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An evaluation of visfatin levels in obese subjects

Ocena stężenia wisfatyny u osób z otyłością

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Abstract

Introduction: Visfatin is a protein secreted by adipose tissue, which shows insulin mimetic properties. The role of visfatin in the development of obesity, diabetes mellitus, and metabolic syndrome continues to raise controversy. The aim of the study was to evaluate visfatin levels and to attempt to establish the relationship between visfatin and selected anthropometric and biochemical parameters in obese individuals.
Material and methods: The study included 68 obese subjects (15 men and 53 women) aged 37.8 ± 13.2 years with body mass index (BMI) values of 39.4 ± 6.4 kg/m^2 without a previous diagnosis of abnormal glucose metabolism. The control group comprised 30 healthy non-obese volunteers (6 men and 24 women) with normal glucose metabolism, aged 38.2 ± 14.9 years with BMI values of 22.8 ± 3.0 kg/m^2.
Results: We found significantly higher visfatin levels in the obese subjects compared to the control group (median visfatin level of 39.6 *v.* 17.3 ng/ml, p = 0.0006). In the obese group there was a statistically significant negative correlation between visfatin levels and age (r = –0.26, p = 0.034), waist-to-hip ratio (WHR) (r = –0.28, p = 0.031) and glycated haemoglobin (HbA_{1c}) (r = –0.36, p = 0.0037). No statistically significant correlations were found between visfatin levels and the remaining parameters under study. In the control group, visfatin levels did not show any significant correlation with any of the parameters under study.
Conclusions: We found elevated levels of visfatin in obese subjects, which did not correlate with the majority of anthropometric parameters with the exception of WHR (negative correlation). This correlation may suggest that elevated visfatin levels are associated with the distribution of adipose tissue characteristic of gynoid rather than visceral obesity. In the group of obese subjects, visfatin levels decreased with age and glycated haemoglobin levels. **(Pol J Endocrinol 2010; 61 (2): 169–173)**

Key words: *visfatin, obesity, adipocytokines.*

Streszczenie

Wstęp: Wisfatyna jest białkiem wydzielanym przez tkankę tłuszczową , które wykazuje działanie insulinomimetyczne. Rola wisfatyny w rozwoju otyłości, cukrzycy i zespołu metabolicznego jest nadal kontrowersyjna. Celem pracy była ocena stężenia wisfatyny i próba znalezienia związku między wisfatyną a wybranymi parametrami antropometrycznymi i biochemicznymi u osób otyłych.
Materiał i metody: W badaniu wzięło udział 68 osób z otyłością (53 kobiety i 15 mężczyzn) w wieku 37,8 ± 13,2 lat, o wskaźniku masy ciała (BMI, *body mass index*) 39,4 ± 6,4 kg/m^2 bez rozpoznawanych dotychczas zaburzeń gospodarki węglowodanowej. Grupę kontrolną stanowiło 30 zdrowych ochotników (24 kobiety i 6 mężczyzn), bez otyłości i zaburzeń gospodarki węglowodanowej, w wieku 38,2 ± 14,9 lat, o BMI 22,8 ± 3,0 kg/m^2.
Wyniki: U osób otyłych stwierdzono istotnie wyższe stężenie wisfatyny w porównaniu z osobami z grupy kontrolnej (średnie stężenie wisfatyny wyrażone jako mediana odpowiednio 39,6 *v.* 17,3 ng/ml; p = 0,0006). W grupie osób otyłych stwierdzono istotną statystycznie ujemną korelację między stężeniem wisfatyny a wiekiem (r = –0,26; p = 0,034), stosunkiem obwodu talii do obwodu bioder (WHR, *waist-to-hip ratio*) (r = –0,28; p = 0,031) i odsetkiem hemoglobiny glikowanej (HbA_{1c}) (r = –0,36; p = 0,0037). Nie stwierdzono istotnych statystycznie korelacji z pozostałymi ocenianymi parametrami. W grupie kontrolnej stężenie wisfatyny nie korelowało istotnie z żadnym z ocenianych parametrów.
Wnioski: U osób otyłych stwierdzono podwyższone stężenie wisfatyny, które nie korelowało z większością parametrów antropometrycznych, poza WHR (korelacja ujemna). Stwierdzona korelacja może sugerować, że podwyższone stężenia wisfatyny wiążą się raczej z rozkładem tkanki tłuszczowej typowym dla otyłości typu gynoidalnego, a nie dla otyłości trzewnej. W badanej przez autorów pracy grupie osób otyłych stężenie wisfatyny malało z wiekiem i wraz ze wzrostem stężenia hemoglobiny glikowanej.
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Słowa kluczowe: *wisfatyna, otyłość, adipocytokiny*

