Elevated Plasma Pentraxin 3 Levels Are Associated With Development and Progression of Diabetic Retinopathy in Korean Patients With Type 2 Diabetes Mellitus

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Submitted: May 23, 2014
Accepted: August 4, 2014

Citation: Yang HS, Woo JE, Lee SJ, Park SH, Woo JM. Elevated plasma pentraxin 3 levels are associated with development and progression of diabetic retinopathy in Korean patients with type 2 diabetes mellitus. *Invest Ophthalmol Vis Sci*. 2014;55:5989–5997. DOI:10.1167/iovs.14-14864

Purpose. To evaluate the association between elevated levels of plasma pentraxin 3 (PTX3) and the development and/or progression of diabetic retinopathy (DR).

Methods. In this case-control study, 92 diabetic patients with DR (group 3), 30 diabetic patients without DR (group 2), and 41 normal subjects (group 1) were enrolled. Log-transformed values of plasma PTX3 and high-sensitivity C-reactive protein (hsCRP) concentrations were measured and used in our analysis. For subgroup analysis, group 3 was divided into four subgroups: mild, moderate, severe nonproliferative, and proliferative DR.

Results. In our 163 participants, average plasma PTX3 levels were 916.1 ± 532.2, 1093.7 ± 1034.2, and 1817.9 ± 1776.9 pg/mL for groups 1, 2, and 3, respectively. The duration of diabetic mellitus (DM), glycated hemoglobin (HbA1c), log hsCRP, and log PTX3 were significantly different between the three groups ($P = 0.008$, $P < 0.001$, $P = 0.046$, and $P < 0.001$, respectively). In subgroup analysis, plasma log PTX3 levels increased in correlation with the severity of DR ($R = 0.372$, $P < 0.001$). Multivariate logistic analysis showed that the correlation between DR development and duration of DM and log PTX3 values was significant ($P = 0.014$ and $P = 0.025$, respectively), whereas correlation with log hsCRP values was not significant in univariate analysis ($P = 0.129$). The receiver operating characteristic curves of DR development were plotted using log PTX3 and log hsCRP values, and the area under the curves was found to be 0.721 ($P = 0.001$) and 0.614 ($P = 0.087$), respectively.

Conclusions. Plasma PTX3 is positively associated with DR development and progression, and may be a more accurate predictor of DR development than hsCRP.

Keywords: C-reactive protein, diabetes mellitus, diabetic retinopathy, pentraxin 3

Diabetes mellitus (DM) is a chronic metabolic disease with a high worldwide prevalence and is now a global health priority. With population growth and aging, economic development, and the increasing prevalence of obesity and physical inactivity, it is estimated that the total number of people with DM will more than double from 171 million in 2000 to 366 million in 2030.[1] The extent of systemic inflammatory reaction in DM has been an important cause of microvascular complications.[2–4] In this regard, several studies have reported that type 2 DM is associated with increased plasma concentrations of acute-phase biomarkers, including C-reactive protein (CRP), which is related to the innate immune response and inflammation.[5–7] Diabetic retinopathy (DR) is another well-known microvascular complication of DM, which is caused by neurovascular inflammation. The relationship between DR and inflammatory reaction has been recently examined, and elevated levels of plasma CRP, such as short pentraxin, are more frequently observed in DM and DR patients compared to patients without DM or DR.[8–11]

