C1q/TNF-Related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients With Type 2 Diabetes and Metabolic Syndrome

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Recent studies have suggested that a novel adipokine, C1q/tumor necrosis factor-related protein-3 (CTRP-3), a paralog of adiponectin, may play an important role in the regulation of glucose metabolism and innate immunity. Pigment epithelium-derived factor (PEDF), a multifunctional protein with antioxidant and anti-inflammatory properties, is associated with insulin resistance and metabolic syndrome. We examined circulating CTRP-3 and PEDF concentrations in 345 subjects with diverse glucose tolerance statuses. Furthermore, we evaluated the involvement of CTRP-3 and PEDF with cardiometabolic risk factors including insulin resistance, high-sensitivity C-reactive protein (hsCRP), estimated glomerular filtration rate (eGFR), and brachial-ankle pulse wave velocity (baPWV). CTRP-3 concentrations were significantly higher in patients with type 2 diabetes or prediabetes than the normal glucose tolerance group, whereas PEDF levels were not different. Subjects with metabolic syndrome showed significantly higher levels of both CTRP-3 and PEDF compared with subjects without metabolic syndrome. Both CTRP-3 and PEDF were significantly associated with cardiometabolic parameters, including waist-to-hip ratio, triglycerides, HDL-cholesterol, alanine aminotransferase, eGFR, hsCRP, and baPWV. In conclusion, circulating CTRP-3 concentrations were elevated in patients with glucose metabolism dysregulation. Both CTRP-3 and PEDF concentrations were increased in subjects with metabolic syndrome and associated with various cardiometabolic risk factors. ***Diabetes*** **61:2932–2936, 2012**

The concept of ectopic fat storage and adipose tissue dysfunction constitutes a paradigm that links obesity and the risk of developing obesity-related metabolic disorders (1,2). Adiposopathy with hypertrophy phenotype results in a proinflammatory, atherogenic, and diabetogenic adipokine pattern, which causes obesity-related cardiovascular disease (2,3). Recently, a novel adipokine was cloned and named C1q/tumor necrosis factor (TNF)-related protein-3 (CTRP-3), which is structurally closely related to adiponectin (4). CTRP-3 is specifically induced during late adipocyte differentiation and induces the adipocyte secretion of adiponectin and resistin (5). Recently, Peterson et al. (6) reported that recombinant CTRP3 administration significantly lowered glucose levels in normal and insulin-resistant *ob/ob* mice. This antidiabetic effect of CTRP3 is linked to activation of the Akt signaling pathway in the liver and marked suppression of hepatic gluconeogenic enzyme expression (6). CTRP-3 is also produced by monocytes and exerts potent anti-inflammatory properties by reducing interleukin-6 (IL-6) and TNF-α secretion through the suppression of nuclear factor-κB signaling (7). Kopp et al. (8) reported that CTRP-3 specifically and effectively inhibits the binding of lipopolysaccharide to Toll-like receptor 4, which leads to the inhibition of proinflammatory pathways involved in obesity and type 2 diabetes. Inflammation has been known to be a pivotal pathogenic mechanism of type 2 diabetes and atherosclerosis. However, no previous reports have measured circulating CTRP-3 levels in humans with type 2 diabetes or metabolic syndrome. We therefore developed an enzyme-linked immunosorbent assay (ELISA) and applied it to blood samples from humans with diverse glucose tolerance levels.

Pigment epithelium-derived factor (PEDF) is a 50-kDa secreted glycoprotein that has been initially proposed as a potent inhibitor of angiogenesis in cell culture and animal models (9). Recently, Crowe et al. (10) showed that adipocyte PEDF expression and serum levels were elevated in several rodent models of obesity and reduced upon weight loss and insulin sensitization. PEDF can induce insulin resistance through several mechanisms, including the acute activation of proinflammatory serine/threonine kinases and stimulation of adipocyte lipolysis that results in ectopic lipid deposition (10).

