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Serum visfatin in relation to visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians

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Abstract

To investigate the role of the novel adipokine visfatin in type 2 diabetes mellitus and obesity and to examine its association with visceral and subcutaneous fat in Asian Indians, who have increased susceptibility to type 2 diabetes mellitus and coronary artery disease, 150 subjects with type 2 diabetes mellitus (75 men, 75 women) and 150 age- and sex-matched subjects with normal glucose tolerance were recruited from the Chennai Urban Rural Epidemiology Study, a population-based study done in Chennai, southern India. Anthropometric and biochemical measurements were done by using standardized techniques. Fasting serum visfatin levels were measured by enzyme-linked immunosorbent assay. Visceral and subcutaneous fat were measured by computerized tomography in a subset of 130 individuals. Serum visfatin levels were significantly higher in diabetic subjects compared with nondiabetic subjects (11.4 ± 5.9 vs 9.8 ± 4.3 ng/mL, $P = .008$). However, this association was lost when adjusted for body mass index (odds ratio [OR], 1.048; 95% confidence interval [CI], 0.997-1.101; $P = .067$) or waist circumference (OR, 1.050; 95% CI, 0.999-1.104; $P = .057$). Serum visfatin showed a significant association with obesity even after adjusting for age, sex, and type 2 diabetes mellitus (OR, 1.060; 95% CI, 1.005-1.119; $P = .033$). Visceral fat, but not subcutaneous fat, was significantly associated with serum visfatin levels even after adjusting for age, sex, type 2 diabetes mellitus, and body mass index ($P = .002$). In Asian Indians, serum visfatin levels are associated with obesity and visceral fat but not with subcutaneous fat. Although visfatin levels are increased in type 2 diabetes mellitus, the association seems to be primarily through obesity.

1. Introduction

Compared with Europeans, Asian Indians have increased visceral fat and central obesity despite lower generalized obesity, and this is referred to as the "Asian Indian phenotype" [1-4]. This could contribute to the high prevalence of diabetes in this ethnic group [5,6]. However, the mechanistic link between visceral fat and type 2 diabetes mellitus is not clear. Fukuhara et al [7] demonstrated that the cytokine pre-B cell colony–enhancing factor is secreted abundantly by visceral fat in both mice and humans and hence renamed it as "visfatin." They also reported that among the Japanese general population, plasma visfatin levels strongly correlated with visceral fat mass [7]. Chen et al reported that visfatin is associated with abdominal obesity and type 2 diabetes mellitus in Taiwanese [8]. Hence, visfatin is considered to be one of the links between intra-abdominal obesity and type 2 diabetes mellitus [9]. However, some studies do not show an association of serum visfatin with visceral fat or insulin sensitivity in Europeans [10-12]. In this context, it is important to look at the association of visfatin with visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians.

The aims of the present study were (1) to investigate the role of serum visfatin in type 2 diabetes mellitus and obesity in Asian Indians and (2) to look at the association of serum visfatin with visceral and subcutaneous abdominal fat.

2. Subjects and methods

The study subjects were recruited from the Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiologic study conducted on a representative population (aged ≥20 years) of Chennai (formerly Madras), the fourth largest city in India. The methodology of the study has been published elsewhere [13]. Briefly, in phase 1 of the urban component of CURES, 26 001 individuals were recruited based on a systematic random sampling technique. Fasting capillary blood glucose was determined in all

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subjects by using a OneTouch Basic glucose meter (LifeScan, Johnson & Johnson, Milpitas, CA). Subjects were classified as "known diabetic subjects" if they stated that they had diabetes and were on the treatment.

In phase 2 of CURES, all the known diabetic subjects (n = 1529) were invited to the center for detailed studies on vascular complications; 1382 responded (response rate, 90.3%). From the rest of the study subjects, 10% of newly diagnosed diabetic subjects (n = 320; response rate, 98.8%), 15% of subjects with impaired fasting glucose (n = 866; response rate, 99.1%), and 10% of subjects with normal fasting glucose (n = 1494; response rate, 97.0%) were recruited. Those who were confirmed by oral glucose tolerance test to have 2-hour plasma glucose value of 11.1 mmol/L (200 mg/dL) or greater, based on World Health Organization consulting group criteria [14], were labeled as "newly detected diabetic subjects"; those with 2-hour postglucose value of 7.8 mmol/L (140 mg/dL) or greater but less than 11.1 mmol/L (200 mg/dL) [26] as having impaired glucose tolerance; and those with 2-hour postglucose value less than 7.8 mmol/L (140 mg/dL) as having normal glucose tolerance.

