Plasma Level of Pigment Epithelium-Derived Factor Is Independently Associated with the Development of the Metabolic Syndrome in Chinese Men: A 10-Year Prospective Study

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Objective: Pigment epithelium-derived factor (PEDF), a serine protease inhibitor, is secreted from the adipose tissue and circulates at high concentrations. A recent study found that PEDF played a causal role in obesity-induced insulin resistance and metabolic dysfunctions in mice. Here we investigated whether circulating PEDF levels predicted the development of the metabolic syndrome (MetS) in a 10-yr prospective study.

Research Design and Methods: Baseline plasma PEDF levels were measured with an ELISA in 520 nondiabetic subjects, recruited from the Hong Kong Cardiovascular Risk Factor Prevalence Study cohort. Multiple logistic regression was used to analyze whether PEDF was an independent factor related to the MetS at baseline. The role of PEDF in predicting the development of the MetS over 10 yr was analyzed using Cox regression analysis.

Results: Plasma levels of PEDF were significantly higher in men than women. At baseline, sex-adjusted PEDF levels were significantly higher in subjects with MetS ($P < 0.001$), and the association remained significant (odds ratio: 1.17, $P = 0.015$), even after adjustment for covariates. Among the components of the MetS, PEDF was independently associated with hypertriglyceridemia ($P = 0.026$) and hypertension ($P = 0.005$). Of the 396 subjects without the MetS at baseline, a total of 80 had developed the MetS over 10 yr. High baseline sex-adjusted PEDF was an independent predictor of the development of the MetS in men (hazard ratio: 1.25, $P = 0.034$) but not in women.

Conclusion: Plasma PEDF was significantly associated with the presence of the MetS and predicted the development of the MetS in Chinese men. **(*J Clin Endocrinol Metab* 95: 5074–5081, 2010)**

Pigment epithelium-derived factor (PEDF) is a 50-kDa secreted glycoprotein, which was first identified in the conditioned medium of cultured human fetal retinal pigment epithelial cells (1, 2) and shown to be a potent inhibitor of angiogenesis in cell culture and animal models (3). Early studies on PEDF have focused on its antiangiogenic functions in diabetic vascular complications (4–7), and PEDF has been proposed as a local protective factor against diabetic retinopathy and nephropathy. More recently, PEDF has been shown to be a *bona fide* adipocyte-secreted factor involved in glucose and lipid metabolism (8). Crowe *et al.* (8) reported that adipocyte PEDF expres-

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Abbreviations: BMI, Body mass index; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment index for insulin resistance; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; OR, odds ratio; PEDF, pigment epithelium-derived factor; WC, waist circumference.

sion and serum levels were elevated in several rodent models of obesity and were reduced on weight loss. Furthermore, they made the original observation that adipocytes make an important contribution to circulating levels of this factor, providing support for PEDF as another adipokine with dysregulated expression in obesity. Acute PEDF administration caused insulin resistance in both muscle and liver through activating the proinflammatory serine/threonine kinases c-Jun terminal kinase, with corresponding reductions in insulin signal transduction and impaired glucose tolerance *in vivo*. Prolonged PEDF administration in lean mice caused enhanced lipolysis, ectopic lipid deposition, and insulin resistance, whereas neutralization with its selective antibody in obese mice enhanced insulin sensitivity. These results identified PEDF as an adipokine that played a causal role in obesity-induced insulin resistance and glucose intolerance in mouse models. Such findings, together with clinical studies reporting increased circulating levels of PEDF in subjects with type 2 diabetes (9, 10) and the metabolic syndrome (MetS) (11), suggest that PEDF might play a pathogenetic role in these obesity-related metabolic disorders in humans. However, previous clinical studies on PEDF (9–11) were cross-sectional in nature and would not allow for any conclusion regarding causality.