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Introduction

Visfatin is a 52-kDa protein originally identified as pre-B cell colony-enhancing factor (PBEF) and showing nicotinamide phosphoribosyl transferase activity [1, 2]. The protein is synthesised by bone marrow cells, activated lymphocytes, liver cells, and skeletal muscle cells [1]. Fukuhara et al. discovered, however, that the largest source of visfatin is visceral adipose tissue [3]. In addition to being secreted by adipocytes, visfatin is also secreted by macrophages infiltrating adipose tissue [4]. Plasma levels of this adipocytokine have been shown to positively correlate with the amount of visceral adipose tissue determined by computed tomography [3].

Visfatin shows an affinity for the insulin receptor. The protein activates the insulin receptor by binding to it at a different site from insulin. The insulin-mimetic actions of visfatin involve decreasing glucose uptake by insulin-sensitive cells (adipocytes and myocytes) and inhibiting glucose release by liver cells. In addition, visfatin promotes the storage of triglycerides in preadipocytes and stimulates adipogenesis [3]. The discovery of visfatin, which could be the link between visceral obesity and abnormal glucose metabolism, has generated considerable interest in this protein.

The results of visfatin studies conducted so far in obese individuals are, however, controversial and fail to unequivocally explain the relationship between this adipocytokine and obesity or glucose metabolism abnormalities.

The aim of this study was to evaluate visfatin levels in obese individuals and to attempt to establish the relationship between visfatin and selected anthropometric and biochemical parameters.

Material and methods

The study included 68 obese subjects (15 men and 53 women) without a previous diagnosis of abnormal glucose metabolism in whom, based on their medical history, physical examination, and the assessment of hormone levels (thyroid-stimulating hormone (TSH), cortisol, prolactin), the most common secondary causes of obesity had been ruled out.

The control group comprised 30 healthy individuals (6 men and 24 women) with body mass index (BMI) values within normal limits and with normal glucose values at baseline and at 2 hours in the oral glucose tolerance test (OGTT) using 75 g of glucose.

In each of the subjects in both groups, we measured body mass, height, waist circumference, and hip circumference, calculated BMI and waist-to-hip ratio (WHR), and performed an OGTT. Table I summarises the characteristics of both groups: the study group and the control group.

In the study group we additionally measured total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, uric acid, C-peptide, glycated haemoglobin (HbA_{1c}), and creatinine. Table II summarises the mean values of these parameters. Visfatin was measured in both groups by enzyme immunoassay (Visfatin C-terminal (Human), Phoenix Pharmaceuticals).

All the subjects, having read the patient information, provided informed consent to participate in the study. The study was approved by the Bioethics Committee of the Medical College at Nicolaus Copernicus University in Toruń, Poland.

We performed statistical analysis of the results, calculating arithmetic means, standard deviations, medi-

Table I. *Characteristics of the study groups*

Tabela I. *Charakterystyka badanych grup*

Parameter (unit)	Study group			Control group			p value
	Mean ± SD	Min	Max	Mean ± SD	Min	Max	
Age (years)	37.8 ± 13.2	17	69	38.2 ± 14.9	20	67	0.8817
Body mass [kg]	110 ± 19.9	75	182.7	67.2 ± 12.6	49	95	0.0000
Height [cm]	167.1 ± 8.6	151	192	171 ± 9.8	155	192	0.0497
BMI [kg/m^2]	39.4 ± 6.4	30.7	63.2	22.8 ± 3.0	17.9	24.3	0.0000
Waist circumference [cm]	115.2 ± 14.3	91	170	80.3 ± 12.9	62	110	0.0000
Hip circumference [cm]	126 ± 12.9	103	166	97.7 ± 9.8	77	116	0.0000
WHR	0.918 ± 0.106	0.710	1.21	0.819 ± 22.1	0.65	0.97	0.000027

BMI — body mass index; max — maximum value; min — minimum value; SD — standard deviation; WHR — waist-to-hip ratio

