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Visfatin levels do not change after the oral glucose tolerance test and after a dexamethasone-induced increase in insulin resistance in humans

Stężenia wisfatyny u ludzi nie ulegają zmianie w doustnym teście tolerancji glukozy oraz po podaniu deksametazonu pomimo zwiększenia insulinooporności

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Abstract

Introduction, material and methods: Visfatin is a cytokine, mainly expressed in visceral fat, that exerts insulin-mimicking effects in rodents through activation of an insulin receptor, although the binding-site is distinct from that of insulin. However, the mechanisms that regulate visfatin synthesis are still not fully understood. In particular, it is not clear whether short-term glucose-induced hyperglycaemia and hyperinsulinaemia as well as a glucocorticoid-induced increase in insulin resistance are reflected in appreciable alterations in serum visfatin levels in humans. In order to investigate this we measured serum visfatin, glucose and insulin concentrations during a 75.0 gram oral glucose tolerance test (OGTT) [Study 1], as well as before and after oral administration of dexamethasone [Study 2].

Study 1 included 17 subjects (2 males), aged 35.7 ± 15.6 (mean ± SD) years of BMI 35.2 ± 9.3 kg/m^2. Blood samples were taken before (0 minutes) and at 60 and 120 minutes after glucose administration. Study 2 included 20 subjects (4 males, 5 subjects with type 2 diabetes), aged 42.1 ± 17.2 years of BMI 36.7 ± 8.38 kg/m^2 who underwent screening for Cushing's disease/syndrome. Dexamethasone was administered at a dose of 0.5 mg every 6 hours for 48 hours. Fasting serum concentrations of visfatin, glucose and insulin were assessed before (D0) and after 48 hours of dexamethasone administration (D2). Insulin resistance was assessed according to the HOMA method in non-diabetic individuals (n = 15).

Results: In Study 1 two subjects were found to have impaired glucose tolerance and one subject was found to have diabetes mellitus. Glucose administration resulted in a highly significant increase in insulin (from 11.4 ± 7.2 μU/mL at 0 min to 98.9 ± 68.6 μU/mL at 60 min and 72.6 ± 45.1 μU/mL at 120 minute of OGTT, $p < 0.001$ for 60 and 120 minutes in comparison to baseline). However, there was no change in serum visfatin concentrations (84.6 ± 11.6 ng/mL at 0 minutes, 82.6 ± ± 12.7 ng/mL at 60 minutes and 81.1 ± 14.5 ng/mL at 120 minutes of OGTT, p = ns).

All subjects in Study 2 achieved suppression of cortisol concentrations below 50 nmo/l. Dexamethasone administration resulted in an increase in fasting insulin (from 11.5 ± 6.9 to 16.9 ± 7.6 μU/mL; $p = 0.011$) and an increase in HOMA (from 2.73 ± 1.74 to 4.02 ± 2.27; $p = 0.015$), albeit without a significant change in serum visfatin concentrations (61.1 ± 19.8 *vs.* 68.3 ± ± 19.4 ng/mL, p = ns). In neither Study 1 nor Study 2 was there any significant correlation between serum visfatin and age, BMI or HOMA.

Conclusions: There is a striking difference between the marked rise in insulin concentrations and the lack of change in visfatin concentrations during the oral glucose tolerance test. This implies that it is highly unlikely that visfatin is involved in the short-term regulation of glucose homeostasis in human subjects. Dexamethasone administration (4 mg/48 hours) induces an increase in insulin resistance, although without significant change in serum visfatin concentrations. Therefore

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in contrast to the *in vitro* data, short term glucocorticoid administration does not result in appreciable changes in serum levels of this adipocytokine. Furthermore, the results of our study do not support the notion that glucocorticoid-induced insulin resistance is likely to be related to changes in serum concentrations of visfatin.

