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Elevated Plasma Level of Visfatin/Pre-B Cell Colony-Enhancing Factor in Patients with Type 2 Diabetes Mellitus

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Context: Visfatin (also known as pre-B cell colony-enhancing factor or PBEF) is a cytokine that is highly expressed in visceral fat and whose blood levels correlate with obesity. Originally isolated as a secreted factor that promotes the growth of B cell precursors and recently found to act as an insulin analog on the insulin receptor, its pathophysiological role in humans remains largely unknown.

Objectives: In this study we investigated whether plasma visfatin level is altered in patients with type 2 diabetes mellitus (T2DM).

Design and Patients: Plasma visfatin as well as adiponectin and resistin concentrations were measured through ELISA in type 2 diabetic and nondiabetic subjects.

Results: A total of 61 patients with T2DM and 59 sex- and age-matched nondiabetic subjects were studied. Plasma visfatin was found to be elevated in patients with T2DM (31.9 ± 31.7 *vs.* 15.8 ± 16.7 ng/ml, $P = 0.002$). In contrast, adiponectin was decreased (4.3 ± 2.5 *vs.* 30.8 ± 10.3 μg/ml, $P < 0.001$), whereas plasma resistin level did not differ between the groups. Increasing concentrations of visfatin were independently and significantly associated with T2DM. Multiple logistic regression analysis revealed visfatin as an independent association factor for T2DM, even after full adjustment of known biomarkers. The association between adiponectin and T2DM was no longer significant after adjustments for body mass index or waist to hip ratio. In a multiple linear regression analysis, only waist to hip ratio was independently associated with plasma visfatin level.

Conclusion: Our results indicate that visfatin may play a role in the pathogenesis of T2DM. **(*J Clin Endocrinol Metab* 91: 295–299, 2006)**

EXCESS ADIPOSITY IS the most important risk in the development of insulin resistance and type 2 diabetes mellitus (T2DM) (1). Adipose tissue produces several proteins (adipocytokines) such as leptin, adiponectin, resistin, TNFα, and IL-6, that modulate insulin sensitivity and appear to play an important role in the pathogenesis of insulin resistance, diabetes, dyslipidemia, inflammation, and atherosclerosis (2–4). However, the mechanisms by which fat tissue induces insulin resistance and the role of adipocytokines in the pathogenesis of T2DM have not been well established. Visfatin, also known as pre-B cell colony-enhancing factor, is a cytokine that is highly expressed in visceral fat and was originally isolated as a secreted factor that synergizes with IL-7 and stem cell factors to promote the growth of B cell precursors (5). Visfatin homologs have been identified in carp (6), invertebrate mollusks (7), and bacteria (8) as well as vertebrates, including humans and the mouse (9, 10). It has been postulated to play a role in innate immunity (7).

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Abbreviations: BMI, Body mass index; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein-cholesterol; OR, odds ratio; T2DM, type 2 diabetes mellitus; WHR, waist to hip ratio.

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However, the biological activity of visfatin is poorly understood. It is secreted by activated lymphocytes (5), monocytes, and neutrophils (11); stimulates the expression of IL-6 and IL-8 in amniotic cells (12); and prolongs neutrophil survival in clinical sepsis (11). Fukuhara *et al.* (13) recently found that visfatin expression in visceral fat is increased in obese subjects and that plasma concentrations of visfatin correlated much more strongly with the amount of visceral fat than that of sc adipose tissue. In the KKAy mouse, a model of obesity with T2DM, visfatin expression in visceral adipose tissue and plasma visfatin concentrations increased as obesity developed, whereas visfatin expression in sc fat and liver showed little change. In mice fed with a high-fat diet, visfatin expression in visceral mesenteric fat and plasma visfatin concentrations were higher than those in control animals.