Table II. *The mean values of the parameters evaluated in the study group*

Tabela II. *Średnie wartości ocenianych parametrów w badanej grupie*

Parameter (unit)	Mean ± SD	Minimum	Maximum
Total cholesterol [mg/dl]	189.3 ± 29.4	136	280
LDL-cholesterol [mg/dl]	114 ± 26.4	59	206
HDL-cholesterol [mg/dl]	47.2 ± 8.3	30	69
Triglycerides [mg/dl]	140.3 ± 67.2	41	323
C-peptide [ng/dl]	3.01 ± 1.99	1.01	12.8
HbA_{1c} (%)	5.79 ± 0.80	4.6	8.6
Uric acid [mg/dl]	5.2 ± 1.61	2.5	10.0
Creatinine [mg/dl]	0.8 ± 1.12	0.55	1.08

ans, minima, and maxima. We used the Shapiro-Wilk test to assess the normality of the distribution of the study variables. In the case of samples characterised by a near-normal distribution, the means were compared with the use of Student's t-test for independent variables. Where a distribution significantly differed from the normal distribution, the significance of between-group comparisons was verified using the non-parametric Mann-Whitney U test. The relationship between two variables was assessed with Pearson's linear correlation coefficient. A significance level of 0.05 was adopted. All the calculations were performed using the Statistica suite.

Results

We found significantly elevated visfatin levels in the group of obese individuals versus the control group (median visfatin level of 39.6 *v.* 17.3 ng/ml, p = 0.0006). The mean values of the remaining parameters assessed in the control group are given in Table II.

We found a statistically significant negative correlation between visfatin levels and age, HbA_{1c} and WHR in the group of obese individuals with no statistically significant correlations between visfatin levels and the other parameters assessed. In the control group there were no correlations between visfatin levels and any of the parameters assessed (Table III).

Based on the OGTT, we diagnosed diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance in 31 subjects with no glucose metabolism abnormalities in the remaining 37 subjects. Visfatin levels in both subgroups of obese subjects, those with and those without abnormal glucose metabolism, did not differ with median visfatin levels of 40.86 and 57.70 ng/ml, respectively (p = 0.1939).

Table III. *Correlations between visfatin and the parameters evaluated in the study group and the control group*

Tabela III. *Korelacje między stężeniem wisfatyny a ocenianymi parametrami w grupie badanej i kontrolnej*

Parameter (unit)	Study group		Control group	
	r	p value	r	p value
Age (years)	–0.26	0.034	–0.35	0.051
Body mass [kg]	0.07	0.594	–0.20	0.25
Height [cm]	0.15	0.217	–0.05	0.780
BMI [kg/m^2]	–0.03	0.822	–0.26	0.161
Waist circumference [cm]	0.06	0.632	–0.22	0.246
Hip circumference [cm]	0.24	0.061	–0.12	0.525
WHR	–0.28	0.031	–0.22	0.247
Fasting glucose [mg/dl]	–0.23	0.060	–0.1194	0.530
Total cholesterol [mg/dl]	0.01	0.944	–	–
LDL-cholesterol [mg/dl]	–0.03	0.831	–	–
HDL-cholesterol [mg/dl]	–0.02	0.867	–	–
Triglycerides [mg/dl]	0.05	0.687	–	–
C-peptide [ng/dl]	0.01	0.962	–	–
HbA_{1c} (%)	–0.36	0.0037	–	–
Uric acid [mg/dl]	–0.03	0.802	–	–
Creatinine [mg/dl]	–0.13	0.337	–	–

Discussion

The pioneering studies by Fukuhara showed that plasma visfatin levels strongly correlated with the quantity of visceral adipose tissue ($r = 0.68$, $p < 0.001$) assessed by computed tomography with a weaker correlation with the quantity of subcutaneous adipose tissue ($r = 0.22$, $p < 0.05$) [3]. Plasma visfatin levels and the expression of visfatin mRNA in visceral and subcutaneous adipose tissue in lean individuals and in individuals with various degrees of obesity were investigated by Berndt et al., who demonstrated a positive correlation between visfatin levels and the expression of visfatin mRNA in the visceral adipose tissue, BMI and the percentage body fat. In contrast to Fukuhara, Berndt et al. did not demonstrate any relationship between visfatin levels and the amount of visceral adipose tissue the mass of which was also assessed by computed tomography. However, plasma visfatin levels did not correlate with the expression of visfatin mRNA in the subcutaneous adipose tissue [5]. Pagano et al., on the other hand, showed that visfatin levels and visfatin mRNA expression were lower in subcutaneous and higher in visceral adipose tissue of obese subjects versus lean individuals. In the obese individuals, plasma visfatin levels and the expression of visfatin mRNA showed a negative correlation with BMI, with the expression of mRNA in the visceral adipose tissue showing a positive correlation with BMI. Based on the positive correlation between visfatin levels and the expression of visfatin mRNA in the subcutaneous adipose tissue, the authors concluded that it is the subcutaneous tissue that determines plasma visfatin levels. They also drew attention to the fact that the subcutaneous adipose tissue is responsible for only 30% of circulating visfatin. Reduced secretion of visfatin by the remaining sources, such as the skeletal muscles, the liver, and immune cells in obese individuals, may be the cause of the reduced plasma levels of this adipocytokine [6].