The findings regarding the metabolic actions in rodents and circulating levels in humans of PEDF are in striking contrast to that of a well-known adipokine, adiponectin, which is insulin sensitizing and levels are reduced in obesity; type 2 diabetes; and MetS (12). Because low levels of adiponectin have been found to predict the development of MetS (12, 13), it is tempting to speculate that high circulating levels of PEDF may also predict the development of the obesity-related MetS. In this study, we tried to establish the clinical relevance of the animal findings of Crowe *et al.* (8) in our cohort, investigate whether serum PEDF was independently associated with MetS, and investigate whether it could predict the development of this syndrome in a long-term prospective study involving a population-based cohort comprising 520 Chinese subjects. All subjects were recruited from the Hong Kong Cardiovascular Risk Factor Prevalence Study and had completed their 10-yr follow-up (14).

Subjects and Methods

Participants

Subjects were recruited from the population-based Cardiovascular Risk Factor Prevalence Study (15). Briefly, between 1995 and 1996, 2843 unrelated subjects, aged 25–74 yr [at least 200 subjects in each 10-yr group (25–34, 35–44, 45–54, 55–64, and 65–74 yr), as recommended by the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease projects (16)] were recruited from the general population using random telephone numbers (17) to participate in a population-based study to assess the prevalence of cardiovascular risk factors in a southern Chinese population. Of the 2843 subjects who participated in the cross-sectional study in 1995–1996, 684 nondiabetic subjects (as defined by 1998 World Health Organization diagnostic criteria) were subsequently invited to participate in a long-term prospective study to assess the progression of diabetes and other cardiovascular risk factors as reported previously (14, 18). Subjects taking regular lipid-lowering agents without an available pretreatment lipid profile were excluded from analysis. This report included data from 520 subjects with available stored plasma samples for measurement of baseline PEDF, who were not on lipid-lowering drugs at baseline and had returned for the 10-yr follow-up assessment. Among these, 239 subjects (46%) had impaired glucose tolerance at baseline. There was no significant difference in baseline characteristics between these subjects and those who did not fulfill the inclusion criteria (n = 164; data not shown).

Measurements

MetS

MetS and its component metabolic risk factors are defined according to the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (19). MetS was defined as having three or more of the following metabolic risk factors: 1) central obesity (waist circumference ≥80 cm in women and ≥90 cm in men), 2) hypertriglyceridemia (fasting triglycerides ≥1.7 mmol/liter), 3) low high-density lipoprotein (HDL) cholesterol (fasting HDL <1.3 mmol/liter in women and 1.0 mmol/liter in men), 4) glucose intolerance (fasting glucose ≥5.6 mmol/liter or already on oral hypoglycemic agents for treatment of type 2 diabetes), and 5) hypertension (sitting blood pressure ≥130/85 mm Hg obtained as a mean of two readings taken after resting for at least 10 min or on regular antihypertensive medication).

Clinical and biochemical assessments

Subjects returned at 10 yr for reassessment but were under the care of their own primary care physicians between visits. Subjects attended each visit after an overnight fast of at least 10 h. Details of anthropometric measurements [height, weight, body mass index (BMI), waist circumference (WC), and blood pressure] and the methods for measuring the biochemical variables [fasting and 2 h glucose during a 75 g oral glucose tolerance test (OGTT), insulin, triglycerides, low density lipoprotein (LDL), and HDL cholesterol] were reported previously (15). Insulin resistance was estimated with the homeostasis model assessment index (HOMA-IR), calculated as fasting glucose (in millimoles per liter) times fasting insulin (in milliinternational units per liter) divided by 22.5 (20). High-sensitivity C-reactive protein (hsCRP) was measured with particle-enhanced immunoturbidimetric assay (Roche Diagnostics, GmbH, Mannheim, Germany) using anti-C-reactive protein mouse monoclonal antibodies coupled to latex microparticles. Adiponectin was measured with an in-house sandwich ELISA established in our labora-

tory. PEDF was measured with an ELISA (BioVendor Laboratory Medicine, Inc., Modrice, Czech Republic), with calibration and quality control performed as previously reported (21). All subjects gave informed consent, and the present study was approved by the Ethics Committee of the Faculty of Medicine, University of Hong Kong.