In this study, we examined the circulating CTRP-3 and PEDF concentrations in patients with diverse glucose tolerance statuses. Furthermore, we evaluated the influence of CTRP-3 and PEDF on cardiometabolic risk factors such as insulin resistance, inflammation, estimated glomerular filtration rate (eGFR), and brachial-ankle pulse wave velocity (baPWV).

RESEARCH DESIGN AND METHODS

Study subjects. We performed a cross-sectional study using the database information and blood samples obtained from participants in the Korean National Diabetes Program, a prospective, multicenter, observational cohort study. The details of the study design and objectives have been described previously (11). Using predefined inclusion and exclusion criteria, we enrolled subjects with normal glucose tolerance (n = 119), prediabetes (n = 111), and type 2 diabetes

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(n = 119). Assignment to one of the three groups was determined by a 75-g oral glucose tolerance test according to the diagnostic criteria of the American Diabetes Association, which defined impaired fasting glucose (IFG) as a fasting plasma glucose concentration of 100–125 mg/dL and impaired glucose tolerance (IGT) as a 2-h value in the oral glucose tolerance test of 140–199 mg/dL (12). Among the prediabetes group, 77 patients had IFG, 52 patients had IGT, and 18 patients had both IFG and IGT simultaneously. All participants had no history of cardiovascular disease (myocardial infarction, unstable angina, stroke, peripheral artery disease, or cardiovascular revascularization), stage 2 hypertension (resting blood pressure ≥160/100 mmHg), malignancy, or severe renal or hepatic disease. We also excluded subjects with histories of inflammatory conditions or those taking medications that could affect their inflammatory status within 6 months. Metabolic syndrome was defined as having three or more of the metabolic risk factors (13). All participants provided written informed consent, and the Korea University Institutional Review Board, in accordance with the Declaration of Helsinki of the World Medical Association, approved this study protocol.

Development of human CTRP-3 ELISA. A Flag tag was incorporated at the COOH-terminal site of CTRP3. The tagged protein was purified from the conditioned media in 293 cells via an affinity column. For the polyclonal antibody, we only used the NH2-terminal half of the protein encompassing Gln23-Ile185 and then expressed in a pET system (Novagen), because this immunogen seemed to be CTRP-5–specific. Immunoglobulin fractions were prepared. By using optimal concentrations of FLAG-tagged CTRP-3 for both ELISA standard and coating antigen, a competitive ELISA format was designed. Fifty microliters of human serum or plasma in 1:4 dilutions together with a given volume of antibody were applied to each well. Fifty microliters of standards and quality control sample were added to each well, followed by adding 50 μL of the detection antibody and being incubated for 1 h at 37°C. One hundred microliters of 3,3′,5,5′-tetramethylbenzidine was added. Optical density was measured at 450 nm using an ELISA reader within 30 min. The assay sensitivity was 1 ng/mL. Whereas the degree of precision of the ELISA system in terms of the intra-assay coefficient of variance (CV) (%) was between 6.1 and 8.3%, the inter-assay CV was between 2.4 and 8.2%. Spike recovery and linearity were in the range of 85–115% and 96–105%, respectively. Specificity was determined using a major human CTRP family. No cross-reactivity was noted. The same held true for a total of 15 kinds of adipokines or hepatokines (data not shown).

Measurements of clinical variables. Plasma PEDF was measured with an ELISA (Millipore, Billerica, MA), with an intra-assay CV of 5.6% and interassay CV of 6.3%. The GFR was calculated from the Modification of Diet in Renal Disease study equation: (mL/min/1.73 m^2) = 175 × $(Scr)^{-1.154}$ × $(age)^{-0.203}$ × (0.742 if female) (14). baPWV were measured using a Colin Waveform Analyzer (model BP-203RPE II; Colin, Komaki, Japan).

Statistical analyses. Differences between groups were tested using a one-way ANOVA test or the Kruskal-Wallis test for continuous variables. Spearman's partial correlation test was performed to determine the relationships between the CTRP-3 or PEDF levels and other variables. Multiple regression analysis was conducted using CTRP-3 or PEDF as a dependent variable. Data were analyzed using SAS for Windows (version 9.2; SAS Institute Inc., Cary, NC).

