

# Association of Plasma Pentraxin-3 Level with Lipid Levels and Cardiovascular Risk Factors in People with No History of Lipid-Lowering Medication: the Dong-gu Study

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**Aim:** To elucidate the role of pentraxin-3 (PTX3) in atherosclerosis, we evaluated lipid and cardiovascular risk profiles according to the plasma PTX3 levels in subjects from the general population.

**Methods:** A sub-cohort of 2,000 subjects was randomly sampled from a Korean community-based cohort study. After excluding those with a medication history for dyslipidemia, 1,747 subjects (902 men and 845 women) were included in the final analyses. Linear and logistic regressions with adjustment for appropriate variables were performed.

**Results:** The PTX3 level was positively associated with the high-density lipoprotein cholesterol (HDL-C) level and negatively associated with the log-transformed triglyceride (TG) level, total cholesterol/HDL-C ratio, and low-density lipoprotein cholesterol (LDL-C)/HDL-C ratio ( $p < 0.05$ ). Subjects with the highest PTX3 levels ( $\geq 1.17$  ng/dl) exhibited a lower risk of metabolic syndrome (odds ratio [OR] 0.73, 95% confidence interval [CI] 0.57–0.94), overweight/obesity (OR 0.65, 95% CI 0.50–0.83), increased TG level (OR 0.66, 95% CI 0.51–0.86), and increased HDL-C level (OR 0.67, 95% CI 0.51–0.88) compared to those with the lowest PTX3 level ( $< 0.7$  ng/dl).

**Conclusion:** The circulating PTX3 level was inversely associated with metabolic syndrome, overweight/obesity, and parameters of dyslipidemia, suggesting a cardioprotective role of PTX3 in atherosclerosis.

**Key words:** Pentraxin 3, Lipid, Atherosclerosis, Cardiovascular risk factor

## Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. According to the 2013 Global Burden of Disease study, 25.5% of all deaths from 1990 to 2013 were attributable to CVD<sup>1</sup>. The

World Health Organization speculated that approximately 20 million deaths from CVD occurred in 2015, which represents approximately 30% of the total number of deaths<sup>2</sup>. Atherosclerosis is the most important underlying cause of CVD, and its pathophysiology is closely linked to chronic or low-grade

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inflammation<sup>3</sup>). Identifying an inflammatory marker of atherosclerosis or predictor of CVD is a focus of research in medicine and public health<sup>4</sup>). C-reactive protein (CRP) is a circulating, acute-phase reactant that reflects active systemic inflammation and is a marker of CVD<sup>5</sup>). Pentraxin-3 (PTX3) is structurally and functionally similar to CRP, is an essential component of innate immunity, and is correlated with various atherosclerosis surrogate markers. However, CRP and PTX3 reportedly play different roles in atherosclerosis and vascular function<sup>6</sup>). CRP is produced primarily by hepatocytes, while PTX3 is produced at inflammation sites by various cell types, including macrophages, smooth muscle cells, adipocytes, and endothelial cells, following stimulation by interleukin-1 or tumor necrosis factor- $\alpha$ <sup>7</sup>). Therefore, PTX3 is a more sensitive biomarker of vascular inflammation than CRP. PTX3 has been investigated as a potential predictor of several CVDs, including unstable angina pectoris<sup>8</sup>), myocardial infarction (MI)<sup>9</sup>), and heart failure in stable coronary heart disease<sup>10</sup>). Prospective studies have shown that PTX3 is positively associated with the risk<sup>11</sup>) and prognosis<sup>12, 13</sup>) of, and mortality due to, CVD<sup>14</sup>). However, studies of the role of PTX3 in atherosclerosis have reported conflicting results<sup>15-17</sup>). In particular, the association between the level of PTX3 and dyslipidemia is unclear. PTX3 levels are reportedly higher in subjects with low high-density lipoprotein cholesterol (HDL-C) level and are positively associated with triglyceride (TG) levels in patients with metabolic syndrome (MS)<sup>18</sup>). Moreover, the PTX3 level is positively correlated with familial hypercholesterolemia<sup>19</sup>). *In vivo*, an elevated HDL-C level is associated with increased PTX3 expression in vascular endothelial cells<sup>20</sup>). However, in a multi-ethnic sub-cohort study, the PTX3 level was not associated with that of lipoproteins<sup>11</sup>).