A total of 150 type 2 diabetic subjects (75 men, 75 women) were randomly recruited from phase 2 of CURES. One hundred fifty age- and sex-matched subjects with normal glucose tolerance were also recruited for the study from phase 2 of CURES. Of the 150 type 2 diabetic subjects selected for the study, 53 were newly identified and had not taken any antidiabetic agents previously. Of the remaining 97 known diabetic subjects, 86 were on oral hypoglycemic agents and 6 were on oral hypoglycemic agents plus insulin, whereas 5 subjects were not on any medication for diabetes.

Anthropometric measurements including weight, height, and waist and hip circumference were obtained by using standardized techniques. The body mass index (BMI) was calculated with the following formula: weight (kg)/height (m^2). The subjects chosen for the study were categorized based on their BMI according to the Asia Pacific guidelines as nonobese (BMI <25 kg/m^2) and obese (BMI ≥ 25 kg/m^2) [15].

Fasting plasma glucose (glucose oxidase-peroxidase method, Roche Diagnostics, Mannheim, Germany) serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method, Roche Diagnostics), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method, Roche Diagnostics), and high-density lipoprotein (HDL) cholesterol (direct method, polyethylene glycol–pretreated enzymes, Roche Diagnostics) were measured on a Hitachi-912 autoanalyzer (Hitachi, Mannheim, Germany). The intra- and interassay coefficients of variation for the biochemical assays ranged between 3% and 7%. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula [16]. Glycated hemoglobin (HbA_{1c}) level was estimated by high-performance liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA).

Serum insulin concentration was estimated by enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark). The intra- and interassay coefficients of variation for insulin assay were 5.7% and 8.9%, respectively, and the lower detection limit was 0.5 μIU/mL. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA IR) with the formula: fasting insulin (μIU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5 [17]. The 6 diabetic individuals who were on insulin were excluded from the HOMA-IR analysis.

Fasting visfatin levels were measured by enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Belmont, CA; catalog no. EK-003-80). The intra- and interassay coefficients of variation were 3% and 5%, respectively.

3. Computerized tomography

A total of 130 subjects (65 from each group) were randomly selected for computed tomography (CT) scan study. The nondiabetic group had 29 (43%) male and 36 female subjects and the diabetic group had 27 (44%) male and 38 female subjects. Subcutaneous and visceral fat were measured using Light Speed Plus helical CT scan (General Electric, Milwaukee, WI). The scans were done at 120 kV, 200 to 250 mA s. Subjects were requested to lie in the supine position with their arms above their head and legs elevated with a cushion. A single scan (10 mm) of the abdomen was done at the level of the L4 vertebra and analyzed for cross-sectional area of adipose tissue, which was expressed in square centimeters. Areas were calculated by multiplying the number of pixels of a given tissue type by the pixel number (pixel density). The external contours of the waist were determined using a threshold of -160 Hounsfield units (HU) and the external bone contours were derived at -30 HU. The parameters studied in this scan are visceral fat and subcutaneous abdominal fat. Visceral fat was distinguished from subcutaneous abdominal fat by tracing along the fascial plane defining the internal wall.

4. Statistical analysis

Student t test or 1-way analysis of variance was used to compare groups for continuous variables, and χ^2 test or Fisher exact test as appropriate was used to compare proportions. Regression analysis was carried out using serum visfatin as the independent variable. Multiple logistic regression was done to analyze the association between visfatin, type 2 diabetes mellitus, and obesity. Odds ratios (ORs) were calculated per nanogram per milliliter increase of visfatin. All analyses were done using Windows-based SPSS statistical package (Version 10.0, SPSS, Chicago, IL) and $P < .05$ was taken as significant. The results are expressed as mean $\pm$ SD. Most of the individuals had complete information except for fasting insulin, which was absent in 5 individuals, and HbA_{1c} in 2 subjects; LDL

cholesterol was not calculated in 2 subjects who had triglyceride values more than 400.

