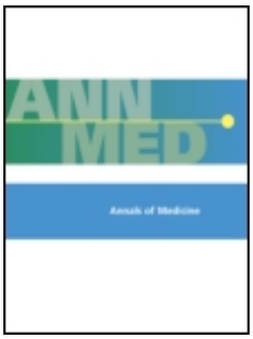

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ORIGINAL ARTICLE

Interactions between ghrelin, leptin and IGF-I affect metabolic syndrome and early atherosclerosis

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Abstract

Background. High leptin and low ghrelin are associated with the metabolic syndrome (MS).

Aims and methods. Ghrelin, leptin (RIA kits), and insulin-like growth factor I (IGF-I) (ELISA kit) concentrations of the population-based cohort of 1045 subjects and their interactions with metabolic parameters were analysed. Intima-media thickness (IMT) was measured with carotid ultrasound.

Results. The interaction between leptin and ghrelin on the MS was significant ($P=0.011$). An additive effect of high leptin and low ghrelin on metabolic disturbances was observed: low ghrelin concentration (adjusted for age and sex) ($P<0.001$) was associated with the MS and type 2 diabetes in the highest but not in the lower leptin quartiles. In the highest leptin quartile, ghrelin concentrations decreased linearly when the number of International Diabetes Federation MS criteria met ($P<0.01$) increased. Ghrelin-leptin relation was independently associated with carotid IMT ($P<0.005$). The independent positive association ($P<0.01$) between the plasma ghrelin quartile and the carotid IMT was evident in the lowest IGF-I quartile.

Conclusions. Low ghrelin is associated with MS and type 2 diabetes in the presence of insulin and leptin resistance. Ghrelin-leptin relation is associated with early atherosclerosis. The interaction between IGF-I and ghrelin modifies the association of ghrelin with early atherosclerosis.

Key words: *Ghrelin, IGF-I, insulin resistance, leptin, type 2 diabetes*

Introduction

Ghrelin and leptin, two peptide hormones, interact with each other in the control of appetite (1). Recent data suggest that ghrelin has an important role in the central regulation of leptin secretion (2). Fasting plasma ghrelin levels are negatively correlated with those of leptin (3) suggesting antagonism of the two peptides. Ghrelin is downregulated in human obesity, and this downregulation may be a consequence of elevated insulin or leptin (3). The main effects of these peptide hormones on obesity-related phenotypes have been explored. Thus, high leptin (4–7) and low ghrelin (8,9) have been associated with the development of the metabolic syndrome (MS) and the risk of type 2 diabetes in some studies (10,11). However, the interactions between leptin and ghrelin, although not yet studied in the clinical setting, could also play a role in the pathogenesis of the clustering of metabolic abnormalities.

In addition to leptin, another significant determinant of ghrelin concentration is potentially the insulin-like growth factor 1 (IGF-I). Ghrelin, a somatotropic peptide (12), is negatively associated with IGF-1 concentrations (13). Obesity, gender, insulin resistance, and type 2 diabetes modify the association between ghrelin and IGF-I (13). IGF-I deficiency has been shown to increase the cardiovascular risk in some studies (14,15). We have recently reported that carotid artery atherosclerosis

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Key messages

- Low ghrelin is associated with the metabolic syndrome and type 2 diabetes in the presence of insulin and leptin resistance.
- Ghrelin-leptin relation is associated with early atherosclerosis.
- The interaction between insulin-like growth factor 1 and ghrelin modifies the association of ghrelin with early atherosclerosis.

Abbreviations

ANOVA	analysis of variance
ANCOVA	analysis of covariance
HDL	high-density lipoprotein
IDF	International Diabetes Federation
IGF-I	insulin-like growth factor I
IMT	intima-media thickness
MS	metabolic syndrome
OR	odds ratio
OPERA	Oulu Project Elucidating Risk of Atherosclerosis
RIA	radioimmunoassay
VLDL	very-low-density lipoprotein

is positively associated with ghrelin (16) and IGF-I (17) concentrations in males and females, respectively. How the inverse relationship and interaction between ghrelin and IGF-I affects early atherosclerosis remains unknown.

Therefore, the effects of ghrelin on metabolic disturbances and related atherosclerosis may be modified by other hormones and growth factors, such as leptin and IGF-I. Our main aim was to study whether leptin is a determinant of ghrelin effects on progression of the metabolic syndrome and atherosclerosis. In addition, we tested whether ghrelin-IGF-I interactions play a role in early atherosclerosis in the population-based cohort of middle-aged subjects.