Visfatin exerts insulin-mimetic effects that are dose dependent and quantitatively similar to those of insulin in stimulating muscle and adipocyte glucose transport and in inhibiting hepatocyte glucose production. Intravenous injection of recombinant visfatin in mice decreased plasma glucose in a dose-dependent fashion. In keeping with its insulin-mimetic effects, visfatin was as effective as insulin in reducing hyperglycemia in insulin-deficient diabetic mice. Visfatin was also found to be bound to and activate insulin receptor, causing receptor phosphorylation and the activation of downstream signaling molecules. However, visfatin and insulin did not compete for binding to the insulin re-

ceptor, indicating that the two proteins were recognized by different regions of the receptor (13). Thus, visfatin might play a role in glucose homeostasis and dysregulation in biosynthesis or signal transduction and might contribute to the pathogenesis of diabetes. To investigate the role of visfatin in diabetes, we measured plasma visfatin level as well as adiponectin and resistin in a Chinese population with T2DM.

Subjects and Methods

Subjects

From February 2004 to December 2004, diabetic patients who consecutively visited the Diabetic Clinic of Pingtung Christian Hospital were studied. Subjects without clinical evidence of major diseases were recruited from an unselected population that underwent routine medical check-up and were used as the control group. The definition of a nondiabetic is a subject who has a fasting plasma glucose level lower than 110 mg/dl and has no family history of T2DM. The diagnosis of T2DM was based on the World Health Organization criteria (14). Patients presenting with symptoms suggestive of type 1 diabetes, defined as diabetic ketoacidosis, acute presentation with heavy ketonuria (3+), or continuous requirement of insulin within 1 yr of diagnosis, were excluded (15). Patients who had had a diagnosis of urinary tract infection, urolithiasis, liver cirrhosis, congestive heart failure, macrovascular diseases, overt proteinuria, or other known major diseases were also excluded on the basis of interview, physical examination, and urinalysis. This case-control study was approved by the human research ethics committee of the hospital, and informed consent was obtained from each patient.

All of the study subjects were of Han Chinese origin and all lived in the same region at the time of the study. All of the patients underwent complete physical examination and routine biochemical analyses of blood and urine as well as an assessment of the presence and extent of macrovascular or microvascular complications. Anthropometric parameters measured included body mass index (BMI) and waist to hip ratio (WHR). Waist and hip circumferences were measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. The hips were measured at their widest point. Seated blood pressure were taken by a trained nurse with a digital automatic blood pressure monitor (model HEM-907; Omron, Omron, Japan) after the subjects had rested for 5 min.

Plasma biochemical parameters were also measured after overnight fasting including triglycerides, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), uric acid, creatinine, and glucose, which were measured by standard commercial methods on a parallel, multichannel analyzer (Hitachi 7170A, Tokyo, Japan) as our previous reports (16, 17). Patients who had smoked within 1 yr of the examination were considered current smokers. Those who had stopped smoking for more than 1 yr before the examination were considered nonsmokers.

Plasma visfatin, resistin, adiponectin, and insulin measurements

All of the blood samples were drawn after overnight fasting and plasma samples were kept at −80 C for subsequent assay. The concentrations of plasma visfatin and resistin were determined by commercial enzyme immunoassay kits (Phoenix Pharmaceuticals, Belmont, CA and Phoenix Pharmaceuticals, respectively). Adiponectin and insulin levels were determined by commercial solid-phase ELISA kits (B-Bridge International, Sunnyvale, CA, and BioSource, Nivelles, Belgium, respectively). The intraassay coefficients of variation were 2.4–2.7% for visfatin, 2.1–5.2% for resistin, 3.2–7.3% for adiponectin, and 3.4–5.7% for insulin. Samples were measured in duplicate in a single experiment. The homeostasis model assessment of insulin resistance ($HOMA_{IR}$) was calculated from fasting insulin and glucose by the following equation: $HOMA_{IR}$ = insulin (microunits per milliliter) × glucose (mmol/liter)/22.5 (18).

