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Short Communication

Relationships between acylated ghrelin with growth hormone, insulin resistance, lipid profile, and cardio respiratory function in lean and obese men

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Abstract

BACKGROUND: Acylated ghrelin, biologically active form of ghrelin, activates growth hormone (GH) secretagogue receptor 1a and play a role in regulating of energy balance. The purpose of this study was to survey relationships between acylated ghrelin with GH, insulin resistance, lipid profile, and cardio respiratory function in lean and obese men.

METHODS: Nineteen obese men (body mass index 31.0 ± 3.5 kg/m^2, aged 27.5 ± 5.8 year) and the same number of lean men (body mass index = 18.47 ± 2.1 kg/m^2, aged 26.9 ± 5.6 year) were selected if they had no experience of regular physical activity during six month ago. After 12 hour fasting, blood samples were collected and blood parameters as well as maximal oxygen uptake (as indicator of cardiorespiratory function) was assessed.

RESULTS: Insulin levels and HOMA-IR (homeostasis model assessment of insulin resistance) were higher, and GH, acylated ghrelin and maximal oxygen uptake levels were lower, in obese versus lean men ($p < 0.01$). No significant differences were observed in systolic and diastolic blood pressure, fasting blood glucose, and lipid profiles between the two groups ($p > 0.01$). Plasma acylated ghrelin concentrations in obese and lean men were negatively correlated to body weight (r= -0.50, r= -0.43, respectively), body fat percent (r = -0.53, r = -0.44, respectively), body mass index (r = -0.53, r = -0.49, respectively), insulin (r = -0.42, r = -0.40, respectively) and HOMA-IR (r = -0.48, r = -0.45, respectively), and positively correlated to GH levels (r = 0.37, r = 0.31, respectively) and maximal oxygen uptake (r = 0.33, r = 0.31, respectively) ($p < 0.01$). No significant correlations were observed between plasma acylated ghrelin concentrations and systolic and diastolic blood pressure, fasting blood glucose, and lipid profiles in both groups ($p > 0.01$).

CONCLUSIONS: Obese and lean inactive young men had different levels of acylated ghrelin, GH, insulin, insulin resistance index, cardiorespiratory function and body fat percent. Body fat percent, insulin, and GH levels appear to be best determinant factors of acylated ghrelin levels. Also, in both obese and lean young men, higher levels of cardiovascular function were associated with higher levels of acylated ghrelin.

KEYWORDS: Adipose, Obesity, Insulin Resistance Index, VO_2max, Gherlin.

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Ghrelin is a gastric peptide stimulating pituitary growth hormone (GH) secretion and regulating feeding behavior and adiposity.[1] Weight gain leads to decreased systemic ghrelin levels,[2-5] and long-term ghrelin administration leads to weight gain in experimental animals.[6,7] Acylated ghrelin is biologically active form of it that activates GHS-R 1a (growth hormone secretagogue 1a) and play a role in regulating of food intake and body weight.[1]

The underlying mechanisms that mediate regulations of systemic ghrelin secretion are not well established.[8-10] It has been indicated that estrogen and recombinant human insulin-like growth factor I increase systemic ghrelin levels,[11] and oral or intravenous glucose, insulin, glucagon, GH, and somatostatin

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suppress systemic ghrelin levels.[12-14] However, Natalucci et al. indicated that in a fasting condition, GH, insulin and glucose do not appear to be involved in ghrelin regulation.[15] Ghrelin inhibits insulin secretion,[16,17] whereas it has been suggested that ghrelin may stimulate insulin secretion.[18] Shiiya et al. suggested that the mechanism of the inhibitory effect of insulin on plasma ghrelin is unknown.[19] In addition, Kraemer and Castracane manifested that long-term chronic exercise produces increases in ghrelin levels, especially when weight loss is produced in overweight patients.[20] Generally, the factors involved regulation of acylated ghrelin levels and underlying mechanisms are not fully known.

Although adiposity (obesity/leanness) factor leads to diversity of plasma levels of ghrelin, insulin, GH, glucose and insulin resistance index, but the relations of these involving factors in energy homeostasis with plasma acylated ghrelin levels are not known. Recognition of these relationships and other homeostatic factors that likely determine plasma acylated ghrelin levels can play a key role in understanding of acylated ghrelin interactions. Likewise, the underlying mechanisms that mediate changes of systemic acylated ghrelin secretion are not well known. In addition, it is not clear whether endocrine or paracrine effects of acylated ghrelin are more physiologically relevant in the regulation of insulin secretion. We expect that study of plasma acylated ghrelin relations to GH, insulin, glucose, insulin resistance index, and lipid profiles, and comparing these relations between lean and obese subjects can partially contribute in manifesting of above topics. Moreover, respecting the confirmed effects of regular physical activities on plasma ghrelin levels, plasma acylated ghrelin relations to maximal oxygen uptake (VO_2max) were studied in obese and lean men. Considering insufficient available data, especially in Iranian population, the aim of this study was to investigate relationships between acylated ghrelin with GH, insulin resistance, lipid profile, and cardiorespiratory function in lean and obese men.