Subjects and methods

This study is a part of the OPERA (Oulu Project Elucidating Risk of Atherosclerosis) project, which is a population-based, epidemiological cross-sectional study designed to address the risk factors and disease end points of atherosclerotic cardiovascular diseases. The study population and selection criteria have been previously described in detail (18). In short, 600 hypertensive subjects (300 men and 300 women, aged 40–59) were randomly selected from the national register for reimbursement of the costs of antihypertensive medication. For each hypertensive subject, an age- and sex-matched control subject was randomly selected. Altogether 1045 subjects volunteered in the study, which was approved by the Ethical Committee of the Faculty of Medicine, University of Oulu. Waist circumference was measured to the nearest 0.5 cm with a tape-measure midway between the lower rib margin and the iliac crest in light expirium. Blood pressure was measured according to the recommendations of the American Society of Hypertension in a sitting position from the right arm with an oscillometric device (Dinamap® model 18465X, Criticon Ltd, Ascot, UK) after an overnight fast and after a 10–15-minute rest. Three measurements were made at 1-minute intervals, and the means of the last two were used in the analyses.

All the laboratory test samples were obtained after an overnight fast (timing of blood samples varied between 7.00 and 10.00 a.m.). Plasma was separated from venous blood and stored at 4°C. The venous blood glucose concentration was determined with the glucose dehydrogenase method. Type 2 diabetes was determined according to the World Health Organization criteria (19). The concentrations of total cholesterol and triglycerides in the plasma and lipoprotein fractions were determined by enzymatic colourimetric methods (kits of Boehringer Diagnostica, Mannheim GmbH, Germany, catalogue nos. 236691 and 701912, respectively) using Kone Specific analyser (Kone Specific, Selective Chemistry Analyser, Kone Instruments, Espoo, Finland). The very-low-density lipoprotein (VLDL) fraction ($d < 1.006$ g/mL) was separated from plasma by ultracentrifugation in a Kontron TFT 45.6 rotor at 105,000 g and 15°C for 18 h. The VLDL fraction was removed from the ultracentrifuged preparation by tube slicing. The plasma high-density lipoprotein (HDL) cholesterol concentration was determined by mixing 1 mL of the VLDL-free fraction with 25 μL of 2.8% (w/v) heparin and 25 μL of 2M manganese chloride and by measuring the cholesterol concentration in the supernatant after centrifugation at 1000 g and 4°C for 30 minutes. Fasting plasma ghrelin concentrations were analysed using a commercial radioimmunoassay (RIA) kit recognizing both acylated and des-acylated ghrelin (Phoenix Pharmaceuticals Inc., Belmont, California, USA) as we have described earlier (11). The intra- and interassay coefficients of variation (CV), as given by the manufacturer, were 4.0% and 7.5%, respectively, for ghrelin. Interassay CV in the analyses of this study was 11.2%. Fasting ghrelin concentrations correlate strongly with the 24-h integrated area under the curve (AUC) ghrelin values (20), and

therefore fasting plasma ghrelin concentrations were analysed to obtain a measure of overall ghrelin concentrations. Fasting plasma leptin concentrations were measured using a commercial double antibody RIA (Human Leptin RIA Kit; Linco Research, Inc., St. Charles, MO) with an intra-assay CV of 3.4%–8.3% and an interassay CV of 3.0%–6.2%. Fasting plasma total IGF-I concentration was determined using a commercial kit which uses a modified version of the standard acid-ethanol extraction procedure (DSL-10-2800 ACTIVE Non-Extraction IGF-I ELISA, Diagnostic Systems Laboratories, Webster, TX, USA) with intra- and interassay CV of 4.5%–8.6% and 3.3%–6.8%, respectively.

The 2005 International Diabetes Federation criteria (IDF) definition of the MS was used (21). According to the IDF definition, for persons to be defined as having the MS, they must have: *Central obesity* (defined as waist circumference $\geq$94 cm for men and $\geq$80 cm for women) plus any two of the following four factors: *raised serum triglyceride level* ($\geq$1.7 mmol/L) (or specific treatment for this lipid abnormality), *reduced serum HDL cholesterol level* ($<$1.03 mmol/L in males and $<$1.29 mmol/L in females) (or specific treatment for these lipid abnormalities), *raised blood pressure* (systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg), or treatment of previously diagnosed hypertension, and *impaired fasting glycaemia* (fasting plasma glucose $\geq$5.6 mmol/L), or previously diagnosed type 2 diabetes.

Intima-media thickness (IMT) was measured with the carotid ultrasound procedure as described in our earlier paper (16). Insulin sensitivity was assessed using fasting plasma insulin concentrations and a quantitative insulin sensitivity check index (QUICKI = 1/(log (fasting insulin) + log (fasting glucose))) (22).