Pentraxin 3 (PTX3) is an acute-phase reactant characterized by a cyclic multimeric structure.[12] Pentraxin 3, in the form of a long pentraxin, is produced by peripheral tissues and reflects impaired vascular endothelial function. In contrast, CRP is mainly produced by hepatocytes and is predominantly under the transcriptional control of the cytokine interleukin-6 (IL-6).[13–15] Pentraxin 3 inhibits angiogenesis, promotes restenosis, and increases formation of advanced atherosclerotic lesions, typically by inhibiting the fibroblast growth factor (FGF2) reaction of angiogenesis.[16–18] In this mechanism, PTX3 inhibits FGF2 binding to endothelial cell receptors, leading to specific inhibition of FGF2-induced proliferation.[18] Thus, the PTX3/FGF2 interaction may modulate angiogenesis in various pathophysiological conditions, including those driven by inflammation, innate immunity, and/or neoplastic transformation.[19] Recently, PTX3 has been shown to be a sensitive biomarker of localized inflammatory reactions and innate immunity in cardiovascular and renal diseases.[15,20–23] Suliman et al.[24] have also reported that PTX3 levels were independently associated with endothelial dysfunction in an end-stage kidney disease population, and suggested the possibility of using PTX3 as a biomarker of peripheral vascular damage. Similarly, reports from Noma et al.[25–27] and ourselves have highlighted the relationship between PTX3 and retinal diseases such as age-related macular degeneration and retinal vascular occlusion. Although DR is believed to be more closely associated with systemic vascular inflammation and innate immunity than other

retinal diseases, to our knowledge, the relationship between DR development/progression and plasma PTX3 levels has never been studied.

Thus, we hypothesized that microvascular inflammation, as reflected by PTX3, could be a marker of DR and its progression, and a better predictor of this comorbidity than CRP.

Methods

Study Design

The human experimentation committee review board of Ulsan University Hospital approved this nested, single-center, case-control study, which was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its revision. Informed written consent was obtained from all the subjects prior to the collection of clinical information and blood samples. Participants over 40 years of age were consecutively recruited from the outpatient clinic of the Division of Ophthalmology at the Ulsan University Hospital, and Ulsan University College of Medicine through universal screening for DR immediately following diagnosis of type 2 DM in the Division of Endocrinology at our hospital between April 2010 and June 2011. All patients underwent basic physical examinations, blood sampling, and complete eye examinations, which included best-corrected visual acuity, tonometry, biomicroscopy, and ophthalmoscopy, using either a 90-diopter lens or indirect ophthalmoscopy following pupil dilation. Patients were excluded if they had a history of hypertension, cardiac disease, cerebral disease, chronic renal disease, liver disease, immunological disorders, cancer, severe infection, major surgery, or severe ocular disease. Ocular diseases were defined as uveitis, retinal vascular occlusion, age-related macular degeneration, retinal detachment, glaucoma, central serous chorioretinopathy, and unknown vasculitis. Additionally, patients with a creatinine level $>$ 2.0 mg/dL, abnormal hepatic function test (more than 2-fold increase over the normal limit), and abnormal leukocyte count were also excluded from the present study. After exclusions, a total of 92 DM patients with DR (group 3), 30 age- and body mass index (BMI)–matched DM patients without DR (group 2), and 41 age- and BMI-matched normal subjects (group 1) were enrolled and underwent all examinations. For subgroup analysis, group 3 was further divided into the following four subgroups: mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR) based on fundus examination during screening. Diabetic retinopathy was graded as absence of apparent retinopathy, while mild NPDR, moderate NPDR, severe NPDR, and proliferative DR were graded based on the international clinical DR severity scale. All fundus exams were performed by two retinal specialists (HSY and JMW) and graded based on consensus.

Laboratory Measurements

Patients' venous blood samples were obtained from their forearms the morning after an overnight fast. Low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and glycated hemoglobin (HbA1c) levels were quantified using routine biochemical methods in a certified laboratory at the Department of Laboratory Medicine of Ulsan University Hospital. Low-density lipoprotein levels were calculated using the Friedewald formula. The plasma was immediately separated by centrifugation and then stored at −80°C for subsequent assays. Plasma high-sensitivity CRP (hsCRP) concentration was measured using a highly sensitive enzyme-linked immunosorbent assay (ELISA) kit (DakoCytomation, Copenhagen, Denmark; human hsCRP standards from Randox Laboratories, County Antrim, UK). Plasma PTX3 concentration was measured using an ELISA kit (R&D Systems, Inc., Minneapolis, MN, USA).

