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Gender dependent dimorphism in adipokines levels and its correlations with insulin resistance in extremely obese patients

Wpływ płci na stężenia adipokin oraz ich korelacje z insulinoopornością u pacjentów z otyłością olbrzymią

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Summary

Introduction. Obesity is closely associated with insulin resistance, and insulin resistance is connected with altered adipokine levels. There are gender differences in some adipokines concentration.

Aim. The aim of this study was to evaluate sex-dependent differences in adiponectin fractions, visfatin and vaspin concentrations and gender dimorphism in association between this adipokines and insulin resistance in obesity.

Material and methods. Thirty four extremely obese (BMI ≥ 40 kg/m^2) patients (12 male and 22 female) were enrolled in the study. In all subjects fasting serum glucose, insulin, adiponectin and its fractions, visfatin, vaspin concentration were measured and HOMA-IR was calculated.

Results. Men presented almost twofold higher HOMA-IR than women. Total adiponectin and HMW adiponectin, leptin and visfatin concentrations were higher in women than in men. Significant negative correlations between: total adiponectin and insulin, total adiponectin and HOMA-IR, HMW adiponectin and insulin, HMW adiponectin and HOMA-IR were observed only in female. Significant positive correlation between leptin and HOMA-IR was find only in male.

Conslusions. In extremely obese patients there is a gender dependent dimorphism in adipokines levels and their correlations with insulin resistance. This dimorphism is not fully understood and it might be due to different adipose tissue distribution.

Key words: obesity, insulin resistance, adipokines, gender

Streszczenie

Wprowadzenie. Otyłość łączy się z insulinoopornością, a insulinooporonność jest związana ze zmianami w zakresie stężeń adipokin. Zaobserwowano również różnice w stężeniach niektórych adipokin związane z płcią.

Cel pracy. Celem pracy była ocena wpływu płci na stężenia adiponektyny i jej frakcji, wisfatyny i waspiny oraz na ich korelacje z insulinoopornością u pacjentów z otyłością olbrzymią.

Materiał i metody. Do badania włączono 34 osoby z otyłością olbrzymią (BMI ≥ 40 kg/m^2, 12 mężczyzn i 22 kobiety). U wszystkich oznaczono stężenia w surowicy krwi na czczo: glukozy, insuliny, adiponektyny i jej frakcji, wisfatyny, wapsiny oraz obliczono wskaźnik insulinooporności HOMA-IR.

Wyniki. Wskaźnik HOMA-IR był prawie dwukrotnie wyższy u mężczyzn niż u kobiet. U kobiet stwierdzono wyższe stężenia adiponektyny i jej frakcji HMW, leptyny i wisfatyny. Ujemną korelację między: stężeniem adiponektyny a insuliny, stężeniem adiponektyny a HOMA-IR, frakcją HMW adiponektyny a insuliną, frakcją HMW adiponektyny a HOMA-IR zaobserwowano tylko u kobiet. Dodatnią korelację między stężeniem leptyny a HOMA-IR zaobserwowano tylko u mężczyzn.

Wnioski. U pacjentów z otyłością olbrzymią występuje dymorfizm płciowy dotyczący stężeń adipokin oraz ich korelacji z insulinoopornością. Zjawisko to nie jest w pełni zrozumiałe ale może być związane z różnicami w zakresie dystrybucji tkanki tłuszczowej.

Słowa kluczowe: otyłość, insulinooporność, adipokiny, płeć

INTRODUCTION

After the past decade discoveries, adipose tissue is no longer regarded as a simple reservoir of energy, but rather as a fundamental endocrine gland of the human body. Adipocyte-derived bioactive substances, named adipokines, are able to influence on numerous physiological and pathological processes. Moreover, adipose tissue is also the largest organ in the whole body and possesses metabolic and endocrine functions. In details, by secreting adipokines, it plays a significant role in regulating lipid and carbohydrates homeostasis, and it is thought to be the major site of steroid metabolism. It influences on vascular function. Furthermore, adipokines mediate appetite and energy balance. Disturbed secretion of adipokines resulting from excessive accumulation of adipose tissue contributes to diabetes, hyperlipidaemia and hypertension. Obesity is closely associated with insulin resistance, and, on the other hand, insulin resistance is connected with altered adipokine levels (1).