Statistical methods

To compare the means of the variables measured, Student's *t* test and analysis of variance (ANOVA) were used. Correlations were tested with Pearson's correlation. The associations were examined using linear and logistic regression analyses. The effect of the confounding factors on dependent variables was controlled for by adding them into the multivariate models. The following variables were entered into the multivariate models as covariates: sex and age. Odds ratios (OR) with 95% confidence intervals (CI) were used to compare the effect of independent variables on the dependent variable.

To normalize the distribution a logarithm transformation was applied to leptin, IGF-1, QUICKI, and to all intima-media thickness (IMT) measurements. All calculations were made with the SPSS (version 9.0; SPSS, Inc.) statistical package. *P*-value <0.05 was regarded as significant.

The possible interaction between leptin and the ghrelin quartile on MS (sum of individual components, maximum 5) was assessed using analysis of covariance (ANCOVA) with the leptin and ghrelin quartile, age, sex, and the interaction term (leptin quartile $\times$ghrelin quartile) included in the model. The interaction between IGF-I and ghrelin on IMT was tested in a similar manner.

The relation between ghrelin and leptin was calculated from direct arithmetical ratio of crude ghrelin and leptin values.

Results

The basic characteristics of study subjects by study group and gender are shown in Table I. Use of selected medication among the hypertensive and control cohorts by gender is shown in Table II.

The interaction between leptin and ghrelin on the MS was statistically significant ($P=0.011$). We analysed the association of plasma ghrelin concentrations (adjusted for age and sex) in relation to the individual clinical features of the MS by IDF criteria in leptin quartiles. Of the criteria, the association of higher waist circumference ($P<0.01$), blood pressure ($P=0.01$), and fasting glucose ($P<0$ .01) with lower plasma ghrelin concentration was significant among subjects in the highest leptin quartile but not in the first, second, or third leptin quartile. The ghrelin concentrations were lower in subjects with MS compared to those without ($P<0.001$) in the presence of the highest leptin quartile (Figure 1).

The ghrelin concentrations (adjusted for age and sex) varied in relation to the number of IDF criteria of MS met ($P<0.01$) in the subjects belonging to the highest leptin quartile (Figure 2). Ghrelin levels decreased with an increase in the number of metabolic abnormalities in this quartile.

We have earlier reported an association of low ghrelin with insulin resistance (11). In this study we studied the association of ghrelin with insulin resistance in leptin quartiles. The ghrelin quartile was associated linearly with the QUICK index only in the individuals who were in the highest quartile of leptin when an adjustment for age and sex was made ($P<0.05$). The mean (95% CI) QUICK index values in different ghrelin quartiles in the highest quartile of leptin were as follows: I (the lowest quartile): 0.55 (0.53–0.58); II: 0.58 (0.55–0.60); III: 0.58 (0.55–0.61); and IV (the highest quartile): 0.61 (0.58–0.64). In other leptin quartiles the

Table I. Main characteristics of the control and hypertensive cohorts by gender. Values are means (SD) or percentages.

	Control cohort			Hypertensive cohort		
	Men ($n=259$)	Women ($n=267$)	All ($n=526$)	Men ($n=261$)	Women ($n=258$)	All ($n=519$)
Age (years)	50.9 (6.1)	51.8 (6.0)	51.4 (6.0)	50.5 (5.9)	51.8 (5.9)	51.2 (5.9)
Type 2 diabetes (%)[a]	5.0	3.4	4.2	14.9[b]	12.4[b]	13.7[b]
BMI (kg/m^2)	26.5 (3.5)	26.2 (4.4)	26.4 (4.0)	29.4 (4.4)[b]	28.7 (5.3)[b]	29.0 (4.9)[b]
Systolic BP (mmHg)	145 (20)	137 (21)	141 (21)	158 (21)[b]	152 (21)[b]	155 (21)[b]
Diastolic BP (mmHg)	88 (10)	82 (12)	85 (12)	97 (10)[b]	90 (11)[b]	94 (11)[b]
Smoking (pack years)	17.1 (14.6)	7.8 (12.4)	12.4 (14.3)	15.4 (13.9)	7.6 (12.3)	11.5 (13.7)
Alcohol consumption (g/week)	90 (100)	23 (36)	56 (82)	106 (126)	31 (48)	68 (103)
Fasting glucose (mmol/L)	4.6 (1.1)	4.3 (0.6)	4.5 (0.9)	5.1 (1.9)[b]	4.9 (1.8)[b]	5.0 (1.9)[b]
Fasting insulin (mmol/L)	13.2 (12.2)	9.7 (6.2)	11.4 (9.8)	17.9 (12.9)[b]	13.8 (10.3)[b]	15.9 (11.8)[b]
QUICKI	0.60 (0.09)	0.67 (0.12)	0.63 (0.11)	0.55 (0.10)[b]	0.60 (0.13)[b]	0.58 (0.12)[b]
Total cholesterol (mmol/L)	5.8 (1.1)	5.5 (1.0)	5.6 (1.1)	5.8 (1.0)	5.7 (1.1)[b]	5.8 (1.0)
LDL cholesterol (mmol/L)	3.7 (1.0)	3.3 (0.9)	3.5 (1.0)	3.6 (0.9)	3.5 (0.9)	3.5 (0.9)
HDL cholesterol (mmol/L)	1.2 (0.3)	1.6 (0.4)	1.4 (0.4)	1.2 (0.3)[b]	1.4 (0.4)[b]	1.3 (0.4)[b]
Triglycerides (mmol/L)	1.6 (0.8)	1.2 (0.7)	1.4 (0.8)	2.0 (1.3)[b]	1.6 (1.1)[b]	1.8 (1.2)[b]
IGF-I (ng/mL)	90 (41)	81 (39)	85 (40)	61 (36)[b]	89 (53)	75 (47)[b]
Ghrelin (pg/mL)	646 (230)	702 (237)	674 (235)	668 (266)	654 (234)[b]	661 (250)
Leptin (ng/mL)	5.1 (3.1)	12.8 (7.3)	9.3 (6.9)	7.0 (4.1)[b]	16.7 (10.1)[b]	11.8 (9.1)[b]