5. Results

The general characteristics of the study groups are shown in Table 1. In men, BMI ($P < .001$), waist circumference ($P < .001$), fasting plasma glucose ($P < .001$), HbA_{1c} ($P < .001$), total cholesterol ($P < .001$), serum triglycerides ($P < .001$), fasting insulin ($P = .005$), and HOMA-IR ($P < .001$) were significantly higher in the diabetic group compared with the nondiabetic group. In women, BMI ($P < .001$), waist circumference ($P < .001$), fasting plasma glucose ($P < .001$), HbA_{1c} ($P < .001$), serum triglycerides ($P < .001$), fasting insulin ($P = .001$), and HOMA-IR ($P < .001$) were significantly higher in diabetic subjects compared with nondiabetic subjects.

The mean serum visfatin level in the study group was 10.5 ± 5.2 ng/mL and no gender differences were observed (men, 10.6 ± 5.3 ng/mL; women, 10.4 ± 5.1 ng/mL; $P = .775$). Serum visfatin levels were significantly higher in the diabetic group compared with the nondiabetic group (11.4 ± 5.9 [diabetic] vs 9.8 ± 4.3 [nondiabetic] ng/mL; $P = .008$). The male diabetic subjects had significantly higher serum visfatin levels (11.5 ± 6.2 [diabetic] vs 9.7 ± 4.1 [nondiabetic] ng/mL; $P = .033$), but the significance was lost when adjusted for BMI. The difference in serum visfatin levels did not reach statistical significance in women (11.2 ± 5.5 [diabetic] vs 9.8 ± 4.6 [nondiabetic] ng/mL; $P = .093$).

Within the nondiabetic group, serum visfatin levels were significantly higher in obese (10.4 ± 4.7 ng/mL) compared with nonobese (9.0 ± 3.8 ng/mL, $P = .048$) individuals and the significance was maintained even after adjusting for age and sex (OR, 1.086; 95% confidence interval [CI], 1.003-1.176; $P = .042$). There was no significant difference between serum visfatin levels among the newly diagnosed (12.0 ± 6.6 ng/mL) and the known diabetic subjects who were on treatment (10.9 ± 5.4 ng/mL, $P = .270$).

Table 2
Univariate and multivariate regression analysis using serum visfatin as independent variable and clinical and biochemical parameters as dependent variables

Parameter	β_1	β_2	β_3
	Visfatin	Visfatin adjusted for age and sex	Visfatin adjusted for age, sex, and type 2 diabetes
BMI	0.178**	0.181**	0.180*
Waist	0.364**	0.363**	0.251*
Fasting plasma glucose	1.450	1.561	0.047
Systolic blood pressure	0.254	0.256	0.213
Diastolic blood pressure	0.037	0.035	0.018
Total cholesterol	0.085	0.095	−0.157
Serum triglycerides	1.551	1.522	0.563
LDL cholesterol	−0.155	−0.158	−0.256
HDL cholesterol	−0.055	−0.047	−0.089
Fasting Insulin	0.101	0.104	0.034
HOMA-IR	0.076**	0.071**	0.038

* $P < .05$.
** $P < .01$.

Table 2 shows the univariate and multivariate regression using serum visfatin as independent variable and various clinical and biochemical parameters as dependent variables. BMI ($P < .05$) and waist circumference ($P < .05$) showed a significant association with serum visfatin even after adjusting for age, sex, and type 2 diabetes mellitus. Although serum visfatin levels showed a significant correlation with HOMA-IR ($r = 0.163$, $P = .006$), the significance was lost when adjusted for type 2 diabetes mellitus. When analyzed separately, there was no significant association of visfatin with HOMA-IR in the nondiabetic group ($r = 0.008$, $P = .920$) or in the diabetic group ($r = 0.126$, $P = .143$). There