In this study, we evaluated the association of the plasma PTX3 level with lipid profiles and CVD risk factors to compare the association with CRP among Korean participants in a community-based cohort study.

## Methods

### Subjects

The prospective Dong-gu Study evaluated the prevalence, incidence, and risk factors of chronic disease in urban area residents in Korea<sup>21, 22</sup>). A total of 9,260 urban residents participated in the baseline examination from 2007 to 2010. Among them, 2,000 subjects were randomly selected for inclusion in this study. After excluding 253 subjects (12.6%) who were consuming lipid-lowering medications at baseline or

had a history of consuming lipid-lowering medication or had missing variables, 1,747 subjects (902 men and 845 women) were included in the analyses. All participants provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Institutional Review Board of Chonnam National University Hospital (no: I-008-05-05).

### PTX3 Assay

The plasma PTX3 level was determined using a quantitative sandwich enzyme-linked immunosorbent assay kit (Quantikine R&D International, MN, USA) according to the manufacturer's instructions. A streptavidin-coated plate was incubated with a biotinylated monoclonal antibody specific for human PTX3. The wells were washed, and pretreated standards and samples were added. After washing away any unbound substances, an enzyme-linked conjugate specific for human PTX3 was added. Subsequently, a substrate solution was added to induce color development, and the color intensity was measured. The PTX3 level (ng/mL) was determined using a standard curve. The minimum detectable dose (MDD) of PTX3 ranged from 0.007–0.116 ng/mL and the mean MDD was 0.025 ng/mL. The intra-assay coefficient of variation (CV) was 3.93% and the inter-assay CV was 5.06% according to the protocol. Reagents of the same lot numbers were used for all determinations to minimize the measurement variability. The assay was performed using plasma that had been stored at  $-70^{\circ}\text{C}$ <sup>23</sup>).

### Measurements of Variables

Demographic factors and health habits (smoking, alcohol drinking, and regular exercise) were assessed using a questionnaire survey. Details of the anthropometric measurements, including height, weight, and waist and hip circumferences are provided elsewhere<sup>21</sup>). Lipid profiles, including total cholesterol (TC), TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C) were analyzed by enzymatic assay using an automatic analyzer (Hitachi-7600; Hitachi, Japan). Dyslipidemia was defined as a TC level  $\geq 200$  mg/dL, TG level  $\geq 150$  mg/dL, LDL-C level  $\geq 130$  mg/dL, and HDL-C level  $< 40$  mg/dL in men or  $< 50$  mg/dL in women. The high-sensitivity CRP level was measured by latex-enhanced nephelometry using a high-sensitivity assay analyzer (Behring Nephelometer II; Dade-Behring Diagnostics, Marburg, Germany). White blood cells (WBCs) were enumerated using fresh ethylenediaminetetraacetic acid samples and a hematology analyzer (Micros 60; ABX, Montpellier, France) within 30 min of blood collection. The intima-media thickness of the carotid arterial wall