[a]Based on World Health Organization criteria.
[b]$P<0.05$ between hypertensive and control cohorts.
BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; IGF-I = insulin-like growth factor I; LDL = low-density lipoprotein.

ghrelin was not associated with the QUICK index values.

When leptin quartiles were considered, low ghrelin was a statistically significant predictor of type 2 diabetes in logistic regression analysis ($P=0.020$) only among the subjects belonging to the highest leptin quartile. In this last subgroup, the subjects in the 1st ghrelin quartile were at higher risk of having type 2 diabetes compared to the subjects in the 4th quartile (OR = 4.2, 95%CI: 1.1–16.1, $P=0.037$) after adjustment for age and sex (Figure 3).

In Figure 4 the association of adjusted means for ghrelin-leptin relation in four IMT quartiles is shown. The highest ghrelin-leptin relation was associated with the highest IMT ($P<0.005$). Analysis was performed for diabetics and non-diabetics separately, and the association was significant in both groups (data not shown).

Interaction between ghrelin and IGF-I quartile on IMT was significant ($P<0.05$). Therefore, we studied whether plasma ghrelin concentrations are associated with the degree of subclinical atherosclerosis measured as IMT of carotid arteries when different levels of IGF-I are considered. For that purpose we divided IGF-I levels into quartiles. The positive linear association ($P<0.01$) between plasma ghrelin quartile and carotid IMT existed only among subjects in the lowest IGF-I quartile (Figure 5).

Table II. Use of selected medications among the hypertensive and control cohorts by gender. Data are n (%).

	Control cohort			Hypertensive cohort		
Medication	Men ($n=259$)	Women ($n=267$)	All ($n=526$)	Men ($n=261$)	Women ($n=258$)	All ($n=519$)
Antihypertensive medication	26 (10.0)	29 (10.9)	55 (10.5)	239 (91.6)	248 (96.1)	487 (93.8)
Diuretics	2 (0.8)	9 (3.4)	11 (2.1)	61 (23.4)	100 (38.8)	161 (31.0)
Beta-blockers	19 (7.3)	11 (4.1)	30 (5.7)	132 (50.6)	124 (48.1)	256 (49.3)
Calcium channel blockers	9 (3.5)	8 (3.0)	17 (3.2)	53 (20.3)	58 (22.5)	111 (21.4)
ACE inhibitors	4 (1.5)	7 (2.6)	11 (2.1)	106 (40.6)	87 (33.7)	193 (37.2)
Others	0	0	0	13 (5.0)	18 (7.0)	31 (6.0)
Lipid-lowering medication	6 (2.3)	4 (1.5)	10 (1.9)	13 (5.0)	7 (2.7)	20 (3.9)
Acetylsalicylic acid	12 (4.6)	6 (2.2)	18 (3.4)	25 (9.6)	15 (5.8)	40 (7.7)
Oral antidiabetic medication	2 (0.8)	2 (0.7)	4 (0.8)	10 (3.8)	9 (3.5)	19 (3.7)
Insulin	2 (0.8)	0	2 (0.4)	6 (2.3)	5 (1.9)	11 (2.1)
Hormone replacement therapy		60 (22.5)			48 (18.6)	

ACE = angiotensin-converting enzyme.