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Key words: *visfatin, glucose tolerance, dexamethasone, insulin resistance*

Streszczenie

Wstęp, materiał i metody: Wisfatyna jest cytokiną, której ekspresja zachodzi głównie w tkance tłuszczowej trzewnej, i która u gryzoni działa podobnie jak insulina. Wisfatyna aktywuje receptor insulinowy, jednak wiążąc się z receptorem w innym miejscu niż insulina. Czynniki regulujące syntezę wisfatyny nadal nie są w pełni poznane. W szczególności nie wiadomo czy krótkotrwała hiperglikemia i hiperinsulinemia po podaniu glukozy, jak również zwiększona insulinooporność wyidukowana glukokortykoidami mogą w istotny sposób zmienić stężenie wisfatyny w surowicy u ludzi. W związku z tym autorzy niniejszego artykułu ocenili stężenie wisfatyny, glukozy i insuliny w surowicy w teście doustnego obciążenia 75,0 g glukozy (OGTT, *oral glucose tolerance test*) — Badanie 1., jak również przed i po doustnym podaniu deksametazonu — Badanie 2.

Badanie 1. obejmowało 17 osób (2 mężczyzn) w wieku 35,7 ± 15,6 (średnia ± SD) lat, u których wskaźnik masy ciała (BMI, *body mass index*) wynosił 35,2 ± 9,3 kg/m^2. Krew pobierano przed (0 min) oraz w 60. i 120. minucie po podaniu glukozy. Badaniem 2. objęto 20 osób (4 mężczyzn, 5 chorych na cukrzycę typu 2) poddanych badaniu przesiewowemu pod kątem choroby/zespołu Cushinga w wieku 42,1 ± 17,2 lat, u których BMI wynosił 36,7 ± 8,38 kg/m^2. Deksametazon podawano co 6 godzin w dawce 0,5 mg przez 48 godzin. Stężenia wisfatyny, glukozy, insuliny w surowicy oznaczono na czczo przed (D0) i po 48 godzinach podawania deksametazonu (D2). U osób niechorujących na cukrzycę (n = 15) oceniono insulinooporność metodą HOMA.

Wyniki: W Badaniu 1. u dwóch osób stwierdzono nieprawidłową tolerancję glukozy, a u jednej rozpoznano cukrzycę. Uzyskano wysoce istotny wzrost stężenia insuliny (z 11,4 ± 7,2 μU/ml w 0 min, do 98,9 ± 68,6 μU/ml w 60. min i 72,6 ± ± 45,1 μU/ml w 120. min OGTT, p < 0,001 zarówno dla 60., jak i 120. minuty testu w porównaniu z wartościami wyjściowymi). Nie stwierdzono jednak istotnych zmian w stężeniu wisfatyny (84,6 ± 11,6 ng/ml w 0 min, 82,6 ± 12,7 ng/ml w 60. min i 81,1 ± 14,5 ng/ml w 120. min OGTT, p = ns).

W Badaniu 2. u wszystkich osób uzyskano supresję stężenia kortyzolu do wartości poniżej 50 nmo/l. Skutkiem podania deksametazonu był wzrost stężenia insuliny na czczo (z 11,5 ± 6,9 do 16,9 ± 7,6 μU/ml; p = 0,011) oraz wzrost współczynnika HOMA (z 2,73 ± 1,74 do 4,02 ± 2,27; p = 0,015). Nie zaobserwowano jednak istotnych zmian stężenia wisfatyny w surowicy (61,1 ± 19,8 *vs.* 68,3 ± 19,4 ng/ml, p = ns). Zarówno w Badaniu 1., jak i 2. nie odnotowano istotnych korelacji pomiędzy stężeniem wisfatyny a wiekiem, BMI czy wartością współczynnika HOMA.

Wnioski: Zaobserwowano uderzające różnice pomiędzy znacznym wzrostem stężenia insuliny a brakiem zmian stężenia wisfatyny w czasie testu doustnego obciążenia glukozą. Zatem jest mało prawdopodobne, aby wisfatyna była zaangażowana w bezpośrednią (to jest poposiłkową) regulację homeostazy glukozy u ludzi. Podanie deksametazonu (4 mg/48 h) powoduje zwiększenie insulinooporności, jednak bez istotnych zmian stężenia wisfatyny. Wynika z tego, że odmiennie niż w badaniach *in vitro*, krótkotrwałe podanie glukokortykoidów nie wywołuje u ludzi istotnych zmian stężenia tej adipocytokiny w surowicy. Jest również mało prawdopodobne, że insulinooporność wywołana glukokortykoidami wiąże się ze zmianami osoczowych stężeń wisfatyny.