(C-IMT) was measured by trained physicians using a B-mode ultrasound scanner. The status of plaque in the carotid arteries—including the common carotid artery, carotid bulb, and internal carotid artery—was determined based on the Mannheim IMT Consensus guidelines<sup>24</sup>. Carotid plaque was defined as a focal structure that encroached into the lumen by at least 100% of the surrounding C-IMT value<sup>25</sup>. Images were analyzed by one investigator using SigmaScan Pro software (SPSS, IL, USA)<sup>26</sup>. Peripheral arterial disease (PAD) was defined as an ankle-brachial index (ABI) <0.9 assessed using a noninvasive, automatic oscillometric device (VP-1000, Colin, Tokyo, Japan) after 5 min of rest in the supine position. The brachial ankle pulse wave velocity (baPWV) also measured to evaluate the arterial stiffness using the same device, VP-1000. MS was defined according to the National Cholesterol Education Program, Adult Treatment Panel III<sup>27</sup>. The estimated glomerular filtration rate (eGFR) was evaluated using the Modification of Diet in Renal Disease equation, as follows:  $186 \times (\text{creatinine} \div 88.4) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$ <sup>28</sup>. The *APOE* genotype was categorized as *E2* (*E2E2* and *E2E3*), *E3* (*E3E3*), or *E4* (*E3E4* and *E4E4*) for allele-based analysis.

### Statistical Analysis

The participants were classified into PTX3 and CRP level tertiles as follows: PTX3 low T, <0.69 ng/mL; middle T, 0.70–1.16 ng/mL; and high T, 1.17–19.93 ng/mL. The chi-squared test and analysis of variance (ANOVA) were used to evaluate differences in demographic and clinical characteristics, respectively, according to PTX3 tertile. Association of the PTX3 level with the lipid profile was evaluated by linear regression. Variables significantly associated with the PTX3 level in chi-square test or ANOVA were included in the regression models as covariates. Demographic variables, including age, body mass index (BMI), waist-hip ratio (WHR), and regular exercise were included in Model I. Model II comprised the Model I variables plus significant serological variables, including WBC, serum CRP concentrations, cortisol, albumin, urine creatinine level, and eGFR. Model III comprised the Model II variables plus clinical parameters of atherosclerotic change (maximal C-IMT, mean baPWV, and mean ABI) and genetic variable of *APOE* alleles [*E2*, *E3*, and *E4*]. A multiple logistic regression was performed to evaluate the association between PTX3 and the intermediate atherosclerosis phenotypes (MS, high BMI [ $\geq 25 \text{ kg/m}^2$ ], thickened C-IMT [ $> 1 \text{ mm}$ ], presence of carotid plaque, elevated TG level [ $\geq 150 \text{ mg/dL}$ ], and reduced HDL-C level [ $< 40 \text{ mg/dL}$  in men or  $< 50 \text{ mg/dL}$  in women]). Covariates,

including age, sex, alcohol drinking, smoking, albumin, WBC, CRP, cortisol, urine creatinine, eGFR, and *APOE* genotype were inserted in the model. Log-transformed TG level values were used to reduce variance.

## Results

The demographic and clinical characteristics of the subjects according to PTX3 level tertile are shown in **Table 1**. Those with a high PTX3 level were more likely to be older, exercise less frequently, and have a lower BMI and WHR. The PTX3 level did not differ according to sex, smoking, alcohol drinking, or history of consuming medication for hypertension or diabetes. Regarding clinical features, WBC count, serum levels of CRP, cortisol, albumin, maximal C-IMT, mean baPWV, mean ABI, urine creatinine concentration, and eGFR were associated with the PTX3 level. However, the systolic blood pressure and HbA1c level did not differ according to the PTX3 level. The PTX3 level was positively associated with the HDL-C level and negatively associated with the TG level, TC/HDL-C ratio, and LDL/HDL-C ratio (**Table 1**).

**Table 2** shows the association between the PTX3 level and the lipid profile. After adjustment for all variables, the PTX3 level was positively associated with the HDL-C level and negatively associated with the log-transformed TG level, TC/HDL-C ratio, and LDL/HDL-C ratio. However, the PTX3 level was not significantly associated with the TC level, LDL-C level, maximal C-IMT, mean ABI, or mean baPWV (data not shown) (**Table 2**).