We found significantly higher visfatin levels in the obese subjects compared to the lean subjects, which did not, however, correlate with BMI or waist circumference. We did notice a significant negative correlation between visfatin levels and age, HbA_{1c} and WHR.

Haider et al. also confirmed significantly higher plasma visfatin levels in patients with morbid obesity compared to lean individuals [7]. Zahorska-Markiewicz et al. also reported higher visfatin levels in obese versus lean women [8]. Garcia-Fuentes et al. found that patients with morbid obesity are characterised by significantly higher visfatin levels compared to lean individuals but only when obesity is associated with glucose metabolism abnormalities [9]. On the other hand, in the above-referenced paper by Pagano et al. [6] and in a study by Jian et al. [10], obese subjects had significantly lower visfatin levels compared to subjects with normal body weight. Other researchers have not reported differences in visfatin levels between obese and lean subjects [11].

Similarly, very disparate results have been obtained regarding correlations between visfatin levels and anthropometric parameters in the obese. Some studies [5] have demonstrated positive, while others [6, 10] negative correlation between visfatin levels and BMI. The lack of correlation between visfatin levels and BMI or waist circumference in our study is consistent with findings obtained by other authors [12–14]. Visfatin levels in the obese subjects participating in our study showed a negative correlation with WHR. We also observed a positive correlation, almost statistically significant, between visfatin levels and hip circumference, which means that the more the body silhouette corresponds to the gynoid type of obesity with a predominance of hip circumference over waist circumference, the higher the visfatin levels. Our results show that elevated visfatin levels are associated with the adipose tissue distribution pattern typical of gynoid rather than visceral obesity. This might suggest that visfatin levels are determined by the subcutaneous adipose tissue located in the thighs and buttocks rather than by the visceral adipose tissue. It should, however, be taken into consideration that most of the subjects in our study were women (72%), in whom the most prevalent type of obesity is the gynoid type, which is associated with fat accumulation in the buttocks and thighs. The study by Jian et al., which analysed a subgroup of obese men, found a positive correlation between visfatin levels and WHR, which, according to the authors, might suggest the involvement of visfatin in the pathogenesis of visceral obesity in men [10].

In the group of obese subjects we found a significant negative correlation between visfatin levels and age. This correlation was also reported by Luis et al., who demonstrated that visfatin levels decreased by an average of 4.1 ng/ml with each year of life [14].

In our study, visfatin levels did not differ significantly whether or not obesity was accompanied by abnormal glucose metabolism, which is consistent with the findings obtained by other authors who evaluated visfatin levels in obese individuals recently diagnosed with glucose metabolism abnormalities [10, 11]. On the other hand, in patients with longer-standing type 2 diabetes mellitus, visfatin levels are higher than in non-diabetics [12, 15]. In a study by Lopez-Bermejo, visfatin levels increased with progressive pancreatic beta-cell dysfunction and with increasing HbA_{1c}, which reflects long-term glucose control [12]. According to the authors, the increase in the level of visfatin, which shows an insulin-mimetic effects, is a compensatory mechanism that

develops in endogenous insulin deficit in patients with longer-standing type 2 diabetes mellitus.