Statistical analysis

Statistical analysis was performed with SPSS version 16.0 (SPSS, Inc., Chicago, IL). Results are presented as mean ± SD or median with interquartile range as appropriate. Data that were not normally distributed, as determined with the Kolmogorov-Smirnov test, were logarithmically transformed to obtain near normality before analysis. PEDF and adiponectin levels were sex adjusted in all analyses because of the different levels of these proteins between men and women (11, 21). The χ^2 test and one-way ANOVA were used for comparisons between two groups, for categorical and continuous variables, respectively. Multiple testing was corrected with Bonferroni correction. Correlations between PEDF and anthropometric and biochemical variables were analyzed with Pearson correlation. To determine the parameters independently associated with PEDF levels, parameters including age, gender, and significant correlates with PEDF in bivariate analyses were tested in stepwise linear regression analysis. Logistic regression analyses were used to examine the association of baseline PEDF and other biologically relevant parameters with MetS or each component of MetS at baseline. The variables selected to enter into multiple logistic regression were variables that were significantly different, after Bonferroni correction, between subjects with and without the MetS or each component of MetS at baseline. MetS-defining parameters were not included in the multiple logistic regression model. In the prospective study, to identify independent predictors of the development of MetS over 10 yr, baseline variables that were significantly different between subjects with and without MetS during 10 yr follow-up (after Bonferroni correction) and were biologically likely to be related with MetS were analyzed using multiple Cox regression. Odds ratio (OR) per SD was used to show the relative strength of relationship. The prospective study included only the 396 subjects without MetS at baseline. Two-sided values of $P < 0.05$ were considered significant.

Results

Plasma PEDF and clinical parameters at baseline

At baseline, 124 of the 520 subjects had the MetS. The baseline clinical characteristics of the cohort are summarized in Table 1. As expected, subjects with MetS at baseline had significantly more adverse risk factors than those without the MetS, including higher age, BMI, and fasting insulin, in addition to MetS-defining parameters (waist circumference, fasting glucose, triglycerides, hypertension, and low HDL cholesterol) ($P < 0.001$ for all parameters). They also had higher hsCRP and lower serum adiponectin levels (both $P < 0.001$). Plasma levels of PEDF in men were significantly higher than in women. For women, but not men, PEDF levels were significantly higher in subjects aged 50 yr or older (8.39 ± 2.36 *vs.* 7.4 ± 1.8 μg/ml in women <50 yr; $P < 0.001$). In men, serum PEDF levels were 8.95 ± 2.13 *vs.* 8.99 ± 2.05 μg/ml for subjects aged

TABLE 1. Baseline clinical parameters of subjects according to presence or absence of MetS at baseline

	MetS	Non-MetS	*P* value
n	124	396	
Age (yr)	55.5 ± 11.1	50 ± 12.4	<0.001
Sex (men/women)	57/67	172/224	0.679
BMI (kg/m^2)	27.9 ± 3.4	23.7 ± 3.5	<0.001
Waist circumference (cm)			
Men	94.2 ± 8.3	81.2 ± 7.6	<0.001[a]
Women	87.3 ± 6.7	74.8 ± 7.8	
Systolic blood pressure (mm Hg)[b]	137 ± 17.6	118 ± 16.2	<0.001
Diastolic blood pressure (mm Hg)[b]	83 ± 9.7	73 ± 8.9	<0.001
Fasting glucose (mmol/liter)	5.6 ± 0.5	5.1 ± 0.5	<0.001
Insulin (mIU/liter)[c]	7.8 (5.3–10.7)	4.6 (3.2–6.8)	<0.001
HOMA-IR[c]	2.0 (1.2–2.7)	1.1 (0.7–1.6)	<0.001
LDL cholesterol (mmol/liter)	3.6 ± 0.9	3.3 ± 0.9	<0.001
HDL cholesterol (mmol/liter)	1.0 ± 0.2	1.3 ± 0.3	<0.001
Triglycerides (mmol/liter)[c]	1.8 (1.4–2.4)	0.9 (0.7–1.3)	<0.001
hsCRP (mg/liter)[c]	1.7 (0.8–3.0)	0.8 (0.3–1.8)	<0.001
Adiponectin (μg/ml)[c]			
Men	4.3 (2.9–5.8)	5.7 (3.7–7.7)	<0.001[a]
Women	5.1 (3.7–7.6)	6.7 (5.0–9.2)	
PEDF (μg/ml)			
Men	10.0 ± 2.5	8.6 ± 1.8	<0.001[a]
Women	9.4 ± 2.5	7.4 ± 1.8	

Data are mean ± SD or median (interquartile range).