Adiponectin is secreted mainly by adipocytes of the white adipose tissue. It increases insulin sensitivity, and reveals anti-inflammatory and anti-atherosclerotic action (2). Interestingly, lower adiponectin levels were found in obesity especially in visceral adiposity (3, 4). Adiponectin circulates in serum in different complexes of multimers, from low molecular weight (LMW) trimmers, through medium molecular weight (MMW) hexamers to high molecular weight (HMW) multimers. It is believed that dependently on the form of adiponectin, different physiologic properties of this adipokine are present (5). Recent clinical and experimental studies showed that HMW form of adiponectin possesses strong anti-diabetic and anti-atherogenic properties (6, 7).

Visfatin is expressed in many tissues although initially it was reported to be released by visceral adipose tissue (8). Primary studies showed that this adipokine activates insulin receptor and presents insulin-mimetic effects, lowering blood glucose and improving insulin sensitivity (8). However, the results of further studies on the role of visfatin in glucose and lipid metabolism were contradictory (9, 10). Our current knowledge about the role of visfatin in the pathogenesis of obesity and metabolic syndrome is limited.

Vaspin (visceral adipose tissue-derived serpin; serpinA12) was originally identified as an adipokine, being predominantly secreted from visceral adipose tissue in Otsuka Long-Evans Tokushima fatty (OLETF) rats, an animal model of obesity and type 2 diabetes. Consistently, both higher vaspin serum concentrations and increased vaspin mRNA expression in human adipose tissue were found to be associated with obesity, insulin resistance and type 2 diabetes in humans. However, the precise mechanisms how vaspin secretion may be linked to deterioration of glucose metabolism and insulin sensitivity are not entirely understood yet (11, 12).

Leptin plays a key role in regulating energy intake and energy expenditure including appetite, hunger and metabolism. In physiological conditions, it reduces food intake on the brain level and enhances expenditure of energy, mainly by influencing on thermoregulation as increase in thermogenesis and metabolic rate were found (1). Besides, this adipokine is regarded as one of the most important adipose-derived hormones as pleiotropic effects of leptin have been reported. Previous studies indicated that human obesity is characterized by increased levels of circulating leptin. Despite the elevated leptin levels, which normally would be anticipated to reduce food intake and to decrease body fat, obese patients are insensitive to the action of leptin and continue to maintain increased amount of body fat (2).

Interestingly, there are gender differences seen in concentration of adipokines. Gender is a major determinant of plasma leptin concentration as women had approximately 40% higher leptin levels than men at any level of adiposity (13). Similarly, adiponectin levels are found to be greater in women (14, 15). Nevertheless, there are no available data concerning sex-dependent differences in adiponectin fractions, visfatin and vaspin concentrations. Finally, to our knowledge there is a lack of information about existing gender dimorphism in association between adiponectin fractions, visfatin, vaspin, leptin and insulin resistance in obesity.

MATERIAL AND METHODS

Subjects

Thirty four extremely obese (BMI $\geq$ 40 kg/m^2) patients (12 male and 22 female) were enrolled in the study. All individuals were Caucasians and were recruited among patients of Department of Family, Internal Medicine and Metabolic Bone Diseases, Orlowski Hospital, Centre of Postgraduate Medical Education in Warsaw, Poland. All patients were admitted to the hospital for internal examination prior to the bariatric surgery. Exclusion criteria from the study were as follows: acute endocrine dysfunction as well as chronic kidney and liver disease. None of examined subjects had a history of excessive alcohol consumption.

The study protocol was accepted by the Bioethical Committee of the Centre of Postgraduate Medical Education. Informed consent was obtained from all study participants.