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 17 (SPSS, Inc., Chicago, IL, USA) with one-way analysis of variance (ANOVA); post hoc analysis was performed using Tukey's test for comparing baseline characteristics between the three groups. For comparison of two groups, χ^2 test for nonparametric analysis and independent *t*-test for parametric analysis were used. Since the values for hsCRP and PTX3 did not follow a normal distribution pattern, the analysis of two variations was based on log-transformed values (log hsCRP and log PTX3), which displayed normal distribution. For trend analysis, the correlation coefficient and linear by linear association method were used. The study population was divided into quartile groups based on the quartile cutoff PTX3 values for only patients with DM, and univariate and multivariate logistic regression analyses were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Prevalence ORs, which describe the association between disease and PTX3, were calculated for each PTX3 quartile group, relative to the lowest quartile group. A test for linear trend was calculated based on the average levels of PTX3 within each quartile group. A P value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

The demographic, clinical, and laboratory characteristics of the study population are summarized in Table 1.

Of a total of 163 participants in this ancillary study, the PTX3 values for groups 1, 2, and 3 were 916.1 ± 532.2, 1093.7 ± 1034.2, and 1817.9 ± 1776.9 pg/mL, respectively. Among the participants, 89 (54.6%) were male and 74 (45.4%) were female, with a mean age of 55.8 years. The sex, age, BMI, statin use, and lipid profiles were not significantly different between the three groups ($P = 0.925$, $P = 0.889$, $P = 0.772$, $P = 0.083$, and $P > 0.236$, respectively). However, the duration of DM, HbA1c, log hsCRP, and log PTX3 values were significantly different between the three groups ($P = 0.008$, $P < 0.001$, $P = 0.046$, and $P < 0.001$). In group 3, the number of patients with mild, moderate, and severe NPDR and PDR was 28, 21, 23, and 20, respectively. Table 2 shows the demographic, clinical, and laboratory characteristics of the four subgroups of group 3. In subgroup analysis, age, sex, HbA1c, and lipid profile were not significantly different among the four subgroups. However, DM duration and localized treatment were significantly different between the subgroups. Direct comparison between log PTX3 level and localized treatment using anti-VEGF intravitreal injection (average 3.1 ± 1.8 times per person) or panretinal photocoagulation (PRP) showed no statistically significant difference ($P = 0.481$ and $P = 0.310$, respectively).

Association Between DR Development/Progression and PTX3

The log PTX3 levels of the non-DM and non-DR groups were significantly lower than the log PTX3 levels of the DR group ($P < 0.001$ and $P = 0.044$, respectively). However, a comparison

Table 1. Demographic Data and Values of Various Parameters (Mean ± Standard Deviation) Between Three Groups (Group 1, Age- and BMI-Matched Normal Healthy Subjects; Group 2, Age- and BMI-Matched Diabetics Without DR; Group 3, Age- and BMI-Matched Diabetics With DR)

	Group 1, $n = 41$	Group 2, $n = 30$	Group 3, $n = 92$	*P* Value
Sex, male:female	23:18	17:13	49:43	0.925*
Age, y	56.3 ± 8.8	55.8 ± 9.8	55.5 ± 8.6	0.889†
BMI, kg/m^2	23.6 ± 4.1	24.1 ± 3.6	23.2 ± 3.7	0.722†
Smoking >20 pack years, *n* (%)	9 (22.0)	5 (16.7)	17 (18.5)	0.354*
Duration of DM, y	-	8.9 ± 6.4	12.4 ± 5.5	0.008‡
Statin use, *n*	-	14	31	0.083*
Type of DR, *n*				
No DMR	-	30	-	
Mild NPDR	-	-	28	
Moderate NPDR	-	-	21	
Severe NPDR	-	-	23	
PDR	-	-	20	
HbA1c, %	5.59 ± 0.34	7.45 ± 1.1	8.31 ± 1.95	< 0.001†
Creatinine, mg/dL	0.99 ± 0.17	0.99 ± 0.17	0.99 ± 0.19	0.975†
LDL, mg/dL	97.9 ± 35.6	100.9 ± 42.7	114.7 ± 35.0	0.645†
TG, mg/dL	106.2 ± 50.4	103.4 ± 57.4	113.9 ± 59.1	0.390†
HDL, mg/dL	53.1 ± 12.6	47.0 ± 8.2	46.8 ± 15.3	0.236†
HsCRP, pg/mL	549.9 ± 485.9	741.7 ± 748.8	1657.3 ± 3361.5	
Log hsCRP	2.61 ± 0.34	2.63 ± 0.50	2.83 ± 0.60	0.046†
PTX3, pg/mL	916.1 ± 532.2	1093.7 ± 1034.2	1817.9 ± 1776.9	
Log PTX3	2.86 ± 0.34	2.93 ± 0.27	3.12 ± 0.35	< 0.001†