Statistical methods

The data are shown as the mean ± SD. All of the statistical analyses were performed using the SAS software (release 8.0; SAS Institute, Cary, NC). Baseline characteristics of case and control subjects were compared by Student's t test, Wilcoxon's rank-sum test, or χ^2 test. The general linear modeling function analysis was used to control for potential confounders other than age (*e.g.* gender, BMI, WHR, and smoking status). Because the distributions of plasma visfatin, adiponectin, resistin, insulin, and $HOMA_{IR}$ values were skewed, logarithmically transformed values were used for statistical analysis. As our primary approach, we included plasma visfatin and adiponectin concentrations as continuous independent variables in the multivariable models.

The association of visfatin and adiponectin with diabetes was examined by multivariate logistic regression analysis that contained: 1) visfatin or adiponectin, age, and gender; 2) visfatin or adiponectin, age, gender, BMI, and WHR; 3) visfatin or adiponectin, age, gender, BMI, WHR, and blood pressure; 4) visfatin or adiponectin, age, gender, BMI, WHR, blood pressure, lipid profile, and smoking status. We further divided the distribution of visfatin in pooled data into tertile and used general linear and logistic regression models to estimate the significant trends across increasing tertile and to estimate the odds ratios (ORs) of diabetes in each tertile using the lowest tertile as the reference category. Multivariate adjusted ORs are presented with 95% confidence interval (CI).

Simple and multiple regression analyses were used to examine the association between plasma concentrations of visfatin or adiponectin and the values of other biomarkers. All of the statistical analyses were two sided, and $P < 0.05$ was considered significant.

Results

The clinical characteristics of our subjects are shown in Table 1. A total of 61 patients with T2DM and 59 sex- and age-matched nondiabetic subjects were studied. Diabetic subjects had higher waist, WHR, fasting glucose, insulin, $HOMA_{IR}$, systolic and diastolic blood pressure, and serum triglyceride measurements than those of control subjects. Plasma visfatin levels were found to be elevated in patients with T2DM (31.9 ± 31.7 *vs.* 15.8 ± 16.7 ng/ml, $P = 0.002$). In contrast, adiponectin decreased (4.3 ± 2.5 *vs.* 30.8 ± 10.3 μg/ml, $P < 0.001$), whereas resistin levels did not differ between the groups (31.8 ± 36.7 *vs.* 25.8 ± 32.0 ng/ml, $P = 0.300$). There are no gender differences among plasma visfatin (23.2 ± 28.4 *vs.* 24.9 ± 24.6 ng/ml), adiponectin (18.7 ± 16.0 *vs.* 15.5 ± 14.2 μg/ml), or resistin (29.8 ± 35.3 *vs.* 27.8 ± 33.8 ng/ml) levels (all P = ns). The visfatin to glucose ratio was not different between patients with type 2 diabetes and controls (22.1 ± 25.2 *vs.* 16.8 ± 16.5, $P = 0.124$).

Fifty-nine diabetic patients were treated with oral hypoglycemic agents alone and two cases with combined insulin and oral hypoglycemic agents. Among patients on treatment with oral hypoglycemic agents, 25 cases were on sulfonylurea alone, five on metformin alone, 25 on sulfonylurea and metformin, and four on sulfonylurea and thiazolidinediones (Table 1). The mean plasma level of visfatin in subjects receiving insulin treatment did not differ from that of patients receiving oral hypoglycemic agents. The mean plasma visfatin levels of diabetic subjects on different oral hypoglycemics did not show any difference among the groups, yet the number of subjects is too small to draw any conclusion. The plasma visfatin and adiponectin levels remained significantly different after adjustment for age, sex, BMI, and smoking status (31.9 ± 3.3 *vs.* 15.9 ± 3.4 ng/ml, $P = 0.004$ and 4.3 ± 1.0 *vs.* 31.4 ± 1.0 μg/ml, respectively, $P < 0.001$) (Table 1). Plasma visfatin concentration was significantly associated

