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Waist circumference, ghrelin and selected adipose tissue-derived adipokines as predictors of insulin resistance in obese patients: Preliminary results

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: The aim of the study was to estimate the association between anthropometric obesity parameters, serum concentrations of ghrelin, resistin, leptin, adiponectin and homeostasis model assessment (HOMA-IR) in obese non-diabetic insulin-sensitive and insulin-resistant patients.

Material/Methods: Study subjects included 37 obese (body mass index [BMI] ⩾30 kg/m^2) out-clinic patients aged 25 to 66 years. Insulin resistance was evaluated by HOMA-IR. Serum fasting concentrations of glucose, insulin, ghrelin, adiponectin, resistin and leptin were measured by using the ELISA method. Body weight, waist and hip circumferences were measured to calculate BMI and waist-to-hip ratio (WHR) values for all the patients. According to HOMA-IR, patients were divided into two groups: A, insulin sensitive (n=19); and B, insulin resistant (n=18).

Results: Patients with insulin resistance have greater mean waist circumference (WC) higher mean serum insulin level and leptin concentration, but lower concentrations of adiponectin and ghrelin. In the insulin-sensitive patient group we observed positive correlations between BMI and HOMA-IR, WC and HOMA-IR, and adiponectin and leptin, and negative correlations between ghrelin and HOMA-IR, WC and adiponectin, and WHR and adiponectin. In the insulin-resistant group, there was a positive correlation between resistin and ghrelin and a negative correlation between WHR and leptin.

Conclusions: Waist circumference, adiponectin, leptin and ghrelin are associated with insulin resistance and may be predictors of this pathology.

key words: **adipokines • ghrelin • insulin resistance • obese patients • waist circumference**

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Background

Adipose tissue is an important source of several cytokines, such as adiponectin, resistin and leptin, which play an important role in pathogenesis of obesity [1–9]. Some of them are also thought to contribute to development of insulin resistance. Adiponectin is one of the most important adipocytokines involved in the pathogenesis of obesity and insulin resistance. Low plasma adiponectin concentrations were noted in obese patients and in patients with insulin resistance [4–7]. Results of some recently performed studies indicated a positive correlation between circulating adiponectin levels and insulin sensitivity [1–3]. Moreover, low adiponectin levels were associated with increased risk of development of type 2 diabetes [3]. Observations from human genetic studies suggest that adiponectin gene variants are strongly connected with obesity and insulin resistance [7].

Resistin is a putative adipocyte-derived signaling polypeptide which belongs to a family of cysteine-rich proteins, resistin-like molecules (RELMs). Resistin is suggested to be an important pathogenic factor of obesity-mediated insulin resistance and type 2 diabetes mellitus, but this hypothesis is still controversial [2]. It was shown that this adipocytokine strongly induces only hepatic but not peripheral insulin resistance [10].

Leptin is another adipocytokine involved in the pathogenesis of obesity and correlates positively with body mass index (BMI), and body fat mass is the most important factor which determines leptin concentration [2,11]. Leptin inhibits appetite and weight gain by decreasing orexigenic and increasing anorexigenic peptide expression in the hypothalamus [10]. High leptin levels observed in obese patients may be a result of leptin resistance [11].

Ghrelin, a hormone secreted by gastrointestinal endocrine cells, plays an important role in the coordination of energy balance and weight regulation [2]. Its secretion is enhanced in human obesity and type 2 diabetes. However, elevated serum levels after chronic weight loss in humans were also observed [2].

Various adipocytokines may influence insulin sensitivity and therefore may be a link between insulin resistance and obesity. However, the correlation between these cytokines in insulin-resistant obese patients is still unknown. Therefore the aim of the study was to determine differences in some important adipocytokines and ghrelin serum levels in patients with obesity with and without insulin resistance and their correlations with obesity parameters: BMI, waist circumference (WC), and waist-to-hip ratio (WHR).

Material and Methods

The study protocol was approved by the Local Bioethical Committee and informed consent was obtained from all patients.