[a] Age- and sex-adjusted *P* value.

[b] Excluded 53 subjects taking antihypertensive medications.

[c] Log transformed before analysis.

TABLE 2. Anthropometric and biochemical parameters showing significant correlations with plasma PEDF concentration

	Univariate[a]		Multivariate (model includes BMI)[b]		Multivariate (model includes WC)[c]	
	β	*P* value	β	*P* value	β	*P* value
Age	0.170	<0.001				
Sex (female)	−0.251	<0.001	−0.198	<0.001	−0.128	<0.001
Waist circumference (cm)	0.467	<0.001			0.187	<0.001
BMI (kg/m^2)	0.400	<0.001	0.263	<0.001		
Systolic blood pressure (mm Hg)	0.346	<0.001	0.166	<0.001	0.166	0.001
Diastolic blood pressure (mm Hg)	0.345	<0.001				
Mean arterial pressure (mm Hg)	0.364	<0.001				
Triglycerides (mmol/liter)[d]	0.434	<0.001	0.212	<0.001	0.199	<0.001
HDL cholesterol (mmol/liter)	−0.209	<0.001				
LDL cholesterol (mmol/liter)	0.141	0.001				
Fasting glucose (mmol/liter)	0.245	<0.001				
2-h postprandial glucose (mmol/liter)	0.233	<0.001	0.080	0.041	0.085	0.032
Fasting insulin (mIU/liter)[d]	0.286	<0.001			0.089	0.038
HOMA-IR[d]	0.311	<0.001				
Adiponectin (μg/ml)[d]	−0.192	<0.001				

β, Standardized regression coefficients.

[a] Univariate coefficients.

[b] A stepwise multivariate regression analysis was performed. Variables included in the original model are age, sex, BMI, systolic blood pressure, triglycerides, HDL, LDL, fasting glucose, 2-h postprandial glucose, fasting insulin, and adiponectin.

[c] A stepwise multivariate regression analysis was performed. Variables included in the original model are age, sex, WC, systolic blood pressure, triglycerides, HDL, LDL, fasting glucose, 2-h postprandial glucose, fasting insulin, and adiponectin.

[d] Log transformed before analysis.

50 yr old or older and younger than 50 yr, respectively. In addition, the plasma concentration of PEDF was significantly higher in subjects with MetS in both sexes (10.0 ± 2.5 *vs.* 8.6 ± 1.8 μg/ml in men and 9.4 ± 2.5 *vs.* 7.4 ± 1.8 μg/ml in women, MetS *vs.* non-MetS, age and sex-adjusted $P < 0.001$) (Table 1).

Univariate analysis revealed significant correlations between PEDF and BMI or WC (both $P < 0.001$). On multiple linear regression analysis (Table 2), PEDF was significantly correlated with triglycerides and systolic blood pressure level (both $P < 0.001$). Partial correlation analysis showed that the significant correlation between PEDF and adiponectin ($P < 0.001$ in univariate analysis) remained unchanged after adjustment for age, sex, or fasting glucose but was attenuated after adjustment for BMI ($P = 0.01$), insulin ($P = 0.012$), or HOMA-IR ($P = 0.027$) and abolished after adjustment for WC ($P = 0.121$). In a stepwise multiple linear regression analysis, sex ($P < 0.001$), BMI ($P < 0.001$), triglycerides ($P < 0.001$), systolic blood pressure ($P < 0.001$), and 2-h OGTT glucose ($P = 0.043$) were independently related to plasma PEDF levels. Similar findings were obtained if WC was included in the model instead of BMI (Table 2).

Plasma PEDF was independently associated with the MetS at baseline

In multiple logistic regression analysis, PEDF (OR 1.17; 95% confidence interval (CI) 1.03–1.33; $P = 0.015$) was independently associated with the presence of the MetS at baseline, together with age ($P < 0.001$), BMI ($P < 0.001$), insulin ($P < 0.001$), and adiponectin ($P = 0.002$) (Table 3). Based on the OR per SD, it would appear that in its independent association with the MetS, PEDF was not as strong as age or adiposity but comparable with the other adipokine, adiponectin.