TABLE 1. Clinical characteristics of study subjects

Factor	T2DM	Controls	*P*
N	61	59	
Age (yr)	65.3 ± 6.7	64.5 ± 9.10	0.559
Gender, male (%)	31 (50.8)	33 (55.9)	0.575
DMDU (yr)	8.4 ± 4.5		
BMI (kg/m^2)	25.4 ± 0.9	25.4 ± 0.8	0.965
Waist (cm)	92.7 ± 5.5	87.6 ± 6.1	<0.001
WHR	0.97 ± 0.06	0.90 ± 0.06	<0.001
Fasting glucose (mmol/liter)	9.2 ± 3.3	5.4 ± 0.4	<0.001
Insulin (pmol/liter)	109.7 ± 87.6	55.6 ± 20.8	<0.001
$HOMA_{IR}$	6.1 ± 4.2	1.9 ± 0.7	<0.001
HbA1c (%)	8.0 ± 1.8		
Systolic BP (mm Hg)	147.4 ± 19.8	136.1 ± 18.9	0.002
Diastolic BP (mm Hg)	87.8 ± 10.1	78.8 ± 11.7	<0.001
Total cholesterol (mmol/liter)	4.9 ± 1.0	5.5 ± 1.2	0.005
Triglyceride (mmol/liter)	1.9 ± 1.0	1.3 ± 0.8	0.001
HDL-cholesterol (mmol/liter)	1.2 ± 0.3	1.2 ± 0.3	0.241
LDL-cholesterol (mmol/liter)	3.0 ± 0.7	3.5 ± 1.0	0.002
Uric acid (μmol/liter)	356.9 ± 89.2	374.7 ± 71.4	0.218
Creatinine (μmol/liter)	83.1 ± 18.6	82.2 ± 16.8	0.641
Adiponectin (μg/ml)	4.3 ± 2.5	30.8 ± 10.3	<0.001
Adiponectin [adjusted (μg/ml)][a]	4.3 ± 1.0	31.4 ± 1.0	<0.001
Resistin (ng/ml)	31.8 ± 36.7	25.8 ± 32.0	0.300
Visfatin (ng/ml)	31.9 ± 31.7	15.8 ± 16.7	0.002
Visfatin [adjusted (ng/ml)][a]	31.9 ± 3.3	15.9 ± 3.4	0.004
Visfatin to glucose ratio × 100	22.1 ± 25.2	16.8 ± 16.5	0.124
Smoking (%)	10 (16.4)	9 (15.3)	0.864
Type of treatment OHA (SU/Met/SU+Met/SU+TZD)/ insulin only/SU+insulin	59 (25/5/25/4)/0/2		

Data are mean ± SD or frequency (percent). DMDU, Known diabetic duration; BP, blood pressure; OHA, oral hypoglycemic agents; SU, sulfonylurea; Met, metformin; TZD, thiazolidinediones; HbA1c, glycosylated hemoglobin.

[a] Mean ± SE by general linear model with adjustment of age, gender, BMI, smoking status.

with T2DM even after controlling for anthropometric variables, blood pressure, lipid profile, and smoking status (Table 2). The association between plasma adiponectin and T2DM disappeared after further adjustments of BMI and WHR, and no more association could be detected by further adjustments (Table 2).

Increasing levels of visfatin showed a significant linear trend and were independently associated with T2DM, especially when concentrations were analyzed both by tertile and a continuous variable (Tables 2 and 3). Multiple logistic regression analysis in fully adjusted ORs in the second and third tertile were 1.84 (95% CI 0.54–6.62) and 4.17 (95% CI 1.17–16.35), respectively.

TABLE 2. Association of plasma visfatin and adiponectin with T2DM in fully adjusted models

Model adjusted for	T2DM		
	OR	95% CI	*P*
Plasma visfatin			
Age, gender	3.247	1.426–7.394	0.005
Age, gender, BMI, WHR	2.320	1.000–4.695	0.043
Age, gender, BMI, WHR, SBP, DBP	2.895	1.113–7.529	0.029
Age, gender, BMI, WHR, SBP, DBP, lipid profile, smoking status	5.534	1.605–19.079	0.007
Plasma adiponectin			
Age, gender	0.451	0.253–0.803	0.007
Age, gender, BMI, WHR	0.176	0.014–2.180	0.176
Age, gender, BMI, WHR, SBP, DBP	0.169	0.019–1.475	0.108
Age, gender, BMI, WHR, SBP, DBP, lipid profile, smoking status	0.256	0.042–1.552	0.138

Results of multivariate logistic regression analysis are presented as the OR of being in T2DM status increases in plasma visfatin and decrease in plasma adiponectin. SBP, Systolic blood pressure; DBP, diastolic blood pressure; lipid profile, includes total cholesterol, triglyceride, and LDL- and HDL-cholesterol.