Methods

Subjects

Twenty lean [body mass index (BMI) < 18.5] and 20 obese (BMI > 30) young male voluntarily participated in this study. General characteristics of subjects are given in table 1. All subjects were inactive (not exercising regularly in six months before initiation of the study). After signing a written informed consent, all subjects were medically examined by a physician before they entered the study and completed a questionnaire to ensure that they were not taking any medication, were not smokers, free of cardiac, respiratory, renal or metabolic diseases, were not under any diets and were not using steroids. The protocol of the study was approved by Ethical Committee of School of Physical Education and Sport Sciences of Islamic Azad University-Central Tehran Branch.

Table 1. General subject characteristics

	Subjects	
	Obese (n = 19)	**Lean (n = 19)**
Age (y)	27.5 ± 5.8	26.9 ± 5.6
Height (cm)	176 ± 5.05	179 ± 6.12
Weight (kg)	93.50 ± 8.95	64.20 ± 7.54*
Body fat percent (%)	32.8 ± 3.5	19.5 ± 2.8*
body mass index (kg/m^2)	31.03 ± 3.59	18.47 ± 2.17*
Systolic Pressure (mmHg)	129 ± 3	122 ± 2
Diastolic Pressure (mmHg)	81 ± 1	82 ± 2

Results are expressed as mean ± standard deviation.

* Denotes statistically significant differences between obese and lean subjects at $p < 0.01$

Study Design and protocol

All assessments carried out during seven successive days and at 08:00 am of each day. On the 1st day, via an explanation session, aims, design, methodology, laboratory assessments (e. g. blood sampling), scheduling of the study and the points that subjects have to follow were explained in details. During the 2nd-4th days, the subjects had to rest and no exercise other than activities of daily living was permitted. Height, weight, body mass index (BMI), body fat percent and rest heart beat were measured on the 5th day. Subjects were weighed on a digital balance accurate to 0.1kg (Beurer, Germany). Height was obtained to the nearest 0.1cm using a wall-mounted stadiometer (Seca, Germany). The BMI was calculated dividing body weight by height^{-2} (kg/m^2). Subcutaneous fat was measured to the nearest 1 mm using a caliper (Harpenden, UK). Then, body density was calculated via Jackson and Pollock (1978) formula.[1,21] Body fat percent was calculated by Siri formula.[2,22] Rest heart beat was measured using digital pulsometer (Fresh Life, Taiwan). On the 6th day, after 12 hour overnight fasting, blood samples were obtained (5 ml EDTA-blood and 5 ml serum) from the forearm vein of the subjects. Blood samples were immediately transferred to chilled polypropylene tubes containing EDTA-2Na (1 mg/ml) and aprotinin (500U/ml), were centrifuged at 4°C. Serum blood was centrifuged after 1h at room temperature. We added 1 mmol/l HCL (10% volume of plasma volume) to the separated plasma, immediately. Plasma levels of acylated ghrelin were measured commercially available ELISA kit (Acylated ghrelin Human ELISA, intra-assay CV 7%, inter-assay CV 8.2%, limit of detection 0.3 pg/ml, BioVendor, Germany, r with RIA method 0.96). Serum levels of GH and insulin were measured using a Microplate Chemiluminescence Assay (Growth Hormone and Insulin kits, Monobind Inc. USA). Insulin resistance index estimated using homeostasis model assessment of insulin resistance (HOMA-IR) formula.[3,23] The units for IF and GF were μU/ml and mmol/l, respectively. On the last day, maximal oxygen uptake (VO_2max) values of subjects were estimated using Astrand-Rhyming submaximal cycle ergometer test (Robimax, Taiwan).[24]

Formulas

Formula 1: Body Density = 1.1125025 – 0.0013125 (X1) + 0.0000055 (X1)2 – 0.0002440 (X2)
X1: sum of pectoral, triceps, and subscapular subcutaneous fat
X2: age
Formula 2: Body Fat Percent = 495/Body Density – 450
Formula 3: HOMA-IR = [IF (KU/ml) × GF (mmol/l)] /22.5
IF: fasting insulin, GF: fasting glucose

Statistical Analysis

All results are expressed as means ± SD. Independent Student's t-tests were used to compare characteristics between lean and obese groups. Relationships between acylated ghrelin and other parameters were calculated by Pearson's correlation analysis. Before statistical analyses were performed, Kolmogorov-Smirnov test was used to test normal distribution of data. P value of less than 0.01 was considered statistically significant. Statistical analyses were performed using SPSS software version 16.0.