Five components contribute to the diagnosis of MetS: central obesity, hypertriglyceridemia, low HDL cholesterol, glucose intolerance, and hypertension. We further investigated which components of the MetS were closely associated with PEDF. Multiple logistic regression analysis showed that sex-adjusted PEDF was independently associated with hypertriglyceridemia (OR 1.15; 95% CI 1.02–1.30; $P = 0.026$) and hypertension (OR 1.18; 95% CI 1.05–1.32; $P = 0.005$) among the components of the MetS.

TABLE 3. Multiple logistic regression analysis showing factors independently associated with MetS at baseline

Parameters	OR	95% CI	*P* value	OR per SD[a]
Age	1.07	1.04–1.10	<0.001	2.28
BMI	1.31	1.20–1.43	<0.001	2.86
Insulin[b]	2.50	1.50–4.16	<0.001	1.74
Adiponectin[b]	0.45	0.27–0.75	0.002	0.65
PEDF	1.17	1.03–1.33	0.015	1.42

Variables included in the original model are age, sex, BMI, insulin, hsCRP, adiponectin, and PEDF.

[a] OR per SD.

[b] Log transformed before analysis.

TABLE 4. Baseline clinical parameters of subjects who had or had not developed MetS by 10 yr

	MetS	Non-MetS	*P* value
n	80	316	
Age (yr)	52 ± 11.7	49 ± 12.5	0.045
Sex (men/women)	34/46	138/178	0.900
BMI (kg/m^2)	25.7 ± 3.6	23.2 ± 3.2	<0.001
Waist circumference (cm)			
Men	87.0 ± 7.0	79.8 ± 7.1	<0.001[a]
Women	79.3 ± 6.7	73.6 ± 7.7	
Central obesity (%)[b]	18.8	3.8	<0.001
Systolic blood pressure (mm Hg)[c]	120 ± 15.8	117 ± 16.3	0.135
Diastolic blood pressure (mm Hg)[c]	75 ± 9.4	73 ± 8.7	0.082
Hypertension (%)[b]	23.8	20.8	0.551
Fasting glucose (mmol/liter)	5.2 ± 0.5	5.1 ± 0.5	0.104
Glucose intolerance (%)[b]	21.3	13.6	0.066
Insulin (mIU/liter)[d]	5.9 (3.7–7.9)	4.3 (3.0–6.5)	<0.001
HOMA-IR[d]	1.4 (0.8–1.9)	1.0 (0.7–1.4)	<0.001
LDL cholesterol (mmol/liter)	3.5 ± 0.8	3.2 ± 0.9	0.003
HDL cholesterol (mmol/liter)	1.2 ± 0.2	1.4 ± 0.3	<0.001
Low HDL cholesterol (%)[b]	66.3	38.2	<0.001
Triglycerides (mmol/liter)[d]	1.2 (0.9–1.6)	0.9 (0.6–1.2)	<0.001
Hypertriglyceridemia (%)[b]	16.3	4.7	0.002
hsCRP (mg/liter)[d]	1.2 (0.6–3.2)	0.7 (0.3–1.6)	<0.001
Adiponectin (μg/ml)[d]			
Men	5.7 (3.1–7.8)	5.7 (3.7–7.7)	0.084[a]
Women	6.5 (4.7–8.8)	6.7 (5.0–9.7)	
PEDF (μg/ml)			
Men	9.3 ± 1.5	8.4 ± 1.9	<0.001[a]
Women	8.1 ± 1.7	7.2 ± 1.8	

Data are mean ± SD or median (interquartile range).

[a] Age- and sex-adjusted *P* value.

[b] Refer to the criteria for clinical diagnosis of the MetS.

[c] Excluded 15 subjects taking antihypertensive medications.

[d] Log transformed before analysis.