RESULTS

The average age of the study subjects was 51.8 ± 10.5 years, and their average BMI was 24.5 ± 3.1 kg/m^2. Plasma CTRP-3 levels significantly increased in patients with type 2 diabetes or prediabetes compared with the control subjects, and there was a trend toward a stepwise increase (516.6 [359.1–787.2], 482.5 [334.2–656.0], and 273.1 [226.2–335.5] ng/mL, respectively; $P < 0.001$) (Fig. 1*A*). However, there was no significant difference in PEDF concentrations between the subject groups (Fig. 1*B*). Subjects with metabolic syndrome showed significantly higher levels of both CTRP-3 (474.0 [313.2–636.4] and 341.3 [241.8–497.2] ng/mL; $P < 0.001$) and PEDF (10.4 [7.9–14.3] and 8.5 [6.7–10.9] μg/mL; $P < 0.001$) compared with subjects without metabolic syndrome (Fig. 2). In addition, women had higher CTRP-3 levels compared with men (433.3 [289.6–694.9] and 357.4 [232.2–489.3] ng/mL; $P < 0.001$). In contrast, plasma PEDF concentrations in women were lower than men (8.4 [6.6–11.3] and 10.5 [8.5–15.3] μg/mL; $P < 0.001$) (Table 1).

In an age- and sex-adjusted Spearman's simple correlation analysis, CTRP-3 levels showed a positive correlation with waist-to-hip ratio (WHR), fasting blood glucose, HbA_{1c}, lipid profiles, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and high-sensitivity C-reactive protein (hsCRP), whereas they exhibited a negative relationship with eGFR (Supplementary Table 1). In contrast, PEDF levels were positively associated with obesity indices, systolic blood pressure, insulin resistance, total cholesterol, triglyceride, ALT, and hsCRP levels, whereas they were negatively associated with HDL-cholesterol and eGFR. Furthermore, both CTRP-3 and PEDF showed a significant positive relationship with baPWV values (Fig. 3).