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Słowa kluczowe: *wisfatyna, tolerancja glukozy, deksametazon, insulinooporność*

Introduction

Visfatin, previously known as pre-B cell colony-enhancing factor (PBEF), is a recently discovered 52-kilodalton protein, produced and secreted abundantly by visceral adipose tissue, that exerts insulin-mimetic effects. This adipocytokine directly activates the insulin receptor in various insulin-sensitive cell types, although it does so in a manner distinct from insulin [1]. In mice visfatin treatment acutely lowered plasma glucose levels [1]. As visfatin acts through the insulin receptor, albeit through a binding site different from that of insulin, the question is raised as to whether visfatin might, in a manner similar to that of insulin, be involved in short-term regulation of glycaemia (post-prandial or after glucose load). If this were the case, then the defects in post-prandial visfatin secretion might also contribute to the development of post-prandial hyperglycaemia and diabetes. In order to investigate this we measured serum visfatin, glucose and insulin concentrations during a 75.0 gram oral glucose tolerance test (OGTT) [Study 1].

Furthermore, a number of factors have been shown to alter glucose tolerance, although the underlying cellular mechanisms are not always understood. It is possible that some of these mechanisms are indirect and

involve alterations to adipocytokines secreted by the adipose tissue [2]. For example, insulin-resistant states are associated with lower adiponectin levels [3, 4] and higher serum visfatin concentrations in some studies [5, 6]. It is, however, unclear whether change in insulin resistance *per se* results in a change in serum visfatin concentrations. It has long been known that glucocorticoids cause insulin resistance *in vitro* and *in vivo* [7]. This seems to be related primarily to a post-receptor effect [8]. It was recently shown that dexamethasone increases visfatin synthesis *in vitro* [9], but still it is not clear whether this is reflected in changes in serum levels of this cytokine. It is also not clear whether a glucocorticoid-induced increase in insulin resistance is related to the change in serum visfatin concentrations. In order to examine this question we have assessed fasting serum concentrations of visfatin, glucose, insulin and cortisol before and after 48 hours of dexamethasone administration during screening for Cushing's disease/ /syndrome [Study 2].

Material and methods

Study 1 included 17 patients, 15 females and 2 males. The mean age of the subjects was 35.7 ± 15.6 (mean ± SD) years and body mass index (BMI) amounted to 35.2 ± ± 9.3 kg/m^2. Obese patients at risk of diabetes or impaired glucose tolerance were recruited either from the Obesity & Metabolic Clinic of the Polish Mother Memorial Hospital Research Institute or from a general practice (NZOZ *Twój Lekarz Rodzinny sp*, Łódź, ul. Socjalna) An OGTT was performed according to the World Health Organisation standard [10]. Serum samples were taken before (0 minutes) and at 60 and 120 minutes after ingestion of a solution containing 75.0 g glucose. Serum visfatin was measured by an ELISA kit (Phoenix Pharmaceuticals, CV < 6%). Insulin was measured by ELISA (DakoCytomation Ltd, Denmark House, Angel Drove, Ely CB7 4 ET, UK).

Study 2 included 20 subjects, 16 females and 4 males, including 5 persons with type 2 diabetes mellitus (all insulin-treated). The mean age of the subjects was 42.1 ± 17.2 years and BMI was 36.7 ± 8.38 kg/m^2. Serum concentration of visfatin, glucose, insulin and cortisol were assessed before (D0) and after 48 hours (D2) of administration of dexamethasone (0.5 mg every 6 hours for 48 hours) during screening for Cushing's disease/syndrome. In non-diabetic individuals (n = 15) insulin resistance was assessed according to the HOMA method (where HOMA = fasting insulin concentration [μU/mL] × fasting glucose concentration [mmol/L]/22.5) [11].