The study included 37 obese (BMI ⩾30 kg/m^2) out-clinic adult patients, 25 women and 13 men, with or without hypertension, aged from 25 to 66 years. Patients with diabetes, psychiatric disorders, pregnancy, cancer, stroke, severe hepatic or renal disease and acute cardiovascular events, or with a history of abdominal surgery, which could have an impact on abdominal fat distribution, were excluded from the study.

Patients were consecutively recruited to the study between May and July 2009. Characteristics of the study population are presented in Table 1. Patients were divided into two groups according to the HOMA-IR index: group A, insulin sensitive (n=19; M – 4, F – 15), and group B, insulin resistant (n=18; M – 7, F – 11). Insulin resistance was estimated by using the homeostasis model assessment (HOMA-IR) index, which was calculated according to the following formula: fasting insulin (µj/mL) × fasting glucose (mmol/L)/22.5 [12]. HOMA-IR index higher than 2.5 was acknowledged

Table 1. Characteristics of the study population.

Parameter	Study group	
	A N=19	B N=18
Age (years) mean ± SD	53.0±13.19	49.56±14.16
Male/female n	4/15	7/11
Hypertension n (%)	13 (68.4%)	17 (94.4%)
Stable angina n (%)	3 (15.8%)	2 (11.1%)
Myocardial infarct n (%)	2 (10.5%)	1 (5.56%)
Heart failure n (%)	3 (15.8%)	8 (44.4%)
Hyperlipidemia n (%)	13 (68.4%)	14 (77.8%)
Hyperuricemia/gout n (%)	3 (15.8%)	4 (22.2%)
Hypothyreosis n (%)	1 (5.26%)	1 (5.56%)

Table 2. Results obtained from particular groups of patients. The data are presented as means ±SD.

Assessed feature or parameter (mean ±SD)	Study group	
	A N=19	B N=18
BMI (kg/m^2)	33.19±3.13	34.77±3.52
WC (cm)	102.44±9.19[a]	109.59±10.06*
WHR	0.90±0.07	0.93±0.07*
Adiponectin (ng/mL)	21.85±13.05[a]	14.69±4.88
Resistin (ng/mL)	0.93±0.42	1.04±0.44
Ghrelin (pg/mL)	1340.44±325.53[a]	1115.40±192.54
Leptin (ng/mL)	6.04±3.18[a]	8.50±4.59
Glucose (mmol/l)	5.46±0.50	5.72±0.52
Insulin (µU/mL)	6.10±1.13[b]	14.29±4.68
HOMA-IR	1.47±0.27[b]	3.64±1.28

[a] $p<0.05$; [b] $p<0.00001$; * n=17.

Table 3. Correlations between compared parameters in group A – insulin-sensitive patients.

Parameters	N	r	P
BMI & HOMA-IR	19	0.5840	**<0.01**
WC & HOMA-IR	16	0.6396	**<0.01**
WHR & HOMA-IR	19	0.2801	NS
Adiponectin & HOMA-IR	19	–0.2368	NS
Resistin & HOMA-IR	19	–0.2000	NS
Ghrelin & HOMA-IR	19	–0.4947	**<0.05**
Leptin & HOMA-IR	19	0.2000	NS
BMI & Adiponectin	19	0.0985	NS
BMI & Resistin	19	–0.0422	NS
BMI & Ghrelin	19	–0.3342	NS
BMI & Leptin	19	0.1469	NS
WC & Adiponectin	16	–0.4893	**0.05**
WC & Resistin	16	–0.0177	NS
WC & Ghrelin	16	–0.2078	NS
WC & Leptin	16	–0.0383	NS
WHR & Adiponectin	19	–0.5575	**<0.05**
WHR & Resistin	19	–0.3126	NS
WHR & Ghrelin	19	0.1858	NS
WHR & Leptin	19	–0.3364	NS
Adiponectin & Resistin	19	0.2842	NS
Adiponectin & Ghrelin	19	0.0404	NS
Adiponectin & Leptin	19	0.5053	**<0.05**
Resistin & Ghrelin	19	0.1158	NS
Resistin & Leptin	19	0.1439	NS
Ghrelin & Leptin	19	–0.1228	NS

as significant for insulin resistance. Serum glucose concentrations were measured by the glucose oxidase method and total activity of ghrelin, adiponectin, leptin, resistin and insulin was measured by using the ELISA method in fasting venous blood samples (8 ml) collected from the patients. Body weight, and waist and hip circumferences were measured to calculate BMI and WHR values for all the patients.