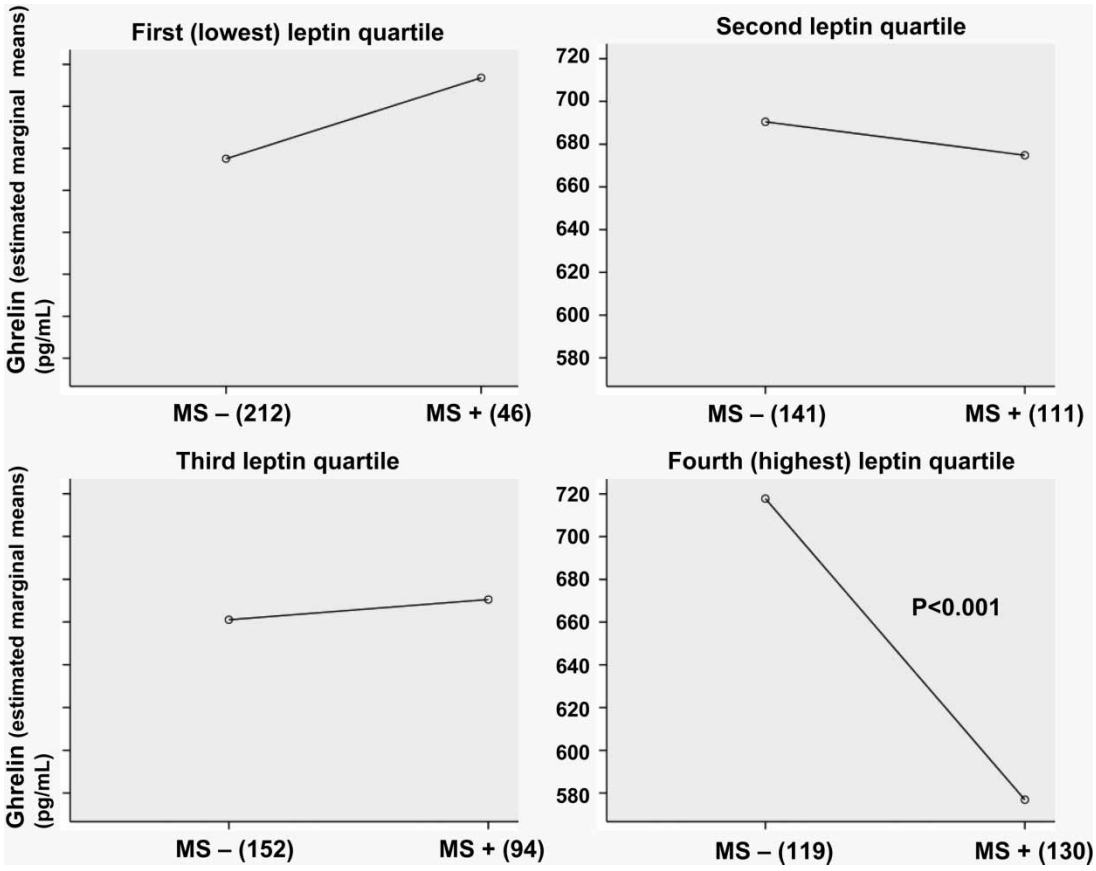

Figure 1. Fasting plasma ghrelin concentrations (adjusted for age and sex) in subjects with the metabolic syndrome (MS) compared to those without in the leptin quartiles. Mean leptin levels (ng/mL) in leptin quartiles (95% confidence intervals) are: I: 3.5 (3.0–4.0); II: 6.6 (6.0–7.1); III: 10.6 (10.1–11.1); IV: 21.9 (21.3–22.4). Standard deviations for ghrelin levels varied from 205 to 249 pg/mL.

In this model, other cardiovascular risk factors (age, sex, smoking, systolic blood pressure, and low-density lipoprotein cholesterol) were adjusted for. When sexes were considered separately, the association was significant only among males ($P<0.05$), and the mean (SD) IMT values in the lowest IGF-I quartile according to ghrelin (I–IV) quartiles in men are as follows: I (the lowest ghrelin quartile) 0.84 mm (0.09) ($n=9$); II: 0.83 mm (0.10); III: 0.86 mm (0.13); and IV: 0.93 mm (0.19).

When the IGF-I quartiles were considered, the negative correlation between ghrelin and IGF-I we have reported earlier (13) was significantly ($r=0.142$; $P<0.03$) observed only in the lowest IGF-I quartile.