TG, triglyceride.
* χ^2 test.
† One-way ANOVA test.
‡ Independent *t*-test.

between the non-DM and non-DR groups did not reveal any significant difference (Fig. 1A; $P = 0.651$). While the difference in log hsCRP levels between the three groups was statistically significant using ANOVA ($P = 0.046$), the two-group comparisons (group 1 vs. 2, 2 vs. 3, and 1 vs. 3) did not detect any significant difference in post hoc analysis using Tukey's method (Fig. 1B). In the subgroup analysis, distributions of log PTX3 and log hsCRP levels were higher in correlation with the severity of diabetic retinal complications (Figs. 2A, 2B; $R = 0.372$, $P < 0.001$ and $R = 0.253$, $P = 0.094$). In addition, average log PTX3 and log hsCRP values in each diabetic subgroup showed an increasing trend among the six groups that displayed severe DR (Figs. 2C, 2D).

Table 3 displays the ORs for the risk of DR development based on the log PTX3 quartiles in patients with DM. The proportion of higher-degree retinal complications increased in direct correlation with log PTX3 levels. Univariate logistic analysis showed that subjects in the higher log PTX3 quartiles had a higher risk of DR relative to those in quartile 1 (Table 3; ORs, 1.85, 9.53, and 9.53 in quartiles 2, 3, and 4, respectively). Following adjustment for HbA1c and duration of DM using multivariate logistic analysis, the trend for an increase in risk remained significant for the higher log PTX3 quartiles relative

Table 2. Demographic and Clinical Data (Mean ± Standard Deviation) for the Subgroups of Group 3 (With Diabetic Retinopathy)

	Mild NPDR, $n = 28$	Moderate NPDR, $n = 21$	Severe NPDR, $n = 23$	PDR, $n = 20$	*P* Value
Sex, male:female	17:11	10:11	15:8	7:13	0.180*
Age, y	54.3 ± 7.6	56.8 ± 9.0	58.1 ± 6.6	52.9 ± 10.0	0.285†
BMI, kg/m^2	22.8	22.4	23.7	23.9	0.427†
Smoking >20 pack years, *n*	7	5	2	3	0.422‡
Duration of DM, y	10.6 ± 4.5	14.5 ± 7.5	12.0 ± 4.1	13.4 ± 5.1	0.041†
Statin use, *n*	5	6	9	11	0.051*
HbA1c, %	8.06 ± 1.86	8.21 ± 1.73	8.49 ± 2.17	8.58 ± 2.18	0.790†
Creatinine, mg/dL	1.00 ± 0.14	1.00 ± 0.20	1.02 ± 0.20	0.91 ± 0.22	0.324†
LDL, mg/dL	110.7 ± 31.0	120.0 ± 28.5	107.3 ± 36.4	125.2 ± 43.9	0.389†
TG, mg/dL	95.7 ± 51.4	80.0 ± 47.5	121.2 ± 53.2	169.1 ± 89.8	0.078†
HDL, mg/dL	49.1 ± 13.9	45.7 ± 9.2	43.8 ± 23.6	47.6 ± 9.87	0.709†
Log hsCRP	2.77 ± 0.55	2.57 ± 0.73	3.07 ± 0.64	2.93 ± 0.35	0.057†
Log PTX3	3.07 ± 0.43	3.12 ± 0.46	3.16 ± 0.21	3.16 ± 0.17	0.761†
Anti-VEGF history, *n* (%)	0	1 (4.8)	6 (26.1)	7 (35.0)	0.002‡
PRP history, *n* (%)	0	0	11 (47.8)	18 (90.0)	< 0.001‡