Statistical analysis

Statistical analysis was performed using the statistical package STATISTICA (StatSoft, Poland).

Shapiro-Wilk test was used to verify whether variable distribution was normal. Student's t-test was applied to compare the data in every group when distribution of the variable in all compared groups was normal or nonparametric. Mann-Whitney U test was used when distribution of the variable was not normal in at least one of the compared groups. P values <0.05 were considered as statistically significant. Chi-square tests were used for comparison of categorical variables of patients' characteristics (Yates correction or Fisher's exact test was applied when appropriate).

Patients' age, sex, concomitant diseases, WC, BMI, WHR and HOMA-IR values, blood level of glucose and insulin, as well as concentrations of adiponectin, resistin, ghrelin and leptin, were compared between groups A and B. Moreover, Spearman's rank correlation coefficient (R) was used to estimate the correlation between BMI, WHR, WC and HOMA-IR, between obesity parameters and concentrations of ghrelin and above-mentioned adipokines, and between ghrelin and adipokines.

Results

There were no statistically significant differences in age, sex, concomitant diseases, BMI, WHR and in resistin and glucose serum levels between both groups of patients (Tables 1 and 2). Hypertensive patients dominated in the insulin-resistant group, but the differences between the groups do not reach statistical significance (Table 1). Waist circumference was higher in the insulin-resistant patients (102.44±9.19 *vs.* 109.59±10.06; $p<0.05$) (Table 2). Serum levels of adiponectin and ghrelin were significantly higher in group A (21.85±13.05 *vs.* 14.69±4.88; $p<0.05$), while serum leptin and insulin levels were higher in insulin-resistant group B (6.04±3.18 *vs.* 8.50±4.59; $p<0.05$ and 6.10±1.13 *vs.* 14.29±4.68; $p<0.00001$ respectively). HOMA-IR index was much higher in group B (1.47±0.27 *vs.* 3.64±1.28; $p<0.00001$) (Table 2).

In group A we noted a positive correlation between BMI and HOMA-IR ($r=0.5840$; $p<0.01$), WC and HOMA-IR ($r=0.6396$; $p<0.01$) and a negative correlation between serum ghrelin level and HOMA-IR ($r=–0.4749$; $p<0.05$) and between WHR and adiponectin level ($r=–0.5557$; $p<0.05$) (Table 3). We also observed a positive correlation between WC and adiponectin serum concentration, but it was bordering on statistical significance ($r=–0.4893$; $p=0.05$). Serum adiponectin level positively correlated with serum leptin level in this group ($r=0.5053$; $p<0.05$) (Table 3).

In group B we observed a positive correlation between resistin and ghrelin serum levels ($r=0.6244$; $p<0.01$) and a negative correlation between WHR and leptin serum level ($r=–0.6835$; $p<0.01$) (Table 4). We did not find any statistically significant correlation between other parameters in this group (Table 4).

Discussion

Obesity plays an important role in development of insulin resistance. The results of our study suggest that waist circumference, which reflects central obesity, may be an important predictor of insulin resistance. It was the only obesity parameter which significantly differed between insulin-sensitive and -resistant patients. Our findings are in agreement with those observations, suggesting that WC better than BMI correlates with abdominal fat and insulin sensitivity [13,14]. A positive correlation between WC and insulin resistance was also reported by Nilsson et al. [15]. However, the authors suggested that this association was stronger in women than in men. Tabata et al. found a linear relation

Table 4. Correlations between compared parameters in group B – insulin resistant patients.