The study protocol was approved by the Ethics Committee of the Medical University of Łódź (Poland).

Statistical analysis

In both studies the data were analysed by means of simple descriptive statistics and non-parametric tests of significance with application of the Wilcoxon matched-pairs test for comparison of distributions of particular parameters in different OGTT time intervals. In Study 2 the data were also analysed by a paired t-test, given normal distribution of the variables. Associations between visfatin concentrations and other parameters were assessed by the Spearman rank correlation method. In all analyses statistical significance was considered to be achieved for a value of $p \leq 0.05$. All the calculations were derived by means of Statistica v6.0 software.

Results

In the first group two subjects were found to have impaired glucose tolerance and one subject was found to have diabetes mellitus [10]. The results of Study 1 are presented in Table I and Figures 1A, 1 B and 1C. Glucose administration resulted in a highly significant increase in insulin (from 11.4 ± 7.2 mU/mL at 0 min to 98.9 ± ± 68.6 mU/mL at 60 min and 72.6 ± 45.1 mU/mL at 120 min of OGTT, $p < 0.001$ for 60 and 120 minutes in comparison to baseline). In contrast, there was no change in serum visfatin concentrations (84.6 ± 11.6 ng/mL at 0 minutes, 82.6 ± 12.7 ng/mL at 60 minutes and 81.1 ± ± 14.5 ng/mL at 120 minutes of OGTT, p = ns).

In Study 2 dexamethasone administration resulted in suppression of serum cortisol below 50 nmol/l (1.8 mg/dL) in all subjects, which allowed us to rule out Cushing's disease or syndrome according to the recent consensus criteria [12]. The results of the study are presented in Table II. Dexamethasone administration resulted in an increase in fasting insulin (from 11.5 ± 6.9 to 16.9 ± 7.6 mU/mL; p = 0.011), an increase in HOMA (from 2.73 ± 1.74 to 4.02 ± 2.27; p = 0.015) but no significant change in serum visfatin concentrations (61.1 ± 19.8 *vs.* 68.3 ± 19.4 ng/mL; p = ns). Analysis of pooled data from both studies revealed no significant correlation between serum visfatin and age, BMI, HOMA, fasting glucose or insulin.

Discussion

Since the discovery of visfatin many researchers have suggested that it could provide a link between obesity and insulin resistance or metabolic syndrome. Yet the results of studies assessing the relationship between visfatin and the metabolic syndrome or diabetes mellitus in humans and rodents appear conflicting.

It has been demonstrated that plasma visfatin concentrations strongly correlate with the amount of visceral fat measured by computer tomography in