**Table 3** shows the associations of the PTX3 level with the risk of MS, overweight/obesity, the intermediate phenotypes of atherosclerosis (thick C-IMT, PAD, arterial stiffness, and presence of carotid plaques), and dyslipidemia. We also compared the association of cardiovascular risk factors with PTX3 versus CRP. A high PTX3 level was associated with a decreased risk of MS, overweight/obesity, raised TG level, and reduced HDL-C level (OR [95% CI], 0.73 [0.57–0.94], 0.65 [0.50–0.83], 0.66 [0.51–0.86], and 0.67 [0.51–0.88], respectively). However, the association of PTX3 with the CVD risk factors seems to be less than CRP (**Table 3**).

## Discussion

Whether an increased circulating PTX3 level is atheroprotective or indicates the inflammation involved in advanced atherosclerosis is still unclear. To evaluate its role in atherosclerosis, and to reveal the

**Table 1.** Baseline characteristics of subjects by plasma PTX3 levels

	PTX3 tertile			<i>p</i> -value
	Low( <i>n</i> =582)	Middle ( <i>n</i> =583)	High( <i>n</i> =582)	
Ranges of PTX3, ng/dl	0.12–0.69	0.70–1.16	1.17–19.93	
Men	300 (51.5)	300 (51.5)	302 (51.9)	0.988
Regular exercise	190 (32.9)	217 (37.5)	168 (29.1)	0.010
Alcohol drinking	364 (63.0)	358 (61.6)	329 (56.8)	0.080
Ever smoking	229 (39.6)	228 (39.2)	233 (40.2)	0.947
HTN medication	188 (32.7)	178 (30.8)	194 (33.6)	0.578
DM medication	64 (11.1)	66 (11.4)	80 (13.9)	0.289
Metabolic syndrome	328 (56.6)	312 (53.6)	299 (51.8)	0.264
<i>APOE E4</i> allele	84 (14.6)	110 (19.2)	94 (16.3)	0.109
Age (years)	64.1 ± 7.9	65.5 ± 8.3	66.4 ± 8.3	<0.001
WBC, (× 10 <sup>3</sup> /μL)	5.72 ± 1.46	5.87 ± 1.58	6.05 ± 2.01	0.005
BMI (kg/m <sup>2</sup> )	24.5 ± 2.7	24.1 ± 2.7	23.8 ± 2.9	0.001
WHR	0.94 ± 0.05	0.94 ± 0.06	0.95 ± 0.06	0.018
hsCRP (mg/dl)	0.13 ± 0.32	0.15 ± 0.45	0.21 ± 0.65	0.014
Cortisol (μg/dL)	9.18 ± 3.34	9.24 ± 3.21	8.77 ± 3.62	0.038
baPWV (cm/sec)	1601 ± 339	1644 ± 390	1657 ± 392	0.028
Maximal IMT (mm)	0.92 ± 0.17	0.90 ± 0.19	0.94 ± 0.18	0.001
Mean ABI	1.12 ± 0.08	1.12 ± 0.09	1.12 ± 0.09	0.101
Urine creatinine	112.7 ± 63.2	122.6 ± 72.7	135.1 ± 79.6	<0.001
eGFR	66.8 ± 11.7	66.0 ± 11.6	64.9 ± 12.4	0.026
Albumin	4.49 ± 0.30	4.45 ± 0.25	4.45 ± 0.30	0.019
Systolic BP (mmHg)	124.4 ± 17.4	124.0 ± 16.9	123.2 ± 17.1	0.524
HbA1c (%)	5.82 ± 0.87	5.80 ± 0.89	5.79 ± 0.95	0.894
TC (mg/dL)	201.5 ± 36.6	197.9 ± 38.4	197.7 ± 40.3	0.160
TG (mg/dL)	151.3 ± 103.8	135.2 ± 83.6	133.6 ± 136.3	0.010
HDL-C (mg/dL)	50.6 ± 11.5	50.7 ± 11.2	53.0 ± 13.4	0.001
LDL-C (mg/dL)	120.7 ± 35.0	120.1 ± 34.4	117.9 ± 39.1	0.402
TC/HDL-C ratio	4.14 ± 1.03	4.04 ± 0.99	3.90 ± 1.04	<0.001
LDL/HDL ratio	2.48 ± 0.86	2.46 ± 0.81	2.32 ± 0.89	0.003