Discussion

These results indicate that the high leptin and low ghrelin signals may synergize with each other to increase the clustering of metabolic abnormalities and eventually type 2 diabetes. Leptin and ghrelin have interaction effects on physiological control of feeding by regulating reciprocally neuropeptide Y neurons (23). The interplay between these two peptides might occur also peripherally and in organs evidenced to be critical for the insulin and glucose metabolism. In the pancreas leptin is able to suppress the secretion of insulin (24). In the presence of leptin deficiency or resistance, there is a failure of leptin to inhibit glucose-stimulated insulin secretion, which could lead to hyperinsulinaemia and insulin resistance (25). Leptin may also have effects on insulin action (26). Ghrelin and its receptor are widely expressed including pancreatic beta-cells (27) supporting the notion that it could have direct effects on insulin secretion, and paracrine function of locally produced ghrelin in the pancreas has been suggested (28). Low ghrelin is also independently associated with fasting insulin concentrations and insulin resistance (11). Recently, ghrelin was reported to affect the insulin signalling system (29) implicating peripheral actions of ghrelin in glucose homeostasis. In hepatoma cells ghrelin

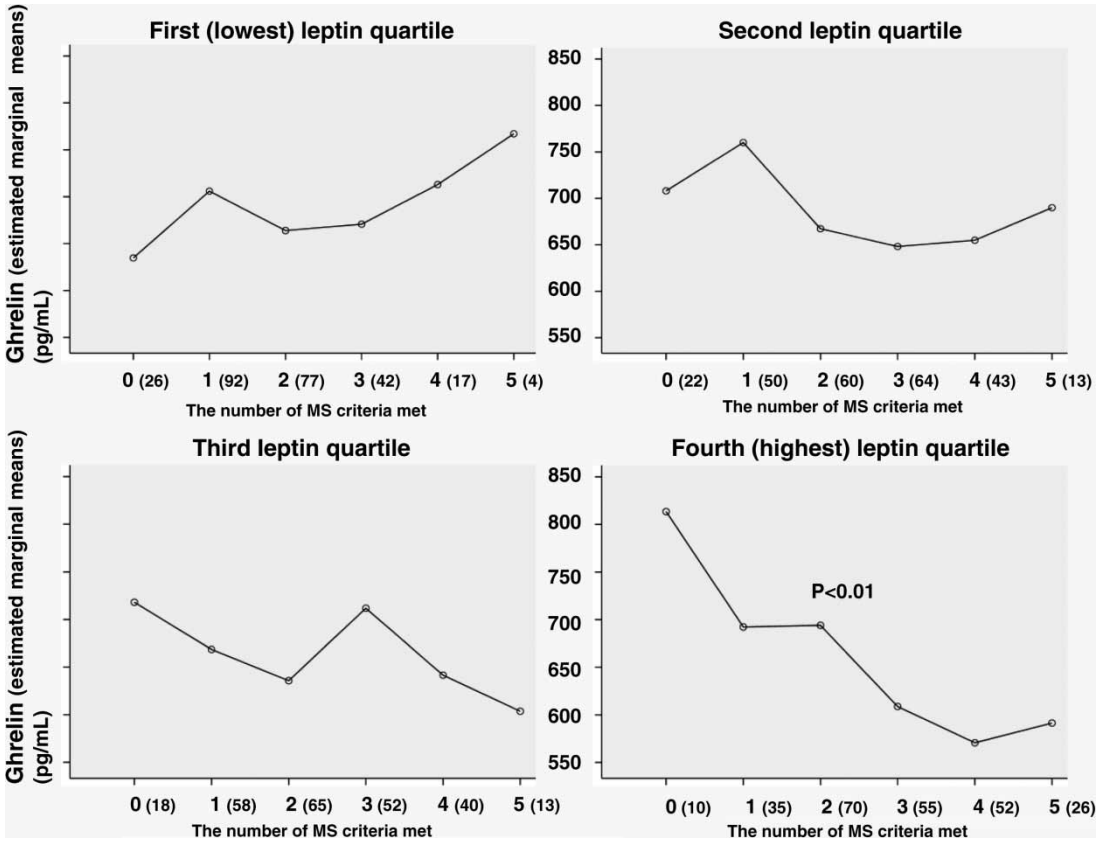

Figure 2. Fasting plasma ghrelin concentrations of the study subjects in relation to the number of International Diabetes Federation criteria of the metabolic syndrome (MS) met in leptin quartiles. Standard deviations for ghrelin levels varied from 176 to 333 pg/mL.

has an anti-insulin action and upregulates gluconeogenesis (29). Ghrelin may therefore influence glucose and insulin metabolism through its effects on adiposity, through paracrine effects on insulin secretion or insulin signalling pathways.

Our data confirm that in patients with the MS low plasma ghrelin levels act as a physiological counterpart to high leptin and that these changes are linked to the insulin resistance observed in our patients. The latter notion was supported by the observed association of low ghrelin with insulin resistance only among the subjects with the highest leptin levels, i.e. in subjects who probably have the highest level of leptin resistance. A large proportion of the subjects with the MS develop type 2 diabetes in later stages of their life. In this study low ghrelin was a statistically significant independent predictor of type 2 diabetes only among the subjects belonging to the highest leptin quartile. Thus, leptin seems to be the major determinant of ghrelin effects on progression of metabolic syndrome. We recognize that diabetic subjects in this study were a small subgroup, and strong conclusions cannot be made based on this material. Undoubtedly the development of MS and type 2 diabetes involves multiple and interactive effects of genetic, hormonal, and environmental factors where interaction between high leptin and low ghrelin seems to play a key role.