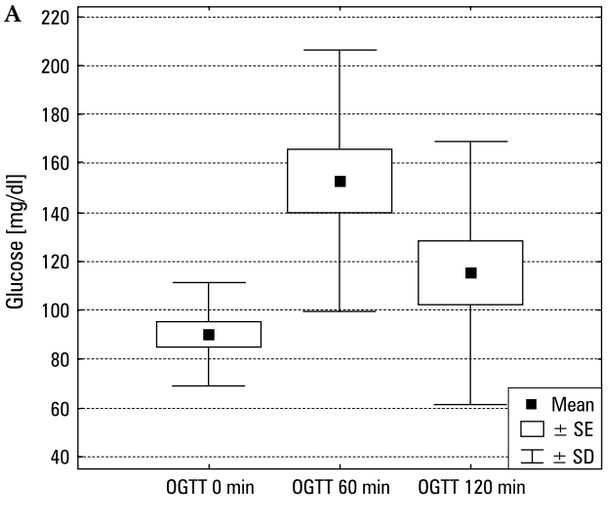
Table I

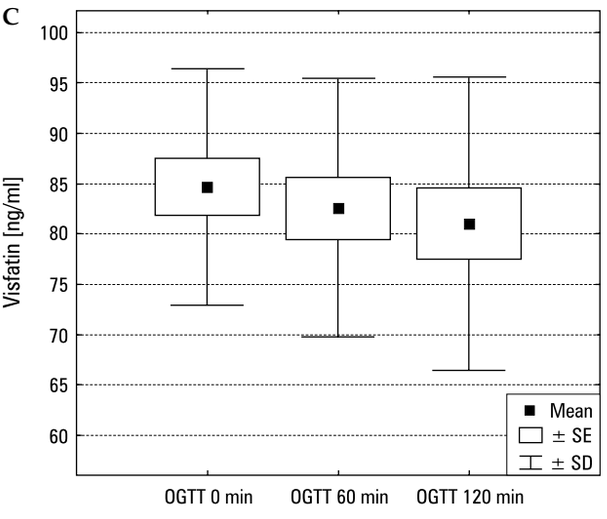
Descriptive statistics of insulin and visfatin during OGTT. P-value represents the significance level of the Wilcoxon matched--pairs test for comparison of the distributions of these characteristics in different OGTT time intervals

Tabela I

Stężenia insuliny i wisfatyny podczas doustnego testu tolerancji glukozy (OGTT). Wartość P oznacza istotność statystyczną dla porównania rozkładów zmiennych przy zastosowaniu testu Wilcoxona dla par danych podczas OGTT

Variable	OGTT	n	Mean	95% CI Mean	Med	SD	Min	Max	*P value*	
Insulin	0′	17	11.4	(7.7; 15.1)	9.4	7.2	2.1	27.8	0′ ÷ 60′	0.0003
[μU/mL]	60′	17	99.0	(63.7; 134.2)	72.3	68.6	19.7	222.0	60′ ÷120′	0.035
	120′	17	72.6	(49.5; 95.8)	75.3	45.1	11.9	149.0	0′÷120′	0.0003
Visfatin	0′	17	84.6	(78.6; 90.6)	84.4	11.7	62.6	99.4	0′ ÷ 60′	0.61
[ng/mL]	60′	17	82.6	(76.0; 89.1)	79.7	12.8	61.5	100.0	60′ ÷120′	0.51
	120′	17	81.0	(73.6; 88.5)	85.8	14.5	56.4	100.0	0′÷120′	0.20
Glucose	0′	17	90.2	(79.4; 101.1)	84.0	21.2	68.0	150.0	0′ ÷ 60′	0.0003
[mg/dL]	60′	17	152.9	(125.4; 180.5)	139.0	53.5	92.0	297.0	60′ ÷120′	0.0003
	120′	17	115.2	(87.7; 142.8)	102.0	53.6	64.0	295.0	0′÷120′	0.016





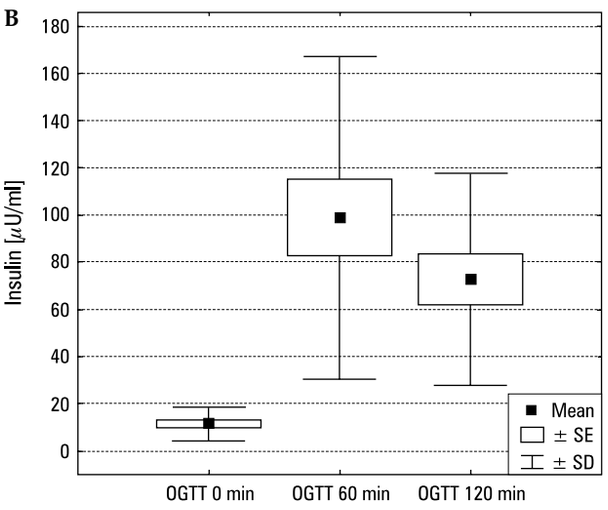


Figure 1. *The changes in glucose (Figure 1A), insulin (Figure 1B) and visfatin (Figure 1C) in 17 individuals during a 75 gram oral glucose tolerance test (OGTT) in Study 1. Marked changes in serum glucose and insulin are in contrast to the lack of significant change in serum visfatin*