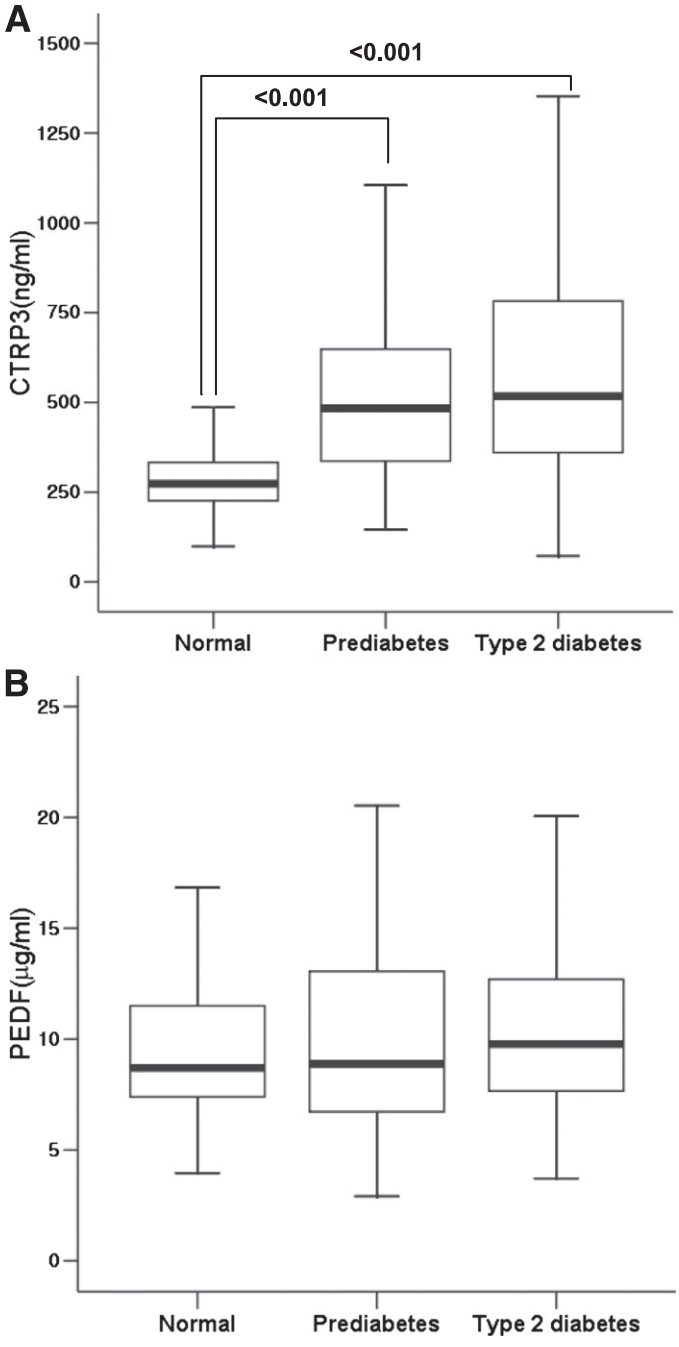

FIG. 1. Difference in plasma CTRP-3 (*A*) and PEDF (*B*) concentrations among normal, prediabetic, and type 2 diabetic subjects.

In a stepwise multiple regression analysis, log-transformed CTRP-3 levels were independently associated with age, sex, eGFR, glucose, AST, and ALT levels (R^2 = 0.244). In contrast, log-transformed PEDF levels were independently associated with sex, BMI, triglyceride, and glucose levels (R^2 = 0.242).

Subjects with a higher tertile of CTRP-3 concentrations exhibited a higher prevalence of type 2 diabetes or prediabetes than those in the lower tertile ($P < 0.001$) (Supplementary Table 2). In addition, sex, WHR, glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, creatinine, eGFR, AST, ALT, hsCRP, and baPWV values significantly changed according to the tertile groups of CTRP-3.

DISCUSSION

CTRP-3 is a newly discovered adipokine, also known as a collagenous repeat-containing sequence of 26-kDa protein, cartonectin, and cartducin and assumed paralog of adiponectin (15). Recently, biological relevance of CTRP-3 as a metabolic regulator of glucose homeostasis was suggested. In this study, plasma CTRP-3 concentrations were significantly higher in patients with type 2 diabetes or prediabetes compared with normal control subjects. Furthermore, subjects with metabolic syndrome also showed increased CTRP-3 levels compared with subjects without metabolic syndrome. This paradoxical increase of plasma CTRP-3 might be a defensive response to counteract the