Values are given as count (%) or mean ± standard deviation; *P*-values by chi-square test or analysis of variance test; HTN, hypertension; DM, diabetes; *APOE* genotype *E3E4* and *E4E4* were categorized into *E4*; WBC, white blood cell count; BMI, body mass index; WHR, waist-hip ratio; hsCRP, high sensitive C-reactive protein; baPWV, brachial-ankle pulse wave velocity; IMT, intima-media thickness; eGFR, estimated glomerular filtration rate; BP, blood pressure; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC/HDL-C ratio, total cholesterol versus high-density lipoprotein cholesterol ratio; LDL/HDL-C ratio, low-density lipoprotein cholesterol versus low-density lipoprotein cholesterol ratio

**Table 2.** Relationship between PTX3 and lipid profiles among middle-aged and elderly Koreans with no lipid-lowering medication history

	Model I		Model II		Model III	
	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value
Total cholesterol	0.005	0.846	-0.005	0.844	-0.003	0.910
Log TG	-0.077	0.002	-0.080	0.001	-0.088	<0.001
LDL-C (mg/dL)	-0.004	0.862	-0.021	0.379	-0.015	0.532
HDL-C (mg/dL)	0.100	<0.001	0.113	<0.001	0.110	<0.001
TC/HDL-C ratio	-0.063	0.009	-0.080	0.001	-0.076	0.002
LDL/HDL-C ratio	-0.049	0.040	-0.072	0.003	-0.065	0.008

Values are given as coefficients and *P*-value by linear regression; Model I, adjusted for age, BMI, WHR and regular exercise; Model II, additionally adjusted for WBC, hsCRP, cortisol, urine creatinine, albumin, and eGFR; Model III, additionally adjusted maximal C-IMT, mean ABI, mean baPWV and *APOE* genotype; Log TG, log-transformed triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC/HDL-C ratio, total cholesterol versus high-density lipoprotein cholesterol ratio; LDL/HDL-C ratio, low-density lipoprotein cholesterol versus high-density lipoprotein cholesterol ratio

**Table 3.** Comparison of the associations with cardiovascular risk profiles of PTX3 versus CRP

	PTX3				CRP			
	Low (n = 582)	Middle (n = 583)	High (n = 582)	p-value for trend	Low (n = 599)	Middle (n = 571)	High (n = 576)	p-value for trend
Metabolic syndrome	1	0.83 (0.66–1.05)	0.73 (0.57–0.94)	0.044	1	1.76 (1.38–2.26)	2.38 (1.83–3.10)	<0.001
BMI ≥ 25 kg/m <sup>2</sup>	1	0.88 (0.69–1.12)	0.65 (0.50–0.83)	0.001	1	2.00 (1.55–2.58)	2.34 (1.78–3.08)	<0.001
C-IMT > 1.1 mm	1	0.87 (0.61–1.23)	1.05 (0.75–1.47)	0.535	1	1.19 (0.83–1.70)	1.26 (0.87–1.84)	0.449
Carotid plaque	1	0.93 (0.73–1.21)	0.98 (0.76–1.27)	0.872	1	1.02 (0.79–1.33)	1.12 (0.84–1.48)	0.723
ABI ≤ 0.9	1	0.93 (0.36–2.39)	0.77 (0.29–2.10)	0.876	1	2.01 (0.59–6.82)	3.74 (1.09–12.8)	0.099
Raised TG	1	0.85 (0.66–1.09)	0.66 (0.51–0.86)	0.008	1	1.37 (1.05–1.79)	2.02 (1.51–2.70)	<0.001
Reduced HDL-C	1	0.88 (0.68–1.15)	0.67 (0.51–0.88)	0.014	1	1.46 (1.11–1.93)	1.88 (1.41–2.51)	<0.001
Raised LDL-C	1	0.86 (0.67–1.09)	0.84 (0.65–1.07)	0.313	1	1.29 (1.01–1.67)	1.34 (1.03–1.75)	0.058