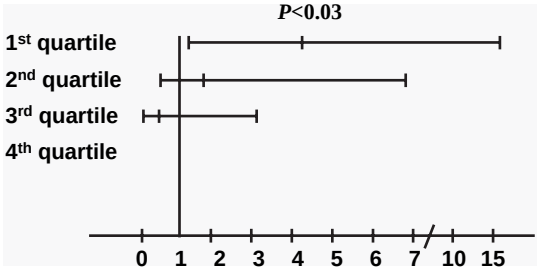

Figure 3. Odds ratios with 95% confidence intervals of ghrelin quartile for type 2 diabetes (the fourth ghrelin quartile is used as a reference category) obtained by logistic regression analysis adjusted for age and sex in the highest leptin quartile. Mean ghrelin levels in ghrelin quartiles (pg/mL) (95% confidence intervals) are: I: 376.6 (364.0–389.2); II: 574.3 (561.7–586.8); III: 743.8 (731.2–756.3); IV: 975.8 (963.2–988.3).

We have recently reported that subclinical atherosclerosis measured as IMT of carotid arteries is positively associated with plasma ghrelin levels (16). In the present study we suggest the ghrelin-leptin relation to be a stronger marker of early

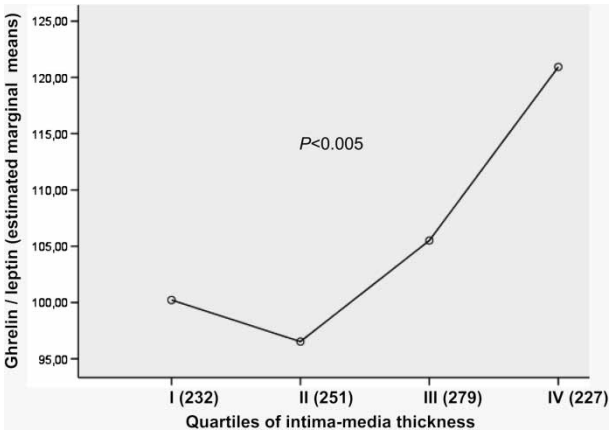

Figure 4. Adjusted (age, sex, smoking, systolic blood pressure, LDL-cholesterol and study group) means for ghrelin-leptin relation in different intima-media thickness (IMT) quartiles. Mean IMT values (mm) in IMT quartiles (95% confidence intervals) are: I: 0.69 (0.68–0.70); II: 0.77 (0.76–0.78); III: 0.84 (0.83–0.85); IV: 1.02 (1.02–1.03). Standard deviations for mean ghrelin-leptin relation varied from 72 to 133.

atherosclerosis than ghrelin alone. The present study also showed plasma ghrelin concentrations to be positively associated with the degree of subclinical atherosclerosis measured as IMT of carotid arteries in the subjects with the lowest IGF-I levels. It is interesting to see that the association was observed among male subjects who also have lower leptin levels than females. These findings remained statistically significant after adjustments for the major commonly recognized risk factors for atherosclerosis, such as age, sex, systolic blood pressure, LDL cholesterol, and smoking. One potential explanation for this association might be found from the strong inverse relation of ghrelin to IGF-I and leptin. In the lowest IGF-I quartile the inverse association between IGF-I and ghrelin was the highest. High plasma ghrelin seems therefore to be associated positively with atherosclerosis among subjects in whom the feedback effect of IGF-I on ghrelin concentrations is the strongest.

One can speculate that the increase in the amount of early atherosclerosis is seen among the subjects who are jointly exposed to the potentially deleterious effects of low IGF-I and high ghrelin. In some studies low IGF-I levels have been associated with an increased incidence of coronary heart disease (14,15). In addition, free but not total serum IGF-I was related inversely to atherosclerosis in a recent study (30). However, Ruotolo et al. suggested