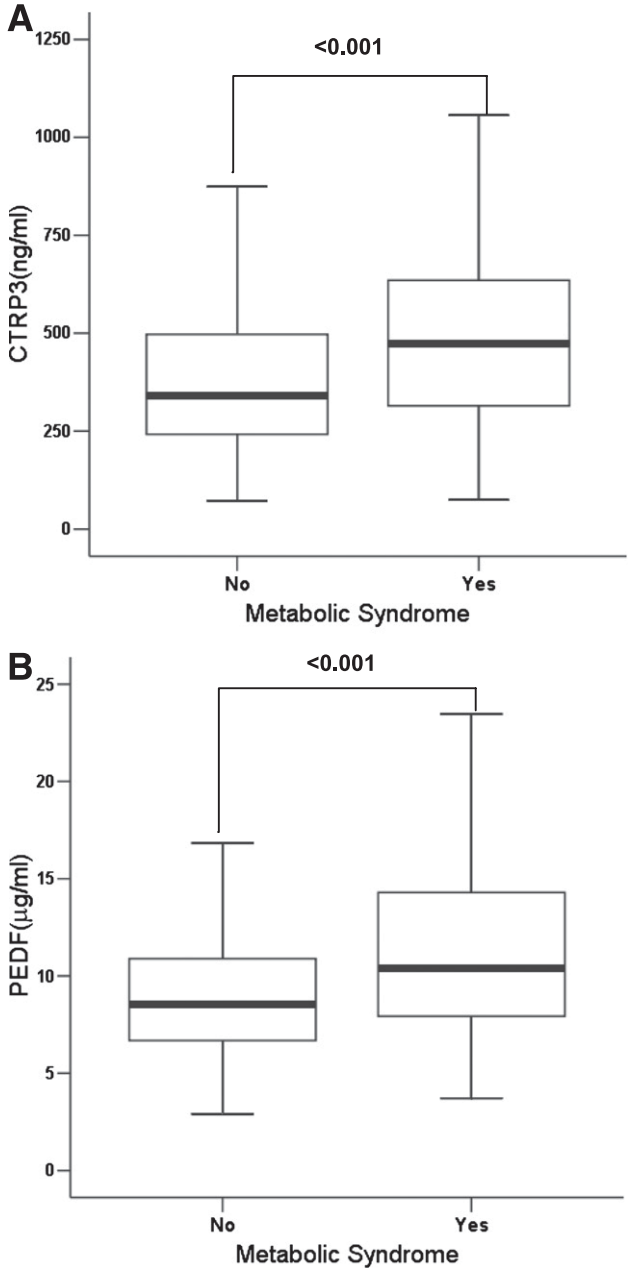

FIG. 2. Difference of plasma CTRP-3 (*A*) and PEDF (*B*) concentrations between subjects with and without metabolic syndrome.

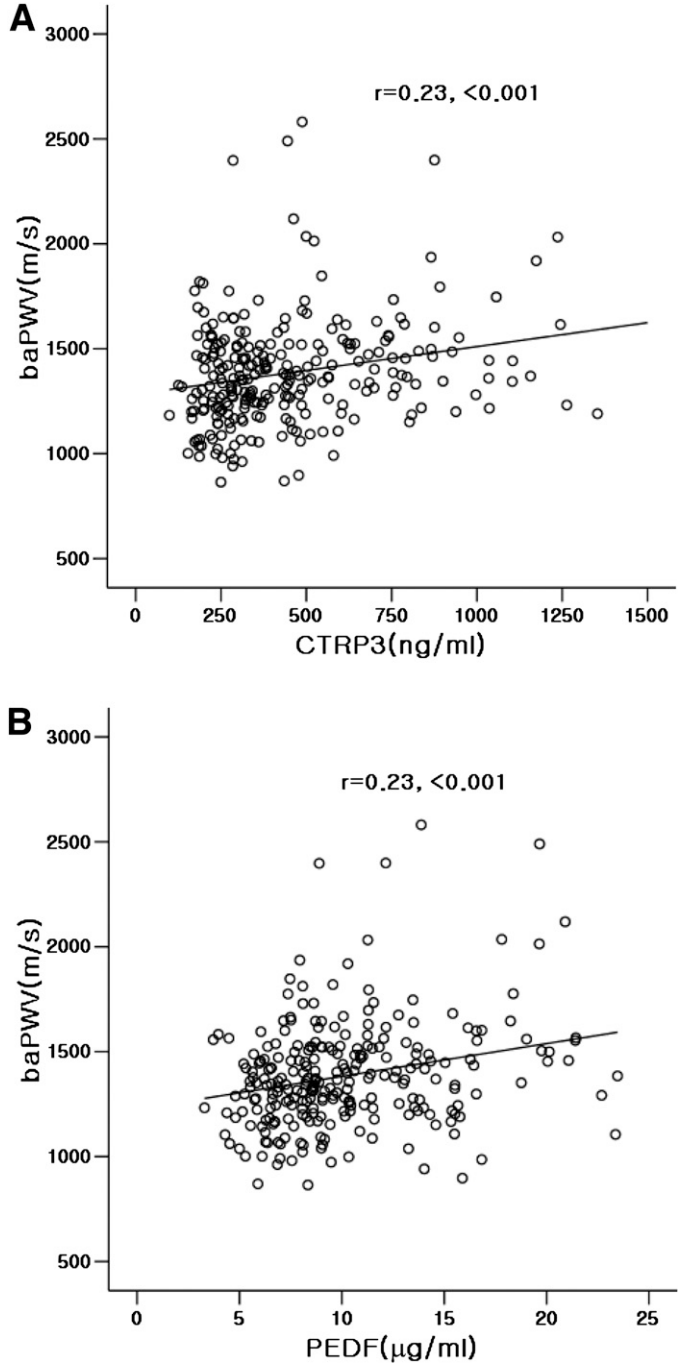

FIG. 3. Relationship between mean baPWV and plasma CTRP-3 (*A*) and PEDF (*B*) concentrations.