Plasma visfatin was associated with age, WHR, fasting plasma insulin, adiponectin levels, and $HOMA_{IR}$ in simple regression analysis in the pooled data, whereas in multiple regression analysis, only plasma visfatin level remained positively associated with WHR (Table 4). When the association between metabolic biomarkers with plasma visfatin in nondiabetics and type 2 diabetics separately, we did not find any association between plasma visfatin and metabolic biomarkers in individual groups. Plasma adiponectin level was negatively associated with WHR, diastolic blood pressure, fasting glucose, plasma resistin, and visfatin levels, as shown in our previous report (data not shown) (19).

Discussion

In the present study, we demonstrated that plasma visfatin level correlated with WHR, which increased in T2DM or even in a fully adjusted model. Furthermore, we found no significant association between plasma adiponectin and resistin with T2DM. To our knowledge, this is the first report to describe the plasma level of visfatin in patients with T2DM.

The biological mechanisms involving visfatin in the pathogenesis of T2DM are not well understood. Visfatin as an adipokine has recently been identified and named as such because of its much greater expression in visceral fat than in sc adipose tissue (13). In keeping with its insulin-mimetic effects, visfatin was as effective as insulin in reducing hy-

TABLE 3. Univariate and multivariate analysis of the impact of plasma visfatin level on T2DM

Factor	Tertiles of visfatin			
	Q1 (95% CI)	Q2 (95% CI)	Q3 (95% CI)	*P* for trend
All subjects				
No. of cases/reference	15/25	18/22	28/12	0.01
Cut-off visfatin (ng/ml)	<7.7	7.7–22.6	22.6–129.2	
Univariate	1.00	1.36 (0.56–3.33)	3.89 (1.53–9.87)	0.003
Multivariate[a]	1.00	1.84 (0.54–6.62)	4.17 (1.17–16.35)	0.038

Values shown are cut-offs of plasma visfatin levels of all subjects, and odds ratios with 95% CIs.
[a] Adjusted for age, sex, BMI, WHR, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, LDL- and HDL-cholesterol, and smoking status.

perglycemia in insulin-deficient diabetic mice. Visfatin was also bound to and activated insulin receptors, causing receptor phosphorylation and the activation of the downstream signaling molecules.

Elevated visfatin level in patients with T2DM in this study may suggest the impairment of visfatin signaling in targets tissues or the dysregulation in biosynthesis or in response to hyperglycemia, hyperinsulinemia, or adipocytokines in state of diabetes. These need to be clarified by further studies. Plasma visfatin level was likewise significantly associated with $HOMA_{IR}$ in simple regression analysis but not in multiple regression analysis. Only WHR remained significantly associated with plasma visfatin level. On the other hand, plasma visfatin did not correlate with BMI and other biomarkers, such as blood pressure and lipid profile. This fact is consistent with findings that visfatin is mainly secreted in the visceral fat, not sc, and suggest that the pathogenetic mechanism of visfatin in T2DM is different from that of insulin resistance.

However, the physiological role and pathological implications of visfatin must be considered with some caution. Whereas plasma concentrations are lower than those of insulin, they do not fluctuate with nutritional state and have been suggested to be released from fat cells during lysis rather than being truly secreted (20). These reservations notwithstanding, it will be of great interest to follow future developments regarding both the mechanisms of production and action of visfatin and its possible implication in the pathophysiology of T2DM.