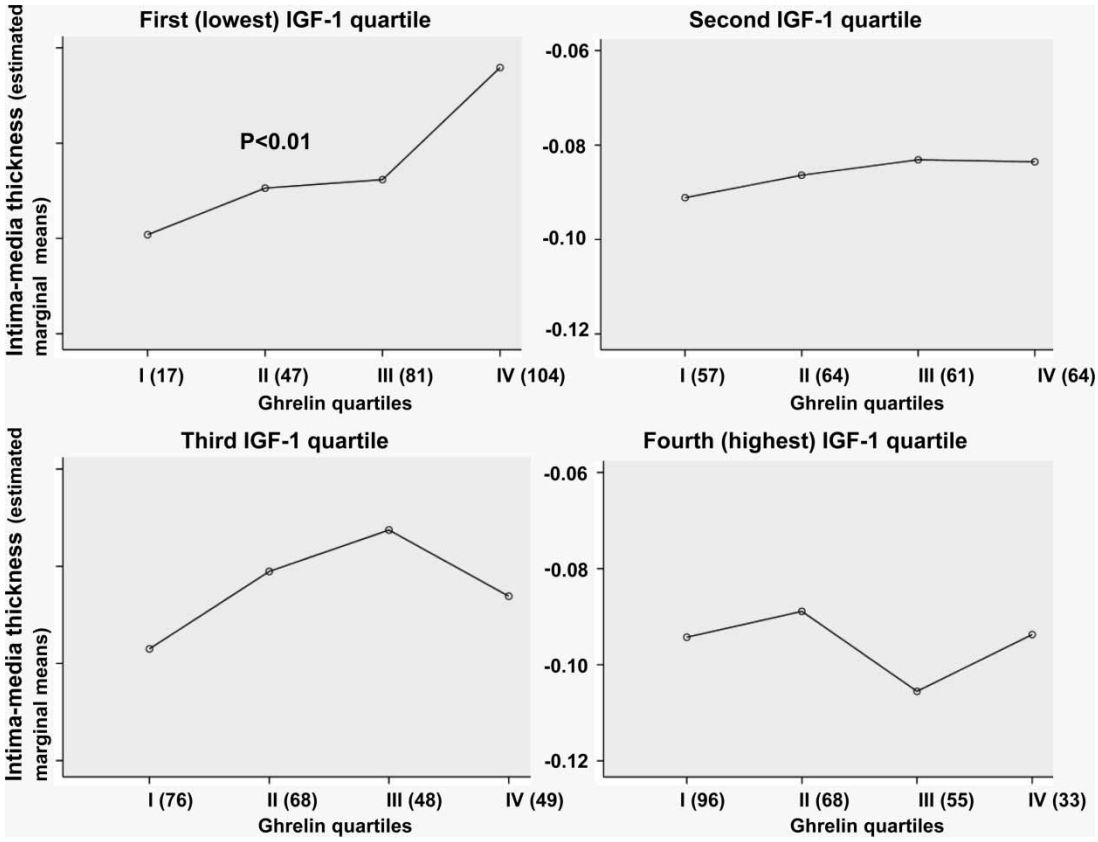

Figure 5. Mean intima-media thickness (IMT) (logarithmically transformed) of carotid arteries in relation to ghrelin and insulin-like growth factor I (IGF-I) quartiles. Mean IGF-I levels (ng/mL) in IGF-I quartiles (95% confidence intervals) are: I: 29.2 (27.1–31.3); II: 60.7 (58.6–62.9); III: 89.3 (87.1–91.5); IV: 139.4 (137.3–141.6). Standard deviations for mean IMT levels varied from 0.05 to 0.75.

IGF-I levels to correlate positively with coronary artery disease progression (31). IGF-I is able to stimulate vascular smooth muscle cell proliferation and migration *in vitro* (32–34) and suppress their apoptosis (34). IGF-I has also effects on endothelial cells and monocyte activation (35). We have earlier explored the effects of IGF-I and ghrelin on early atherosclerosis and reported IGF-I levels to be strongly and positively associated with IMT in women but not in men (17). A similar positive association between ghrelin and carotid artery atherosclerosis was seen in men (16). Several earlier studies have provided evidence of beneficial (36–44) effects, with some deleterious (45) effects, of ghrelin in the cardiovascular system. Growth hormone secretagogue receptor density has been shown to be upregulated in both atherosclerotic carotid arteries and saphenous vein grafts (46), which has been interpreted to reflect the beneficial role of ghrelin in atherosclerosis. It is difficult to know whether ghrelin is a marker for the disease or if it plays an active role, or both. Ghrelin might have different effects on atherogenesis, depending on other risk factors, the modifying effect of other growth factors, and hormones. IGF-I and leptin seem to be among such modifying factors. The cross-sectional nature of the study does not allow us to say whether changes in ghrelin and leptin levels are causes or consequences of the disorders.

In summary, novel interactions between leptin and ghrelin influencing insulin resistance and associated co-morbidities, and between IGF-I and ghrelin affecting atherosclerosis, were observed. The joint occurrence of low ghrelin and high leptin seems to be associated with the cluster of metabolic complications, while the higher ghrelin-leptin relation to the higher amount of early atherosclerosis. The combined status of the highest ghrelin and the lowest IGF-I quartiles was associated with the greatest extent of early atherosclerosis.

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