TABLE 1
Clinical and laboratory characteristics of the study subjects

	Normal (n = 119)	Prediabetes (n = 111)	Type 2 diabetes (n = 119)	P value
Sex (male/female)	40/79	40/71	54/65	0.145
Age (years)	50.7 ± 13.3	53.4 ± 9.3	51.5 ± 8.1	0.262
BMI (kg/m^2)	23.8 ± 3.0[a]	25.0 ± 3.2[b]	24.6 ± 3.0[a,b]	0.037
Waist circumference (cm)	82.7 ± 8.1[a]	86.8 ± 8.0[b]	87.1 ± 7.4[b]	<0.001
WHR	0.88 ± 0.05[a]	0.89 ± 0.05[b]	0.92 ± 0.05[c]	<0.001
Systolic blood pressure (mmHg)	121.3 ± 14.6	123.0 ± 15.3	125.3 ± 15.6	0.146
Diastolic blood pressure (mmHg)	77.8 ± 10.2	79.5 ± 12.1	79.4 ± 9.4	0.380
Total cholesterol (mmol/L)	3.8 ± 0.9[a]	4.7 ± 0.9[b]	4.8 ± 1.1[b]	0.645
HDL-cholesterol (mmol/L)	1.1 (0.9–1.3)[a]	1.3 (0.9–1.3)[b]	1.2 (1.0–1.5)[b]	0.008
LDL-cholesterol (mmol/L)	2.3 ± 0.7[a]	2.6 ± 0.8[b]	2.7 ± 0.9[b]	<0.001
Triglycerides (mmol/L)	0.8 (0.6–1.1)	1.4 (1.0–1.9)	1.1 (0.8–1.6)	0.824
Fasting blood glucose (mmol/L)	4.1 ± 0.7[a]	5.7 ± 0.5[b]	9.0 ± 3.2[c]	<0.001
HbA_{1C} (%)	—	5.8 ± 0.3[a]	8.4 ± 2.1[b]	<0.001
HOMA-IR	—	2.1 (1.2–3.3)[a]	2.4 (1.3–3.7)[b]	0.044
AST (IU/L)	12.2 ± 10.0[a]	26.6 ± 10.9[b]	26.6 ± 18.8[b]	<0.001
ALT (IU/L)	17.9 ± 8.6[a]	26.8 ± 21.6[b]	31.0 ± 25.9[b]	<0.001
Creatinine (mg/dL)	0.5 ± 0.2[a]	0.8 ± 0.2[b]	0.8 ± 0.2[b]	<0.001
eGFR (mL/min/1.73 m^2)	144.9 (127.6–183.8)[a]	92.0 (83.1–106.0)[b]	95.2 (84.6–106.2)[b]	<0.001
hsCRP (mg/L)	0.4 (0.2–0.8)[a]	0.8 (0.5–1.5)[b]	1.4 (0.7–2.6)[c]	<0.001
Left baPWV (m/s)	1,316.9 ± 232.7[a]	1,397.4 ± 284.7[b]	1,487.1 ± 225.7[b]	<0.001
Right baPWV (m/s)	1,305.1 ± 232.2[a]	1,390.7 ± 293.6[b]	1,506.8 ± 228.0[b]	<0.001

Data are presented as the mean ± SD or the median (interquartile range) unless otherwise indicated. HOMA-IR, homeostasis model assessment of insulin resistance. [a,b,c]Same letters indicate no statistical significance based on Tukey's post hoc analysis or Wilcoxon's rank-sum test.