Results

There were no significant differences in age and height between obese and lean groups (Table 2).

BMI was significantly higher up to 12.56 kg/m^2 in the obese subjects than the lean subjects ($p < 0.001$). Weight was 29.3kg more in the obese subjects than the leans ($p < 0.001$). Body fat percent was significantly 13.3% lower in the lean subjects than the obese subjects ($p < 0.001$).

No significant differences were seen between the systolic or diastolic blood pressure of two groups. Plasma acylated ghrelin levels were significantly 131.3 pg/ml higher (2.2 times) in the lean group than the obese group ($p = 0.008$).

Table 2. Physiological characteristics of obese and lean men (Means ± SD)

	Subjects	
	Obese	**Lean**
Acylated Ghrelin (pg/ml)	110.5 ± 18.5	241.8 ± 21.4*
GH (ng/ml)	1.66 ± 0.15	2.08 ± 0.26*
Insulin (µU/ml)	14.2 ± 1.7	10.5 ± 1.3*
FBS (mmol/l)	4.9 ± 0.2	4.2 ± 0.2
HOMA-IR	2.9 ± 0.3	2 ± 0.3*
Lipid Profiles (mg/dl)		
TC	154.5 ± 20.9	139.2 ± 21.3
TG	126.9 ± 45.7	78.6 ± 39.6
HDL	47.6 ± 10.9	54.1 ± 12.4
LDL	88.4 ± 18.4	82.1 ± 20.5
VO_2max (ml/kg.min)	26.21 ± 6.54	32.17 ± 5.35*

Results are expressed as mean ± standard deviation**.**

* Denotes statistically significant difference between obese and lean subjects at $p < 0.01$.

FBS: fasting blood glucose, GH: growth hormone, HOMA-IR: homeostasis model assessment of insulin resistance, HDL: high density lipoprotein, LDL: low density lipoprotein, TC: total cholesterol, TG: triglyceride, VO_2max: maximal oxygen uptake.

ghrelin levels ($p = 0.008$, $p = 0.005$, $p = 0.009$, $p = 0.001$, $p = 0.004$, and $p = 0.007$ subjects ($p = 0.009$). Serum insulin concentrations were 3.7 µU/ml more in the obese group than the lean group ($p = 0.007$). There was no significant difference in fasting blood glucose between two groups. HOMA-IR values were significantly higher in the obese subjects than the lean subjects ($p = 0.007$). Lipid profiles were not significantly different in the obese and lean groups. VO_2max values were significantly higher by 5.91 ml/kg.min in the lean subjects than the obese subjects ($p = 0.005$).

Correlations are shown in table 3. In both groups, body weight, body fat percent and BMI were inversely correlated with plasma

Table 3. Pearson's correlation coefficients between acylated ghrelin levels and selected physiological characteristics in both obese and lean groups

	Subjects	
	Obese	Lean
Body weight (kg)	- 0.50	- 0.43*
Body fat percent (%)	- 0.53	- 0.44*
BMI (kg/m^2)	- 0.53	- 0.49*
SBP (mmHg)	- 0.162	- 0.091
DBP (mmHg)	- 0.203	- 0.111
GH (ng/ml)	+ 0.37	+ 0.31*
Insulin (µU/ml)	- 0.42	- 0.40*
FBS (mmol/l)	- 0.16	- 0.23
HOMA-IR	- 0.48	- 0.45*
Lipid Profiles (mg/dl)		
TC	- 0.019	- 0.101
TG	- 0.162	- 0.037
HDL	+ 0.135	+ 0.201
LDL	- 0.013	- 0.129
VO_2max (ml/kg.min)	+ 0.33	+ 0.31*

Results are expressed as mean ± standard deviation**.**

* Denotes statistically significant difference between obese and lean subjects at $p < 0.01$.