Blood analyses

Blood samples were obtained at 8.00 am after overnight fasting and were immediately centrifuged at 4°C and obtained plasma were stored at – 30°C for further analyses. Blood glucose concentration was measured by certified hospital laboratory applying standard clinical biochemistry methods. Insulin concentration was measured using IRMA methods (Immunotech, Czech Republic). Adiponectin and its fractions as well as c-terminal fragment of visfatin were estimated by EIA methods (ALPCO and Phoenix Pharmaceutical Inc., respectively). Plasma vaspin concentration was measured using ELISA kit (AdipoGen). Intra- and inter

assay coefficient was below 10% for all investigated parameters. All adipokines and insulin levels were investigated in the Department of Neuroendocrinology, Centre of Postgraduate Medical Education in Warsaw.

In all subjects HOMA-IR was calculated according to the following formula: HOMA-IR = fasting glucose (mmol/dl) x fasting plasma insulin (μIU/ml)/22.5.

Statistical analysis

Statistica 6.1 was used for statistical analysis. Data are shown as means ± standard deviation (SD). The presence of normal distribution was analysed using Kolmogorow-Smirnoff test and differences in parametric variables were calculated with t-Student test. Non-parametric variables were analysed using Mann-Whitney U test. The Spearman test was applied to calculate correlations coefficients between estimated adipokines and biochemical parameters Significance level was defined as $p < 0.05$.

RESULTS

Data concerning clinical and biochemical parameters are presented in table 1. We found significant differences between extremely obese men and women in age, glucose levels and HOMA-IR. Men presented almost twofold higher HOMA-IR than women.

Table 1. Clinical and biochemical parameters of investigated groups.

Parameter	Male (n = 12)	Female (n = 22)	p
Age (y)	47.7 ± 7.1	39.6 ± 11.6	< 0.05
BMI (kg/m^2)	45.6 ± 8.2	42.3 ± 5.5	ns
Glucose (mg/dl)	124.3 ± 39.5	96.8 ± 13.4	< 0.05
Insulin (μIU/ml)	28.8 ± 18.3	17.6 ± 9.4	ns
HOMA-IR	8.4 ± 4.8	4.3 ± 2.5	< 0.05

ns – non significant

Total adiponectin and HMW adiponectin were significantly higher in women than in men. Plasma leptin concentration as well as visfatin were also eleveted in extremely obese women in comparison with morbidly obese men (tab. 2).

Table 2. Plasma adipokines concentration in all investigated groups.

Parameter	Male (n = 12)	Female (n = 22)	p
Adiponectin total (μg/ml)	2.754 ± 0.685	3.587 ± 1.149	< 0.05
Adiponectin HMW (μg/ml)	1.024 ± 0.448	1.605 ± 0.770	< 0.05
Adiponectin LMW (μg/ml)	0.997 ± 0.217	1.119 ± 0.355	ns
Adiponectin MMW (μg/ml)	0.733 ± 0.137	0.861 ± 0.284	ns
Leptin (ng/ml)	28.957 ± 11.577	40.975 ± 0.355	< 0.05
Visfatin (ng/ml)	8.370 ± 0.987	11.671 ± 6.439	< 0.05
Vaspin (ng/ml)	0.178 ± 0.059	0.210 ± 0.119	ns

ns – non significant

Statistical analysis showed significant correlations between analysed adipokines and clinical and biochemical parameters. Correlations are presented in table 3 and 4.

Table 3. Correlations between adipokines and clinical and biochemical parameters in women.

Parameter A	Parameter B	R	p
Total adiponectin	Glucose	-0.43	< 0.05
Total adiponectin	Insulin	-0.55	< 0.01
Total adiponectin	HOMA-IR	-0.61	< 0.01
Total adiponectin	Visfatin	-0.43	< 0.05
HMW adiponectin	Insulin	-0.58	< 0.01
HMW adiponectin	HOMA-IR	-0.63	< 0.01

Table 4. Correlations between adipokines and clinical and biochemical parameters in men.