Parameters	N	r	p
BMI & HOMA-IR	18	0.3530	NS
WC & HOMA-IR	17	0.1817	NS
WHR & HOMA-IR	17	–0.3850	NS
Adiponectin & HOMA-IR	18	–0.2487	NS
Resistin & HOMA-IR	18	0.1662	NS
Ghrelin & HOMA-IR	18	0.1723	NS
Leptin & HOMA-IR	18	0.3044	NS
BMI & Adiponectin	18	0.2919	NS
BMI & Resistin	18	0.1822	NS
BMI & Ghrelin	18	0.2402	NS
BMI & Leptin	18	0.1201	NS
WC & Adiponectin	17	–0.0884	NS
WC & Resistin	17	0.0368	NS
WC & Ghrelin	17	–0.0552	NS
WC & Leptin	17	–0.3917	NS
WHR & Adiponectin	17	–0.2357	NS
WHR & Resistin	17	–0.0691	NS
WHR & Ghrelin	17	–0.1703	NS
WHR & Leptin	17	–0.6835	**<0.01**
Adiponectin & Resistin	18	0.0650	NS
Adiponectin & Ghrelin	18	–0.0774	NS
Adiponectin & Leptin	18	0.2611	NS
Resistin & Ghrelin	18	0.6244	**<0.01**
Resistin & Leptin	18	–0.0134	NS
Leptin & Ghrelin	18	0.1538	NS

between WC and insulin resistance [16]. These observations were confirmed by other authors, which indicated WC as an independent predictor of insulin resistance [17–21].

The results of our study suggest that resistin is not associated with insulin resistance. It has been shown that resistin induced only hepatic but not peripheral insulin resistance [22]. Nevertheless, its role in insulin sensitivity is still controversial. Recent genetic studies indicated an association between resistin and insulin resistance and between resistin and obesity [13]. Hivert et al. observed a positive correlation between resistin and HOMA-IR in patients with metabolic syndrome [23]. Some clinical studies showed increased serum resistin levels in obese patients compared to lean subjects [2,24]. Nevertheless, Lee et al. did not find any association between resistin serum levels and BMI [14]. Furthermore, the authors did not find any correlation of resistin with any parameters or markers of adiposity or insulin resistance such as BMI, WC, WHR, FM (fat mass), insulin and HOMA-IR in lean healthy volunteers, in obese insulin-resistant and in type 2 diabetes patients [14]. Serum resistin levels also did not differ between investigated groups of patients in our study. Other investigators confirmed that serum resistin is not a significant predictor of insulin resistance in humans [13,24,25].

Adiponectin, an adipokine produced by differentiated adipocytes, is inversely correlated with central adiposity and insulin resistance [1,23–26]. Decreased adiponectin levels were observed in patients with insulin resistance and hyperinsulinemia as well as in those with type 2 diabetes [25]. Circulating adiponectin negatively correlates with obesity [25]. This adipocytokine is considered to be a molecular link between obesity and insulin resistance [7]. It has been suggested that low levels of adiponectin may result from obesity-induced insulin resistance rather than being the cause or the result of obesity [7]. The significantly lower adiponectin serum level in the insulin-resistant group observed in our study may indicate adiponectin as a predictor of insulin resistance also in obese patients. We suggest that it could be related to central obesity rather than body mass, because there was no difference in BMI between the two investigated groups. However, we observed an inverse correlation between WHR, WC and adiponectin serum level only in the insulin-sensitive group [27–30].

The question of a direct impact of leptin on insulin sensitivity is still controversial [10]. We observed a significantly higher serum leptin level in insulin-resistant patients. Therefore we could not exclude that hyperleptinaemia may play a role in insulin resistance. It is well known that insulin stimulates both leptin biosynthesis and secretion from adipose tissue as an endocrine adipo-insular feedback loop ("adipo-insular axis") and leptin improves peripheral insulin sensitivity and modulates pancreatic β-cell function [13]. Thus higher leptin secretion may be the response to hyperinsulinemia. Singh et al., based on the results of several clinical experiments, pointed out that elevated leptin levels were associated with increased risk of development of type 2 diabetes mellitus [31]. However, other authors found that diabetes does not influence leptin secretion in either lean or obese individuals [25].