BMI: body mass index, FBS: fasting blood glucose, GH: growth hormone, HDL: high density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, LDL: low density lipoprotein, TC: total cholesterol, TG: triglyceride, VO_2max: maximal oxygen uptake, SBP: systolic blood pressure, DBP: diastolic blood pressure.

acylated ghrelin levels ($p = 0.008$, $p = 0.005$, $p = 0.009$, $p = 0.001$, $p = 0.004$, and $p = 0.007$, respectively in obese and lean). Systolic or diastolic blood pressure had no significant correlation with plasma acylated ghrelin levels. Serum GH and insulin levels were significantly correlated with plasma acylated ghrelin levels (directly and inversely, respectively) ($p = 0.002$, $p = 0.003$, $p = 0.005$, and $p = 0.009$, respectively in obese and lean). No significant correlation was seen between fasting blood glucose and plasma acylated ghrelin levels. HOMA-IR was inversely correlated with plasma acylated ghrelin levels ($p = 0.007$ and $p = 0.006$, respectively in obese and lean). There were no significant correlations between lipid profiles and plasma acylated ghrelin levels. VO_2max values were directly correlated with plasma acylated ghrelin levels ($p = 0.008$ and $p = 0.006$, respectively in obese and lean).

Discussion

In line with previous studies,[25,26] plasma acylated ghrelin concentrations in the lean subjects were 119% more than the obese subjects. In addition, serum GH concentrations in the obese subjects were less than the lean subjects. Scacchi et al. believed that GH secretion is markedly blunted in obesity.[27] Benatti and Junior indicated that obese animals and humans had higher basal concentrations of plasma insulin in relation with non-obese individuals and animals.[28] Insulin resistance index in obese men was more than leans (as calculated by HOMA-IR). English et al. confirmed that obese subjects were more resistant to insulin than lean subjects.[25] According to the values of estimated VO_2max and to the low mean of subjects' ages, cardiorespiratory readiness levels of subjects were low, but lean subjects had higher fitness level than obese subjects. Perhaps, we can attribute this difference to varied body weights of two groups. Moreover, it appears that obese subjects have less spontaneous locomotor activity, and in regard to motor habits, their life style is partially motionless, and thus, their physical (especially cardiovascular) fitness level is low.[29] Castaneda et al. believed that obesity is often associated with lowered rates of energy expenditure.[29]

Body weight, body fat percent, and BMI were inversely correlated with plasma acylated ghrelin levels too. Tolle et al. showed inverse correlation between ghrelin and BMI.[30] In addition, Leidy et al. indicated that the changes in ghrelin were negatively correlated with changes in body weight.[31]

In case of positive correlation between acylated ghrelin levels and GH, our findings were consistent with statements of Tritos and Kokkotou.[32] Although no correlation was observed between acylated ghrelin levels and fasting blood glucose, obvious negative correlations were found between acylated ghrelin levels and insulin or insulin resistance index. Tschop et al. showed that fasting plasma ghrelin was negatively correlated with percent body fat, fasting insulin and leptin concentrations.[33] Previous researchers have gained approximately similar results.[19,32,34-36] Marzullo et al. showed a significant correlation between active and total ghrelin, and between total ghrelin and insulin or insulin resistance.[1] Our results were consistent with mentioned results.[1] We found that in line with findings of Choi et al.,[37] none of lipid profiles had any relationship with plasma acylated ghrelin levels.

In acordance with results of Kraemer and Castracane, we found that there was positive relation between acylated ghrelin plasma levels and VO_2max.[20] Leidy et al. investigated changes in ghrelin after three months training in normal-weight women and indicated that in comparison with women with unchanged weight, women that their weight decreased showed more increases in ghrelin levels.[31]

The main limitation of this study was that only inactive (and not active) subjects were studied. In addition, it had been better if more subjects would have been studied. Performing similar study on active lean and obese subjects can provide more accurate view about acylated ghrelin levels and some of its most important biochemical and hormonal relationships. Knowing about relationships between acylated ghrelin and variables such as blood pressure and lipid profile needs more studies.

Conclusion

There were differences between lean and obese men in terms of acylated ghrelin levels, GH, insulin resistance index, body fat percent, body mass index, and cardiorespiratory function, but not in cases of blood pressure, fasting blood glucose, and lipid profiles. Acylated ghrelin had obvious relationships with GH, insulin, insulin resistance index, body fat percent, BMI, and cardiorespiratory function. Directions of observed relationships in this study were the same for both of the lean and obese groups, and values of the relationships, almost in all of them, were more in the obese group than the lean group. It appears that body fat percent, insulin, and GH can predict acylated ghrelin changes. It may be concluded that in young men, inactivity is associated with obesity and related abnormal conditions such as diabetes mellitus and in both obese and lean groups of young men, higher levels of cardiovascular function are associated with higher levels of acylated ghrelin.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

All authors were responsible for the conception and design of the study. HMH supervised the design of the study. FM coordinated the study, carried out all experiments and anthropometrics, analyzed the data, and drafted the manuscript. HMH, MAA and MP provided assistance for all experiments, and revised and commented on the draft. All authors participated in analysis of data and interpretation of the findings. All authors read and approved the final version of the paper.

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