Table 1
General characteristics of the study groups

Parameter	Men (n = 150)			Women (n = 150)		
	Nondiabetic group (n = 75)	Diabetic group (n = 75)	P	Nondiabetic group (n = 75)	Diabetic group (n = 75)	P
Age (y)	45 ± 13	46 ± 9	.586	45 ± 12	45 ± 9	.891
BMI (kg/m^2)	23.4 ± 5.0	26.9 ± 4.7	<.001	25.7 ± 5.6	28.4 ± 4.5	<.001
Waist circumference (cm)	87 ± 12	96 ± 11	<.001	88 ± 13	95 ± 10	<.001
Systolic blood pressure (mm Hg)	122 ± 14	126 ± 18	.057	124 ± 18	128 ± 18	.163
Diastolic blood pressure (mm Hg)	77 ± 10	79 ± 10	.386	76 ± 12	78 ± 12	.365
Fasting plasma glucose (mg/dL)	85 ± 9	154 ± 56	<.001	86 ± 9	169 ± 66	<.001
HbA_{1c} (%)	5.5 ± 0.5	8.8 ± 2.1	<.001	5.7 ± 0.5	8.9 ± 2.1	<.001
Total cholesterol (mg/dL)	175 ± 42	200 ± 41	<.001	189 ± 36	200 ± 44	.104
Serum triglycerides[a]	102	162	<.001	105	145	<.001
LDL cholesterol (mg/dL)	109 ± 35	120 ± 40	.090	118 ± 31	122 ± 31	.544
HDL cholesterol (mg/dL)	43 ± 10	40 ± 9	.310	47 ± 11	44 ± 10	.069
Fasting insulin (μIU/mL)	7.6 ± 5.4	10.3 ± 6.1	.005	8.9 ± 5.6	12.6 ± 7.5	.001
HOMA-IR	1.6 ± 1.2	3.9 ± 2.5	<.001	1.9 ± 1.3	4.9 ± 3.1	<.001
Serum visfatin (ng/mL)	9.7 ± 4.1	11.5 ± 6.2	.033	9.8 ± 4.6	11.2 ± 5.5	.093

[a] Data expressed as geometric mean.

Table 3
Multiple logistic regression analysis with obesity and type 2 diabetes mellitus as dependent variables

	β	OR[a] (95% CI)	P
Dependent variable: obesity			
Serum visfatin (unadjusted)	.068	1.071 (1.017-1.127)	.009
Adjusted for age and sex	.071	1.074 (1.019-1.131)	.007
Adjusted for age, sex, and type 2 diabetes mellitus	.059	1.060 (1.005-1.119)	.033
Dependent variable: type 2 diabetes mellitus			
Serum visfatin (unadjusted)	.063	1.065 (1.015-1.117)	.010
Adjusted for age and sex	.063	1.065 (1.016-1.118)	.010
Adjusted for age, sex, and BMI	.047	1.048 (0.997-1.101)	.067
Adjusted for age, sex, and waist circumference	.049	1.050 (0.999-1.104)	.057

[a] Odds ratios were calculated per nanogram per milliliter increase of visfatin.

was no association between serum visfatin levels and any other clinical or biochemical parameter.

Multiple logistic regression analysis (Table 3) showed that serum visfatin was significantly associated with obesity even after adjusting for age, sex, and type 2 diabetes mellitus (OR, 1.060; 95% CI, 1.005-1.119; $P = .033$). There was a significant association of serum visfatin with type 2 diabetes mellitus (OR, 1.065; 95% CI, 1.015-1.117; $P = .010$) but the significance was lost when adjusted for BMI (OR, 1.048; 95% CI, 0.997-1.101;$P = .067$) or waist circumference (OR, 1.050; 95% CI, 0.999-1.104; $P = .057$).

There were no major differences in the demographic and clinical parameters in the subjects who participated in the CT study compared with the nonparticipants. Serum visfatin levels were not significantly different in subjects who underwent CT scan compared with nonparticipants in both the nondiabetic (9.7 ± 4.4 vs 9.8 ± 4.3 ng/mL, $P = .895$) and the diabetic group (10.9 ± 5.6 to 11.6 ± 6.0 ng/mL, $P = .831$).

The visceral (128.6 ± 61.6 vs 144.8 ± 66.8 cm^2, $P = .153$) or the subcutaneous fat (218.0 ± 136.17 vs 227.5 ± 102.1 cm^2, $P = .657$) did not show any significant difference between the nondiabetic and the diabetic groups. Univariate and multivariate linear regression analysis (Table 4) showed that visceral fat was significantly associated with serum visfatin levels even after adjusting for age, sex, type 2 diabetes mellitus, and BMI ($P = .002$). However, there was no association between serum visfatin and subcutaneous fat.