On the other hand, we cannot exclude that higher leptin levels in the insulin-resistant group might also be associated with hypertension, which occurred more often in this population, although this difference was not statistically significant (perhaps due to the small study group). Results of previous studies indicated positive relations between elevated leptin levels and hypertension [31]. Moreover, hypertension is also associated with insulin resistance but not with insulinemia in non-diabetic subjects, as observed by Saad et al., although ethnic differences in this relation existed [32]. Therefore hypertension should be taken into consideration as a factor connected with higher leptin levels and also with insulin resistance.

It is well known that leptin expression and secretion are increased in obesity and there is a strong correlation between body fat accumulation and leptin plasma level. On the basis of our observations, it seems that WHR better than BMI correlates with plasma leptin level in patients with insulin resistance. We suggest that WHR better reflects visceral fat deposit than BMI. This opinion is also confirmed by other

authors [33–35]. However, it was also found that leptin plasma level positively correlates with BMI [2].

Another hormone interesting from the possibility of association with insulin resistance is ghrelin. We observed a significantly lower serum ghrelin level in insulin-resistant patients. Moreover, we found a negative correlation between ghrelin and HOMA-IR, but only in insulin-sensitive patients. This finding is in accordance with the result obtained by Kim et. al [33]. Vendrell et al. observed a significantly lower ghrelin level in patients with morbid obesity compared with nonmorbidly obese subjects and found a correlation between ghrelin and resistin in nonmorbidly obese patients [36]. However, the authors did not estimate insulin resistance and its relations with measured cytokine levels. Pöykko et al. found lower ghrelin concentrations in diabetic patients and postulated ghrelin as an independent predictor of insulin resistance or even type 2 diabetes [37]. Other authors observed significantly lower ghrelin levels in obese normotensive postmenopausal women compared to healthy non-obese subjects from the control group and elevated levels of this hormone in hypertensive obese women [38]. Nevertheless, ghrelin levels were lower independently of hypertension in obese women with BMI above 35 kg/m^2. The authors concluded that ghrelin was positively correlated with hypertension in obese women and increase of BMI can inverse this association, and suggested that lower ghrelin levels in obese subjects might be a result of physiological adaptation to the positive energy balance in obesity [38].

Based on the results of our study, we suggest that the lower level of ghrelin in obese insulin-resistant patients may result from visceral obesity and related insulin resistance rather than from BMI, because BMI was comparable in both investigated groups. This is in agreement with the observations of other authors that low ghrelin concentrations were associated with higher risk of development of type 2 diabetes independently of BMI [39]. Moreover, most authors suggest that decreased ghrelin secretion in obese patients is associated with visceral obesity and concomitant insulin resistance [39]. We have also found a positive correlation between ghrelin and resistin similarly as Vendrell et al., but the clinical implication of this association is unclear based on our results or the literature [36].

The mechanisms of association between ghrelin and insulin resistance are still unknown. It has been postulated that ghrelin decreases insulin secretion [39,40]. However, other authors suggested that decreased ghrelin concentrations in obese insulin-resistant patients may be a result of inhibition of ghrelin expression and secretion by insulin [39]. A genetic background of this phenomenon is also possible [39]. It was confirmed that obese patients with the Arg51Gln mutation of the ghrelin gene have lower ghrelin levels and greater risk of type 2 diabetes development. Nevertheless, based on the results of previous studies it is still unclear whether low ghrelin level is the cause or rather the result of insulin resistance [39–44].

This study has some important limitations. The patient groups were small and therefore some results could not reach or were bordering on statistical significance. Also we could not evaluate sex-dependent differences in the groups because of too few patients, especially men.

Conclusions

Based on the results of our preliminary study, we conclude that WC, adiponectin, leptin and ghrelin are associated with insulin resistance and may be predictors of this pathological state. Further detailed studies based on greater populations are needed to confirm these relations and explain their mechanisms.

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