Plasma PEDF was a predictor for development of the MetS over 10 yr in men but not women

Among the 396 subjects who did not have MetS at baseline, a total of 80 subjects (20.2%) had developed MetS during the 10-yr follow up (26 new cases by 2 yr, another 30 by 5 yr, and a further 24 by 10 yr). The clinical parameters of subjects who subsequently developed MetS are shown in Table 4. The baseline PEDF concentration was significantly higher in subjects who had developed MetS by yr 10 compared with those who did not (MetS *vs.* non-MetS: 9.3 ± 1.5 *vs.* 8.4 ± 1.9 μg/ml in men; 8.1 ± 1.7 *vs.* 7.2 ± 1.8 μg/ml in women, $P < 0.001$). In addition, subjects who had progressed to MetS over 10 yr had significantly higher baseline BMI ($P < 0.001$), WC ($P < 0.001$), triglycerides ($P < 0.001$), fasting insulin level ($P < 0.001$), LDL cholesterol ($P = 0.003$), and hsCRP ($P < 0.001$) levels and lower HDL cholesterol ($P < 0.001$). These subjects also tended to have lower baseline adiponectin level ($P = 0.084$, sex and age adjusted) (Table 4). Of the components of the MetS, the presence of central obesity ($P < 0.001$), hyperglyceridemia ($P = 0.002$), and low HDL cholesterol ($P < 0.001$) at baseline were significantly higher among those who subsequently developed the MetS.

Independent predictors for the development of MetS were identified using a multiple Cox regression model including the above three MetS components, age, sex, insulin, hsCRP, and PEDF. As shown in Table 5, baseline plasma PEDF [hazard ratio (HR) 1.17; CI 1.03–1.32; $P = 0.015$], age ($P = 0.001$), low HDL cholesterol ($P = 0.001$), hyperglyceridemia ($P = 0.001$), central obesity ($P = 0.009$), and hsCRP ($P = 0.035$) were independent predictors for the development of MetS. Because serum PEDF levels were significantly higher in men, we also performed a subgroup analysis and found that baseline plasma PEDF was a significant independent predictor of the development of MetS in men (HR 1.25; 95% CI 1.02–1.54; $P = 0.034$), together with central obesity, hypertriglyceridemia, and hsCRP. However, PEDF was not an independent factor for the development of MetS in women (Table 5).

Discussion

In this study, we demonstrated for the first time that circulating PEDF level was independently associated with MetS at baseline and was predictive of the development of

TABLE 5. Baseline predictors of the development of MetS over a median 10 yr of follow-up, examined using multiple Cox regression analysis (final model)[a]

Parameters	HR	95% CI	*P* value
All (77/305)			
Age	1.03	1.01–1.06	0.001
Central obesity	2.10	1.20–3.66	0.009
Hypertriglyceridemia	2.96	1.55–5.66	0.001
Low HDL cholesterol	2.36	1.41–3.96	0.001
hsCRP[b]	1.21	1.01–1.45	0.035
PEDF	1.17	1.03–1.32	0.015
Male (32/135)			
Central obesity	4.89	2.07–11.52	<0.001
Hypertriglyceridemia	2.49	1.00–6.17	0.050
hsCRP[b]	1.69	1.21–2.35	0.002
PEDF	1.25	1.02–1.54	0.034
Female (45/170)			
Age	1.05	1.03–1.08	<0.001
Hypertriglyceridemia	2.95	1.11–7.81	0.029
Low HDL cholesterol	2.32	1.23–4.39	0.009

[a] Variables included in original models included age, sex, central obesity, hypertriglyceridemia, low HDL cholesterol, insulin, hsCRP, and PEDF.

[b] Log transformed before analysis.

MetS over 10 yr in men, with the risk being increased by 25% for every 1 μg/ml increment in baseline PEDF. Serum PEDF correlated with several factors closely related to insulin resistance, including BMI, systolic blood pressure, triglycerides, and 2-h OGTT glucose. Therefore, our study is supportive of the findings from the animal-based studies (8) and suggesting that PEDF is not just a biomarker of MetS but might have a causal role in the development of obesity-related MetS in humans.

Previous studies had found higher serum PEDF levels in subjects with type 2 diabetes (9, 10), especially those with proliferative retinopathy (10). PEDF was also elevated in subjects with type 1 diabetes mellitus with microvascular complications (22), raising the possibility that elevated serum PEDF might have occurred as a counterregulatory response to the presence of vascular injury. However, our finding that plasma PEDF predicted the development of MetS, at least in men, suggests a possible role of PEDF in mediating the effect of obesity on insulin resistance, leading to increased risk of MetS and other obesity-related disorders, such as type 2 diabetes, among subjects with high baseline PEDF.