Multiple logistic regression adjusting for age, sex, alcohol drinking, smoking, albumin, WBC, CRP (or PTX3), cortisol, urine creatinine, eGFR and *APOE* genotype; raised TG defined as ≥ 150 mg/dl; reduced HDL defined as < 40 mg/dl in men or < 50 mg/dl in women; raised LDL-C defined as ≥ 130 mg/dl; C-IMT, carotid intima-media thickness; ABI, ankle-brachial index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

possible mechanism, we compared lipid profiles and cardiovascular risk factors according to the circulating PTX3 level in healthy subjects.

In this study, the PTX3 level was significantly positively associated with the HDL-C level and negatively associated with the TG level, TC/HDL ratio, and LDL/HDL ratio among the Korean subjects with no history of lipid-lowering medication. Moreover, the risk of MS and obesity were significantly lower in the highest PTX3 tertile compared to the lowest group. However, no association with hypertension, diabetes, intermediate atherosclerosis phenotypes in carotid and peripheral arteries, and lifestyle factors was found in this study. Thus, PTX3 is negatively associated with the cardiovascular risk factors of atherosclerosis, contrary to CRP, and this association is likely to involve lipid metabolism. Therefore, an increased circulating PTX3 level may be a protective response and may exert an anti-inflammatory effect in atherosclerosis. To our knowledge, no previous epidemiological study has reported an association of the circulating PTX3 level with lipid parameters and the risk of MS in subjects with no history of lipid-lowering medication.

PTX3, the prototype protein of the long pentraxin group, is an essential component of innate immunity. It is produced by immune cells and vascular cells in response to proinflammatory signals, such as cytokines, microbial components, and HDL-C and oxidized LDL-C<sup>20, 29</sup>. PTX3 production is rapidly induced in inflamed tissue and is released into plasma at the sites of atherosclerosis, vascular damage, or inflammation<sup>15</sup>. Therefore, a persistently elevated PTX3 level may be associated with morbidity due to, or the severity of, CVDs, including unstable angina

pectoris<sup>8</sup>), MI<sup>9</sup>), and renal damage<sup>30</sup>). In addition, the circulating PTX3 level is positively associated with risk factors for CVDs, including obesity<sup>31</sup>, low-HDL-C and high fibrinogen<sup>32</sup>, C-IMT and coronary artery calcification<sup>11</sup>), arterial stiffness<sup>33</sup>), and a reduced eGFR<sup>34</sup>). The PTX3 level is elevated in patients with MS<sup>18, 35</sup>) and those with familial hypercholesterolemia<sup>19</sup>); it indicates advanced atherosclerosis in patients with subclinical coronary stenosis<sup>36</sup>). The PTX3 level in aortic wall tissue is correlated with the severity of coronary artery disease as well as various risk factors for atherosclerosis among patients who underwent coronary artery bypass graft surgery<sup>33</sup>). These findings suggest that PTX3 may be a useful biomarker of inflammatory or atherosclerotic CVD<sup>37</sup>).

PTX3 reportedly delays atherosclerosis progression. *In vivo*, plasma PTX3 levels were significantly increased in mice injected with HDL. Moreover, HDL modulated the mRNA level of PTX3 and protein secretion by human umbilical vein endothelial cells and human aortic endothelial cells in a dose-dependent manner. However, it did not alter the expression of the short pentraxin CRP and serum amyloid P component<sup>20</sup>). Prior reports indicate its deficiency is associated with vascular inflammation<sup>38</sup>), neointimal hyperplasia after vascular injury<sup>39, 40</sup>), and MI<sup>41</sup>), which supports the cardiovascular protective role of PTX3. In human studies, the plasma PTX3 level was negatively associated with BMI<sup>42</sup>), TG<sup>43</sup>), and fat body mass<sup>7, 42</sup>), and positively associated with the adiponectin level<sup>42, 44, 45</sup>) and glucose-stimulated insulin secretion<sup>45</sup>). In longitudinal studies, decreased BMI and fat mass were associated with an increased serum PTX3 level<sup>42, 46</sup>). In addition, the plasma PTX3 level is an independent predictor of left-ventricle dys-