* χ^2 test.
† One-way ANOVA test.
‡ Fisher's exact test.

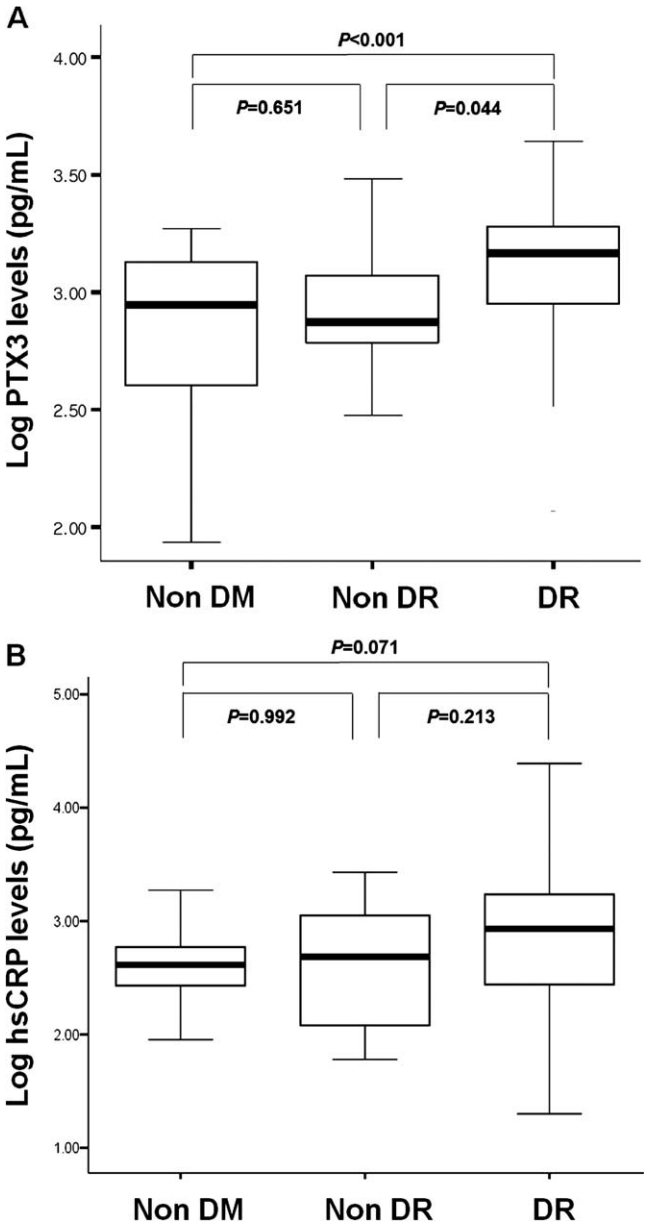

FIGURE 1. The concentrations of (**A**) log-transformed plasma pentraxin 3 (PTX3) and (**B**) high-sensitivity C-reactive protein (hsCRP) associate with the presence of diabetic retinal complications. The *P* values were estimated using one-way ANOVA and post hoc analysis using Tukey's test. *Thick lines* in the *middle of the boxes* represent the median value for each group. DM, diabetes mellitus; DR, diabetic retinopathy.

to quartile 1 (Table 3; ORs, 2.59, 8.69, and 8.47 in quartiles 2, 3, and 4, respectively). Table 4 shows the factors that might significantly affect the development of DR, and multivariate logistic analysis showed that duration of DM and log PTX3 values were significant factors ($P = 0.014$ and 0.025, respectively). However, univariate logistic analysis showed that log hsCRP was not significantly related to DR development ($P = 0.129$).

