obestatin had a negative correlation with obesity (characterized by $WC > 102$ cm). We therefore can conclude that greater WC measurement is associated with lower Ghrelin and Obestatin levels.

Obesity can be caused by imbalance of energy homeostasis. The gastrointestinal tract consists of endocrine cells that produce some useful hormones that

regulate secretion of enzymes and other mechanisms of food processing (11). These hormones give many signals to the brain to process energy homeostasis (10). Ghrelin and Obestatin are hormones that are produced by the gastrointestinal tract and are involved in energy homeostasis. Patient with bigger waistline and overweight patients ($\text{BMI} > 25 \text{ kg/m}^2$), however, production of these hormones is decreased causing disruption of the dynamic equilibrium between the two.

Conclusion

Results of this study showed no significant correlation of Ghrelin and Obestatin with WC in obese men. However, there was a negative correlation tendency found in patients with greater WC ($\geq 102 \text{ cm}$).

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