TABLE 4. Linear regression analysis of variables associated with plasma visfatin levels in subjects studied

Variable	Simple		Multiple	
	Estimate	*P*	Estimate	*P*
Age	0.196	0.032		
Sex	0.085	0.358		
BMI	0.004	0.967		
WHR	0.250	0.006	0.242	0.011
Smoking	−0.078	0.399		
Systolic BP	−0.016	0.865		
Diastolic BP	−0.051	0.582		
Fasting glucose	0.046	0.621		
Fasting insulin	0.204	0.031		
$HOMA_{IR}$	0.212	0.027		
Total cholesterol	−0.033	0.717		
Triglyceride	0.051	0.580		
HDL-cholesterol	−0.044	0.639		
LDL-cholesterol	−0.097	0.299		
Uric acid	−0.099	0.282		
Creatinine	−0.098	0.289		
Adiponectin	−0.26	0.004		
Resistin	0.111	0.230		

In multiple linear stepwise regression analysis, values included for analysis were age, sex, smoking status, BMI, WHR, systolic BP, diastolic BP, fasting glucose, insulin, $HOMA_{IR}$, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, resistin, and adiponectin levels. BP, Blood pressure.

It is becoming clear that adipose tissue is not simply a reservoir for excess nutrients but an active and dynamic organ capable of expressing several cytokines and fat-derived peptides (2). More recently there has been increasing evidence of the association between insulin resistance and subclinical inflammation involving cytokines derived from adipose tissue or adipocytokines (2–4, 21). Knowledge of how these adipose tissue-derived factors influence metabolic and cardiovascular disease has recently expanded, and growing evidence implicates adipocyte-derived factors as major regulator of insulin resistance (21, 22). Interestingly, visfatin and not adiponectin or resistin levels were associated with T2DM.

Hypoadiponectinemia was reported in patients with obesity and T2DM (23). In the present study, we also observed decreased plasma adiponectin levels in patients with T2DM. As previously reported, plasma adiponectin levels correlated well with WHR, diastolic blood pressure, and fasting glucose levels (19, 24). Although studies observed a significant positive association between adiponectin and insulin sensitivity in nondiabetic subjects after adjusting for BMI or WHR (25), Kim *et al.* (26) reported that the association between plasma adiponectin and $HOMA_{IR}$ disappear after adjustment for sex, age, BMI, and WHR in patients with T2DM. These facts suggest that the association is largely explained by obesity-related factors that induce hypoadiponectinemia and indicate that adiponectin may not act directly on the pathogenesis of T2DM.

Resistin is identified in adipose tissue by the screening for molecules expressed during adipocyte differentiation and in response to an insulin-sensitizing drug. It has been suggested to play a part in the pathogenesis of insulin resistance and was thought to be a link between obesity and diabetes (27). Its effects on insulin resistance has been extensively investigated in mice (28, 29), whereas in humans its role in insulin resistance, obesity, and T2DM has been controversial (30–32). Our result shows that plasma resistin level is not different between the controls and type 2 diabetic subjects and supports the hypothesis that resistin may not play a role in the pathogenesis of T2DM.

Some limitations of this study need to be considered. The cross-sectional design limits our ability to infer a causal re-

lationship between increased plasma visfatin level and T2DM. Our analyses are based on single measurements of blood visfatin, which may not reflect the relationship over time. It would be interesting to measure serial changes of plasma visfatin levels in obese, insulin-resistant, or prediabetic subjects to further clarify the role of visfatin in the pathogenesis of T2DM. Moreover, the cases studied in the present study are patients under a disease management program, and all are free of macrovascular and microvascular complications. Whether visfatin is related to plasma insulin or insulin resistance in these subjects is not determined. Further experiments designed to investigate the role of visfatin in association with insulin resistance will help clarify the role of visfatin in T2DM. Also, the blood samples were drawn without stopping the diabetic medication of diabetic patients. Hence, the effects of oral hypoglycemic drugs with plasma visfatin levels also need to be clarified.

In conclusion, our results of elevated visfatin in uncomplicated type 2 diabetic subjects indicate that visfatin may play a role in the pathogenesis of T2DM. However, further experiments need to be done to clarify the role of visfatin.

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