We enrolled obese patients without a previous diagnosis of abnormal glucose metabolism. In some of them, based on an OGTT, we diagnosed prediabetes or type 2 diabetes mellitus. In the entire group of obese subjects we found a negative correlation between visfatin levels and HbA_{1c}. This means that lower visfatin levels accompanied higher glucose values in the period of three months preceding the measurement of HbA_{1c}. This is a correlation that is opposite to that found in the above-referenced study conducted in patients previously diagnosed with type 2 diabetes mellitus, with endogenous insulin deficiency (more than a third of the patients were being managed with insulin) [12]. Obese patients with preserved insulin secretion participated in our study (the mean C-peptide level in the entire group was 3.01 ± 1.99 ng/dl), and this is the most likely explanation for the negative correlation between visfatin levels and HbA_{1c} that we observed, which was in opposition to the findings of Lopez-Bemejro et al. [12]. This correlation was also demonstrated by Li et al. in a group of individuals who had recently been diagnosed with glucose metabolism abnormalities [16]. The potential mechanism explaining the negative correlation between visfatin and glycated haemoglobin observed by us remains unclear. In the study by Haider, conducted in healthy volunteers, visfatin levels increased following an intravenous infusion of glucose, while an intravenous infusion of insulin that was being administered in parallel to the glucose infusion suppressed the secretion of visfatin [17]. It may, therefore, be hypothesised that in endogenous insulin deficit, hyperglycaemia raises visfatin levels, and where the function of pancreatic beta cells is preserved, visfatin secretion may be suppressed by insulin.

Conclusions

We found elevated levels of visfatin in obese subjects which did not correlate with the majority of anthropometric parameters we evaluated, with the exception of WHR (negative correlation). This correlation may suggest that elevated visfatin levels are associated with the distribution of adipose tissue characteristic of gynoid rather than visceral obesity. In the group of obese subjects, visfatin levels decreased with age and glycated haemoglobin levels.

References

1. Samal B, Sun Y, Stearns G et al. Cloning and characterization of cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol 1994; 14: 1431–1437.
2. Rongvaux A, Shea RJ, Mulks MH et al. Pre-B-cell colony-enhancing factor, whose expression is upregulated in activated lymphocytes, is nicotinamide phosphoribosylotransferase, a cytosolic enzyme involved in NAD biosynthesis. Eur J Immunol 2002; 32: 3225–34.
3. Fukuhara A, Matsuda M, Nishizawa M et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 2005; 21: 426–430.
4. Curat CA, Wegner V, Sengenes C et al. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia 2006; 49: 744–747.
5. Berndt J, Klöting N, Kralisch S et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005; 54: 2911–2916.
6. Pagano C, Pilon C, Olivieri M et al. Reduced plasma visfatin/pre-B cell colony enhancing factor in obesity is not related to insulin resistance in humans. J Clin Endocrinol Metab 2006; 91: 3165–3170.
7. Haider DG, Schindler K, Schaller G et al. Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. J Clin Endocrinol Metab 2006; 91: 1578–1581.
8. Zahorska-Markiewicz B, Olszanecka-Glinianowicz M, Janowska J et al. Serum concentration of visfatin in obese women. Metabolism 2007; 56: 1131–1134.
9. Garcia-Fuentes E, Garcia-Almeida JM, Garcia-Arnes J et al. Plasma visfatin concentrations in severely obese subjects are increased after intestinal bypass. Obesity 2007; 15: 2391–2395.
10. Jian WX, Luo TH, Gu YY. The visfatin gene is associated with glucose and lipid metabolism in a Chinese population. Diabet Med 2006; 23: 967––973.
11. Hofsr D, Ueland T, Hager H et al. Inflammatory mediators in morbidly obese subjects; associations with glucose abnormalities and changes after oral glucose. Eur J Endocrinol 2009; 161: 451–458.
12. Lopez-Bermejo A, Chci-Julia B, Fernandez-Balsells M et al. Serum visfatin increases with progressive β-cell deterioration. Diabetes 2006; 55: 2871––2875.
13. Hammarstedt A, Pihlajamaki J, Sopasakis VR et al. Visfatin is an adipokine, but it is not regulated by thiazolidinediones. J Clin Endocrinol Metab 2006; 91: 1181–1184.
14. de Luis DA, Sagrado MG, Conde R et al. Effect of a hypocaloric diet on serum visfatin in obese non-diabetic patients. Nutrition 2008; 24: 517–521
15. Chen MP, Chung FM, Chang DM et al. Elevated plasma level of visfatin/ /pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2006; 91: 295–299.
16. Li L, Yang G, Li Q et al. Changes and relations of circulating visfatin, apelin and resistin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Diabetes 2006; 114: 544–548.
17. Haider DG, Schaller G, Kapiotis S et al. The release of the adipocytokine visfatin is regulated by glucose and insulin. Diabetologia 2006; 49: 1909––1914.