Parameter A	Parameter B	R	p
Total adiponectin	BMI	-0.57	< 0.05
Total adiponectin	Leptin	-0.62	< 0.05
Total adiponectin	Vaspin	-0.57	< 0.05
Leptin	BMI	0.89	< 0.001
Leptin	HOMA-IR	0.58	< 0.05

DISCUSSION

Obesity is associated with increased adipose deposits and disturbances of adipokines secretion. Regulatory factors of adipose tissue-derived hormones still remain incompletely understood, but they may include some endocrine components, including sex-steroid hormones. Our present results indicated that in extremely obese patients there is a gender dependent dimorphism in adipokines levels as well as there is also a presence of correlations between adipokines and insulin resistance. Our data indicated that with the same body mass index (BMI) parameters, men and women significantly differed in degree of insulin resistance, being higher in men, and levels of total adiponectin and its HMW form, leptin and visfatin as all those adipokines levels were found to be higher in women.

It has been reported previously that there are body composition differences between the sexes even if BMI is identical. Men tend to have central fat distribution named android or “apple” shaped, whereas women tend to have peripheral adiposity with with fat deposited in the limbs and hips, named gynoid, or “pear” shaped obesity (16). This gender differences in adipose tissue distribution are thought to be due to the effects of the sex steroids, although the exact mechanisms by which hormones influence on adiposity are not fully understood (17). Data indicate that visceral fat and subcutaneous fat differ in their histology as well as in metabolic activity. The fact that there is a well-known association between visceral obesity and metabolic syndrome may explain gender differences seen in some of adipokines levels, and their correlations with insulin resistance that were observed in our study.

Study by Kwon et al. indicated that in healthy women visceral, but not subcutaneous abdominal fat, was inversely associated with plasma adiponectin levels (18). Similarly, in Asian Indians visceral but not subcutaneous fat were associated with total and HMW adiponectin levels (19). In the other study visceral fat levels were associated with decreased levels of adiponectin and enhanced levels of visfatin (20). Interestingly, in African Americans, abdominal visceral adipose tissue had an inverse association with serum adiponectin concentrations only among women (21). Hypoadiponectinemia is also related with presence of metabolic syndrome. Eglit et al. demonstrated that the association of lower level of HMW adiponectin and metabolic syndrome depends of gender differences and is stronger in women than in men (22).

Among other factors of gender dependent dimorphism in adipokines levels that should be considered coare sex hormones. The interrelationship between sex hormones and adipokine levels has been observed in different studies.

Firstly, adiponectin levels were positively correlated with SHBG and negatively correlated with the free androgen index independently of BMI and fat mass (23). In another study adiponectin level was associated with levels of free and bioavailable testosterone and DHEA-S in postmenopause (24). In spite of adiponectin level is higher in woman, in few studies an inverse relationship between estradiol and adiponectin was observed (25, 26).

Secondly, visfatin over expression was observed in pregnant women (27). Moreover, experimental study by Zhou and co-workers showed that in 3T3-L1 cells the estriol, estradiol and progesterone exert a synergistic effect on visfatin gene expression (28). Additionally, in lean women with PCOS, visfatin was associated with serum testosterone and free androgen index (29).

Thirdly, in males, negative correlations between testosterone and leptin were clearly shown in different cross-sectional studies (30). In addition, testosterone therapy reduces serum leptin concentrations in subjects with low testosterone levels (30). Conversely, no significant association of leptin, HMW adiponectin with gonadal steroids in both sexes was found in one study (31).

Furthermore, it has been demonstrated that vaspin serum concentrations were significantly higher in women in comparison with men (32, 33). In our study vaspin concentration was higher in woman than in man but this difference was non statistically significant.

Our study have some limitations. Among them are small number of recruited subjects, lack of estimation of sex-hormone levels. We plan to enlarge the group under study and to perform hormonal analyses.

CONCLUSIONS

In extremely obese patients there is a gender dependent dimorphism in adipokines levels and their correlations with insulin resistance. This dimorphism is not fully understood and it might be due to different adipose tissue distribution.

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