function and mortality in MI patients with ST elevation<sup>47</sup>). The discrepancies among the study findings may be due to their analysis of relatively few subjects and/or selection bias caused by including disease-specific populations<sup>42</sup>). Therefore, we analyzed a large number of subjects in a community-based cohort study and excluded users of lipid-lowering drugs to enhance the generalizability of the results. In our study, the PTX3 level was negatively associated with an elevated TG level as well as a reduced HDL-C level, TC/HDL-C ratio, LDL/HDL-C ratio, and risk of MS. Therefore, PTX3 is negatively associated with the cardiovascular risk factors of atherosclerosis and, thus, may play a protective role in CVD development.

PTX3 has complex effects in the vasculature and is involved in multiple pathways. It has similar properties to the anti-inflammatory and antidiabetic adipokine, adiponectin. Circulating PTX3 and adiponectin may dampen or enhance inflammation by similar modes of action<sup>42</sup>). Oxidative stress may affect PTX3 production by adipocytes in obese individuals, and in MI patients, the level of PTX3 is correlated with several markers of oxidative stress<sup>47</sup>). PTX3 inhibits the classical complement pathway by blocking the interaction of C1q with immunoglobulins<sup>48</sup>), thereby reducing tissue injury. Expression of *PTX3* is regulated by HDL-C<sup>20</sup>) and a decrease in the HDL-C level may explain the lower PTX3 level in obese individuals<sup>44</sup>). HDL-induced *PTX3* expression in the endothelium, which is dependent on the PI3K/Akt pathway, may explain the vascular-protective effect of PTX3<sup>20, 49</sup>). PTX3 has several advantages compared to CRP as a biomarker of CVDs risk. Circulating PTX3 is a faster responding biomarker in cardiovascular pathologies<sup>50</sup>) and a better predictor of CVD risk than CRP<sup>36</sup>). Plasma concentration of PTX3 peaked earlier than that of CRP among patients with acute MI (AMI). Maximal PTX3 concentration was reached within 6 hours, and CRP was reached 48 hours after onset of chest pain<sup>9</sup>). In our results, PTX3 showed lower performance than CRP, so the combination of PTX3 and CRP can provide a better tool for CVDs risk prediction.

The main strength of the present study was the relatively large sample size and inclusion in the analysis of numerous clinical variables. The subjects were a general population sampled from a community-based cohort, and those with dyslipidemia were excluded from the analysis to enhance the results generalizability. This study also had limitations. First, because of the cross-sectional design, we could not determine the causality of the relationships of the circulating PTX3 level with the lipid profile or the risk of CVD. Second, the biologic and functional relevance of the

above-mentioned relationships were not evaluated. Finally, although the association between PTX3 and lipid profiles is statistically significant, the beta values seem to be small, indicating that the contribution of PTX3 for predicting these lipid levels is relatively small.

In conclusion, the plasma PTX3 level was positively associated with the HDL-C level and negatively associated with the TG level, risk of MS, overweight/obesity, and dyslipidemia. Our study provides additional evidence, especially from community-based study, that PTX3 plays an atheroprotective role and may be a simple biomarker of CVD risk. Further studies are required to elucidate the mechanism by which PTX3 influences the cardiovascular system.

### Conflict of Interests

The authors declare that they have no conflict of interest.

### Author Contributions

Kweon SS, conceptualization and data analysis; Lee R, manuscript writing; Ahn HR, laboratory work and financial support; Kim HN, laboratory work support; Shin MH, Choi SW and Lee YH, cohort data collection; and all authors approved the final manuscript.

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