Rycina 1. *Zmiany stężeń glukozy (ryc. 1A), insuliny (ryc. 1B) oraz wisfatyny (ryc. 1C) u 17 badanych osób podczas doustnego testu tolerancji glukozy (75 gram – Badanie 1). Znaczne zmiany stężeń glukozy i insuliny kontrastują z brakiem zmian stężeń wisfatyny*

Table II

Visfatin and other parameters before (D0) and after 48 hours of administration of dexamethasone (D2) in 20 individuals included in Study 2. Dexamethasone was administered orally at a dose of 0.5 mg every 6 hours for 48 hours.

Tabela II

Wisfatyna i inne parametry oceniane przed (D0) oraz po 48 godzinach podawania deksametazonu (D2) u 20 biorących udział w Badaniu 2. Deksametazon był podawany w dawce 0,5 mg co 6 godzin przez 48 godzin

Parameter	D0	D2	P value#	P value##
Glucose [mg/dL]*	93.6 ± 20.8	94.2 ± 20.4	0.76	0.88
Insulin [μU/mL]	11.6 ± 6.9	16.9 ± 7.6	**0.031**	**0.011**
HOMA** (Glucose [mmol/l] × Insulin [μU/mL)/22.5]	2.73 ± 1.74	4.02 ± 2.27	**0.036**	**0.015**
Visfatin [ng/mL]	61.1 ± 19.8	68.2 ± 19.4	0.23	0.30

*In order to convert mg/dL into mmo/L for plasma glucose divide by 18; **HOMA calculated for non-diabetic individuals (n = 15); #P values according to paired t-test; ##P values according to the Wilcoxon matched-pairs test

humans, and the visfatin plasma concentrations and visceral fat mRNA levels in KKAy mice significantly increase as the mice become obese [1]. Furthermore, increased plasma visfatin concentrations were reduced after weight loss in morbidly obese subjects [13]. Interestingly, in this study there was a correlation between the change in serum visfatin and individual changes in HOMA, although without an overall correlation between visfatin and the baseline HOMA index. A relationship of this kind between individual changes in visfatin and insulin concentration as observed in these patients may suggest that visfatin is potentially involved in the beneficial effect of weight loss on insulin resistance, although further studies are required in order to confirm or refute this hypothesis.

Administration of visfatin in mice results in a significant fall in plasma glucose within 30 minutes. This effect is dose-dependent and is not due to changes in plasma insulin levels. Moreover, similar effects have been observed in both insulin-resistant and insulin-deficient mice [1]. The same authors comment, however, on important differences between visfatin and insulin. In particular, plasma visfatin levels do not change significantly upon fasting or feeding in mice, whereas plasma insulin levels increase in the fed state and decrease in the fasting state [1]. In turn, Haider et al. [14] have demonstrated that in humans basal plasma visfatin concentrations are not altered by hyperinsulinaemia or somatostatin, the compound capable of suppressing pancreatic insulin excretion during clamp studies. In contrast, hyperglycaemia substantially increased plasma visfatin concentration, a phenomenon which has subsequently been prevented by hyperinsulinaemia or somatostatin [14]. In our study, on the other hand, we found no significant change in serum visfatin in response to short-term (following oral glucose load) hyperglycaemia and hyperinsulinaemia. There are, however, significant differences in the design of our study and the study of Haider et al. [14]. In particular, they observed a significant rise in serum visfatin after 90 minutes of continuous glucose infusion in clamp conditions, where glucose concentrations were maintained at 8.3 mmol/l (149.4 mg/dL). This contrasts with a rapid rise in plasma glucose in our subjects to a mean value of 152.9 mg/dL at 60 minutes of OGTT followed by a fall to a mean value of 115.2 mg/dL at 120 minutes of OGTT. We note that Haider et al. [14] did not observe a rise in serum visfatin when the glucose level was 5 mmo/l (90 mg/dL). It is therefore likely that post-prandial changes in plasma glucose or changes after OGTT are too short-lasting to induce any significant change in serum visfatin.