metabolic stress or resistance to CTRP-3 action, which is reminiscent of insulin or leptin resistance. As an alternative interpretation, other confounding factors, such as eGFR, may underlie the difference in CTRP-3 levels in patients with abnormal glucose metabolism. Recent studies showed that serum levels of adipokines, such as retinol binding protein 4, were independently associated with renal function (16). In this study, multiple regression analysis showed that CTRP-3 levels were independently associated with eGFR in addition to other parameters including fasting glucose levels. Further study might be needed to evaluate the role of CTRP-3 as a pathogenic mediator or a simple bystander in humans with glucose metabolism dysregulation.

CTRP-3 reduced TNF-α and IL-6 secretion but did not increase IL-10 in primary monocytes (7). The anti-inflammatory effects of CTRP-3 may be explained by the suppression of nuclear factor-κB signaling (17). CTRP-3 expression in cultured vascular smooth muscle cells was induced by transforming growth factor-β1 (18). CTRP-3 promoted the proliferation and migration of mouse endothelial cells in a dose-dependent manner through the activation of extracellular signal-regulated kinase 1/2 (19). Moreover, the CTRP-3 gene was upregulated in the carotid artery tissue of a balloon-injured rat (20). Interestingly, this study first showed that plasma CTRP-3 levels were significantly associated with arterial stiffness as well as circulating hsCRP levels, reflecting systemic subclinical inflammation. These results suggest a possible role of CTRP-3 as a novel link between innate immunity and atherosclerosis.

PEDF is produced from a variety of tissues, including adipocytes, vascular, and inflammatory cells (21). Chen et al. (22) reported that plasma PEDF levels predicted the development of metabolic syndrome in Chinese men. Consistent with previous results, our study showed that PEDF concentrations were significantly associated with obesity, hypertension, dyslipidemia, and insulin resistance. In addition, we observed a significant negative relationship between circulating PEDF levels and eGFR values in subjects with diverse glucose tolerances. Motomiya et al. (23) previously reported increased serum concentrations of PEDF in patients with end-stage renal disease.

Yamagishi et al. (24) found that advanced glycation end product- or angiotensin II-induced endothelial cell damage is inhibited by PEDF, which possesses antioxidative, anti-inflammatory, and antiatherogenic properties in both cell culture and animal models. Although these results suggest a protective role of PEDF against atherosclerosis, few studies have examined the relationship between PEDF and atherosclerosis in humans. Tahara et al. (25) first reported that serum PEDF levels are positively related with vascular inflammation and carotid intima-media thickness in healthy subjects. They interpreted the elevation in the PEDF level as a compensatory mechanism to attenuate the inflammation and atherosclerosis (25). In this study, plasma PEDF levels showed a significant positive relationship with arterial stiffness, which is an independent predictor of cardiovascular risk.

There were some limitations to this study. First, this study was performed using baseline data and samples from an ongoing prospective cohort study; therefore, it is not possible to impute causality. Secondly, because this study included only East Asian subjects, our results may not apply to other populations.

In conclusion, we found significantly elevated CTRP-3 concentrations in patients with type 2 diabetes or prediabetes compared with subjects with normal glucose tolerance. Considering the relationship of CTRP-3 and PEDF with arterial stiffness as well as various cardiometabolic risk factors, including the components of metabolic syndrome, kidney function, and inflammation, both CTRP-3 and PEDF might be useful as novel biomarkers for atherosclerosis in humans.

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B.-S.Y. is employed by AdipoGen, Inc. No other potential conflicts of interest relevant to this article were reported.

K.M.C. researched the data and wrote the manuscript. S.Y.H., H.C.H., S.J.Y., H.Y.C., and H.J.Y. researched the data. K.W.L., M.S.N., Y.S.P., J.T.W., and Y.S.K. contributed to the discussion and reviewed and edited the manuscript. D.S.C., B.-S.Y., and S.H.B. researched the data and reviewed and edited the manuscript. K.M.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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