Although PEDF is widely expressed in many tissues (23–26), the adipose tissue has been demonstrated to be the main contributor of circulating PEDF (8). The mRNA and protein expression and secretion of PEDF in adipocytes was increased in obese mice (8). In isolated human omental adipocytes, mRNA expression of PEDF was also found to increase in parallel with the increasing BMI of subjects (27). The close correlation between circulating PEDF and BMI observed in our study is consistent with these findings. Our results are also consistent with previous cross-sectional studies demonstrating positive correlations of PEDF with BMI as well as various obesity- and insulin resistance-related metabolic parameters, including triglycerides, blood pressure, and waist circumference (9, 11, 27). Therefore, PEDF might represent a new class of adipokine that links obesity with its associated medical complications.

Interestingly, the metabolic actions of PEDF in mouse models appear to be completely opposite to that of the better known adipokine, adiponectin, which enhances insulin sensitivity in muscles and liver through the activation of AMP-activated protein kinase and fatty acid oxidation (and hence reducing ectopic fat deposition) (12). In contrast, PEDF reduces insulin sensitivity in muscles and liver via c-Jun N-terminal kinase activation and subsequent reduction of insulin signaling (reduced activation of insulin receptor substrate-1 and Akt) and ectopic fat deposition, through the enhancement of lipolysis (8). In our study, we found a significant inverse relationship between serum levels of PEDF and adiponectin, which, however, was attenuated after adjustment for BMI, hyperinsulinemia, or insulin resistance and abolished after adjustment for WC, suggesting the relationship between these two adipokines to be indirect, occurring secondary to the opposite effect of increased adiposity (8, 12). Hyperinsulinemia, consequent to increased insulin resistance in subjects with PEDF, may also contribute to a reduction in serum adiponectin as hyperinsulinemia has been shown to suppress circulating adiponectin levels in humans during insulin clamp studies (28). We also noted that high PEDF and low adiponectin levels were independent determinants of MetS, of comparable strength, in the cross-sectional baseline study.

Many adipose tissue-derived adipokines display sexual dimorphism, including adiponectin (12), leptin (29), and adipocyte fatty acid binding protein (14, 18). In our study, serum levels of PEDF were significantly higher in men than women. This sexual dimorphism was also found in another study involving subjects recruited from the general population (11). However, the mechanism underlying the sexual dimorphism in PEDF levels remains unknown at this stage. Notably, a recent study suggested that estrogen may be an important upstream regulator of PEDF expression in humans. Treatment of cultured human ovarian surface epithelial cells with 17β-estradiol inhibited the expression of PEDF at a transcriptional level (30), implicating that the lower level of PEDF in women may be due to the suppressive effect of estrogen. Our finding of an increase in circulating levels of PEDF in women over the age of 50 yr, the presumed age of menopause for most women, is in keeping with this hypothesis as circulating levels of estrogen are reduced in the perimenopausal women and become very low after menopause. Further studies are

needed to examine the effects of the sex hormones on circulating levels of PEDF in humans.

In our cohort, PEDF was only predictive of the development of MetS in men and but not women, despite a larger number of women in the cohort. We acknowledge that the number of subjects with incident MetS in each gender subgroup was small, and it remains possible that PEDF may also be predictive of MetS in women in larger cohorts. In addition, another limitation of this study is that this cohort has an overrepresentation of subjects with impaired glucose tolerance and has excluded subjects with preexisting diabetes. Furthermore, we do not have sufficient end points on cardiovascular outcome in these subjects to make meaningful assessment of the role of PEDF in vascular injury or cardiovascular disease.

In summary, plasma PEDF levels correlated with obesity indices and various cardiometabolic risk factors and were significantly associated with MetS. In our prospective study, a high circulating PEDF level was an independent predictive factor of MetS over 10 yr in men, together with central obesity and hypertriglyceridemia at baseline, two components of the MetS previously reported to be important predictors of its development in southern Chinese (31). Whether PEDF may be useful in the prediction of MetS and cardiovascular outcomes in the general population needs to be confirmed in larger population-based prospective studies.

Acknowledgments

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