Therefore our study demonstrates a striking difference between the brisk change in serum insulin and the lack of change of serum visfatin after oral glucose load. In our opinion, this indicates that visfatin, in contrast to insulin, does not seem to be involved in direct regulation of post-prandial glucose levels in humans, at least in those who maintain a robust insulin secretory capacity.

The mechanisms controlling cellular visfatin secretion have not yet been characterised. Taking into consideration the eventuality that insulin-like activity of visfatin is of physiological importance and given the fact that visfatin binds to the insulin receptor without competing with insulin, it is not unreasonable to assume that visfatin concentrations may correlate with parameters of glucose metabolism and insulin sensitivity. The data on this issue are, however, highly conflicting. Berndt et al. [5] were unable to find a relationship between visfatin plasma concentrations and parameters of insulin sensitivity or glucose homeostasis, including fasting plasma insulin and glucose concentrations, and the glucose infusion rate during the steady state of the euglycaemic-hyperinsulinaemic clamp, independent of percentage body fat. Jian et al. [15] examined a group

of 241 Chinese subjects and demonstrated that serum visfatin concentrations are similar in patients with type 2 diabetes mellitus, subjects with impaired glucose tolerance and normal glucose-tolerant subjects. Some authors report a lack of correlation between plasma visfatin and insulin/HOMA [5, 16], while others [6], including our group [17], have observed a correlation between plasma visfatin and fasting insulin and HOMA. Chan et al. [18], surprisingly, showed decreased concentrations of plasma visfatin in gestational diabetes mellitus subjects, those in a state characterised by increased insulin resistance. In contrast, Krzyzanowska et al. [19] and our group [20] have demonstrated that women with gestational diabetes mellitus had significantly higher visfatin concentrations than healthy pregnant controls. Interestingly, Krzyzanowska et al. [19] did not observe any associations between visfatin levels and fasting glucose and insulin concentrations or HOMA, while our group noted a significant correlation between visfatin and fasting insulin concentrations and HOMA in women with gestational diabetes mellitus. We note, however, that in a multivariate model glucose and insulin still explained only 18% of the variability of serum visfatin [20]. In contrast to our data on pregnant women, this study failed to demonstrate any significant correlation between serum visfatin and glucose, insulin or HOMA.

Furthermore our study indicates that oral administration of dexamethasone in the dose of 0.5 mg every 6 hours for 48 hours does not alter serum visfatin concentrations in overweight subjects despite a clear increase in insulin resistance. We have found this result surprising, given that dexamethasone has been found to induce visfatin mRNA expression in 3T3-L1 adipocytes [9]. In this experiment treatment with 100 nM dexamethasone for 16 hours increased visfatin mRNA almost 1.5-fold ($p < 0.05$). In contrast, other factors which induce insulin resistance, such as tumour necrosis factor a, isoproterenol (catecholamine) or growth hormone, down-regulated visfatin expression, whereas insulin did not significantly influence visfatin mRNA synthesis [9]. The results of our study have demonstrated, however, that the *in vitro* effects of glucocorticoid administration may not necessarily be reflected in changes in serum levels of visfatin and other adipocytokines, as we have recently demonstrated in the case of adiponectin and resistin [21]. In view of the discrepancies between the results of the *in vitro* and *in vivo* studies we postulate that further research, including administration of glucocorticoids at different doses and/or duration, is necessary in order to determine whether these hormones are indeed capable of influencing serum visfatin concentrations.

Conclusions

In summary, our study demonstrates marked differences between sharp changes in serum insulin and an absence of significant change in serum visfatin after the oral glucose tolerance test. In our opinion, this observation contradicts the notion that visfatin may be directly involved in regulation of post-prandial glycaemia in humans. Furthermore, the lack of any significant change in serum visfatin after glucocorticoid administration, despite the increase in insulin resistance, points to the conclusion that so far there is no convincing evidence that a glucocorticoid-induced change in insulin resistance is mediated, at least in part, through a change in serum visfatin.

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