6. Discussion

Visfatin corresponds to pre-B cell colony–enhancing factor, a 52-kd cytokine secreted by activated lymphocytes [18] and is up-regulated in neutrophils and monocytes after exposure to inflammatory stimuli [19-21]. Earlier reports have raised questions regarding the origin and clinical relevance of visfatin, as it is ubiquitously expressed in different cell types [19,22-28]. However, recent studies support the view that visfatin is a true adipokine that is clearly expressed in human adipocytes [7,29,30]. It was also shown that hyperglycemia induced visfatin overexpression in cultured human adipocytes [29]. There have been contradictory findings on the association between visfatin and obesity. Haider et al [31] showed that visfatin levels were substantially increased in morbidly obese individuals and gastric banding surgery lowered the circulating visfatin levels in them. However, a recent study showed that the plasma levels of visfatin were significantly lower in obese subjects [30].

In the current study, we found that serum visfatin levels were significantly higher in the diabetic compared with the nondiabetic group, but the significance was lost after adjusting for BMI. Similar findings were reported in an earlier study [11], which had suggested that the increased circulating levels and messenger RNA expression of visfatin in the diabetic subjects may be related to their increased adipose tissue mass. We found that serum visfatin levels showed a significant positive correlation with BMI and waist circumference even after adjusting for age, sex, and type 2 diabetes mellitus. Again, serum visfatin levels were significantly associated with obesity as defined by the modified Adult Treatment Panel III guidelines, and this association persisted even after adjusting for the diabetic status. This finding supports the studies by Berndt et al [10] and Haider et al [31] that visfatin is associated with obesity. Contrary to Berndt et al, we found that visfatin was significantly correlated with waist circumference, suggesting that in Asian Indians visfatin is also associated with abdominal obesity.

It is still unclear whether circulating visfatin levels are associated with increased visceral fat mass or increased total fat mass as suggested by Berndt et al [10]. Although Fukuhara et al [8] demonstrated that visfatin is predominantly expressed in visceral adipose tissue, Berndt et al [10] did not find an association between plasma visfatin and visceral fat area. A recent study demonstrated visfatin messenger RNA may be differentially regulated in subcutaneous abdominal and visceral fat [30]. We looked at the association of visceral and subcutaneous abdominal fat with serum visfatin levels in a subset of the study group. Visceral

Table 4
Linear regression analysis with serum visfatin as dependent variable and visceral and subcutaneous fat as independent variables

	β	P
Visceral fat (unadjusted)	.026	<.001
Adjusted for age and sex	.030	<.001
Adjusted for age, sex, type 2 diabetes mellitus, and BMI	.023	.002
Subcutaneous fat (unadjusted)	.006	.115
Adjusted for age and sex	.007	.123
Adjusted for age, sex, type 2 diabetes mellitus, and BMI	.004	.402

fat showed a significant association with serum visfatin levels even after adjusting for age, sex, type 2 diabetes mellitus, and BMI, whereas subcutaneous fat did not show an association with serum visfatin levels. This study thus supports the report by Fukuhara et al [8] that visfatin is associated with visceral fat but not subcutaneous fat.

Although there is no clear evidence for the exact cellular role of visfatin, a recent review suggests that visfatin could have autocrine and paracrine functions in the differentiation of adipocytes and may also have an endocrine function in modulating insulin action at the peripheral tissues [9]. In vitro studies on 3T3 L1 adipocytes and L6 monocytes revealed that visfatin increased glucose transport and lipogenesis [7], which supported experimental studies on the insulin mimetic effect of visfatin and hyperglycemia observed in mice heterozygous for a target mutation in visfatin gene [7]. Furthermore, it was also hypothesized that visfatin may be released from dying adipocytes, raising the possibility that it may be released through apoptosis of adipocytes rather than some direct metabolic or mechanistic effect [32]. Hence, there is controversy about the association of visfatin with metabolic abnormalities.

We did not find an association of serum visfatin with insulin resistance as measured by HOMA-IR. This finding is in contrast to that of Chen et al [8] but supports other studies that showed a lack of association between visfatin and insulin resistance [10,11,30]. Moreover, we did not find an association of serum visfatin with any of the lipid parameters. The limitation of this study is that being a cross-sectional study, it cannot explain the causal relationship between visfatin and obesity.

In summary, we report that in Asian Indians, serum visfatin levels are associated with obesity and visceral fat but not with subcutaneous fat. Although visfatin levels are also increased in type 2 diabetes mellitus, the association seems to be primarily through obesity and not with diabetes per se. Further studies are needed to elucidate the mechanisms behind visfatin overexpression in humans.

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