PTX3 as a Biomarker for Predicting DR Development Compared to hsCRP

Currently, hsCRP is the most popular biomarker for systemic inflammation. Therefore, to evaluate the relationship between PTX3 and hsCRP, we calculated the correlation and coefficients of the log-transformed variables, as shown in Figure 3. The graph showed a weak but significant positive correlation between log PTX3 and log hsCRP levels ($R = 0.196$, $P = 0.014$).

The receiver operating characteristic (ROC) curves for developing DR using log PTX3 and log hsCRP values revealed that the area under the receiver operating characteristic curves (AUC) were 0.721 ($P = 0.001$) and 0.614 ($P = 0.087$), respectively (Fig. 4, Table 5). To determine the cutoff value, we chose the maximum of combining sensitivity value and one minus specificity value. With a cutoff value of 1406.0 pg/mL for PTX3, the diagnostic sensitivity and specificity for DR development were 53.3% and 91.7%, respectively. With a cutoff value of 841.7 pg/mL for hsCRP, the diagnostic sensitivity and specificity for DR development were 51.1% and 70.8%, respectively.

DISCUSSION

Vascular complications of DM can affect both large- and medium-sized arteries, as well as small vessels, leading to retinopathy and nephropathy. Diabetic retinopathy has therefore been considered a microcirculatory disease of the retina, which is closely correlated with chronic hyperglycemia, and can negatively affect the regulation of the polyol and hexosamine pathways, renin-angiotensin system, and proinflammatory cytokines.[28,29] In addition, DM leads to endothelial dysfunction and accelerated progression of atherosclerosis, with intravascular inflammation playing a definite role in these processes. Endothelial dysfunction may result in increased vascular permeability, alteration of blood flow, oxidative stress, angiogenesis, and microaneurysms in DR, ultimately leading to a higher risk of retinopathy.[30,31] Acute-phase reactants such as CRP and PTX3 are known to be involved in the inflammatory response, endothelial dysfunction, and atherosclerosis.[13,22,32,33] Their increase in patients with DM suggests that they are potentially valuable as prognostic factors for vascular complications such as DR.[4,34,35] In the present study, PTX3 and hsCRP were higher in DR patients compared to normal and non-DR patients, which implies that DR is closely associated with systemic inflammation in type 2 DM patients.

Pentraxin 3 is the prototypic long pentraxin, with a high degree of conservation from mice to humans. While CRP is mainly produced by hepatocytes, PTX3 is produced by various peripheral tissues, including hematopoietic cells, macrophages, myeloid-derived dendritic cells, neutrophils, adipocytes, fibroblasts, smooth muscle cells, endothelial cells, and renal epithelial cells.[12,13,36–42] In addition, we have previously reported that the retinal pigment epithelium and vascular tissues can express PTX3.[43] These findings indicate that PTX3 might play a localized role and hence can be a more specific biomarker of vascular inflammations such as DR.[44]

One recent study showed that CRP is increased in DR.[8] However, other studies have shown that CRP was not significantly associated with DR,[45–47] with a few studies reporting lower serum levels of CRP in type 2 diabetic patients with DR compared to those without DR.[48,49] The discrepancy in these studies might arise from differences in the sites of inflammation and production of inflammatory cytokines or the effects of confounding factors, such as drugs or liver disease. In our study, levels of log hsCRP showed a significant difference between the three groups ($P = 0.046$). However, we were unable to find a good model for multivariate logistic analysis to predict the development of DR while still considering the other variables, due to the low statistical significance ($P > 0.129$ in all models). In addition, log hsCRP did not show any statistically significant difference in the subgroup analysis of

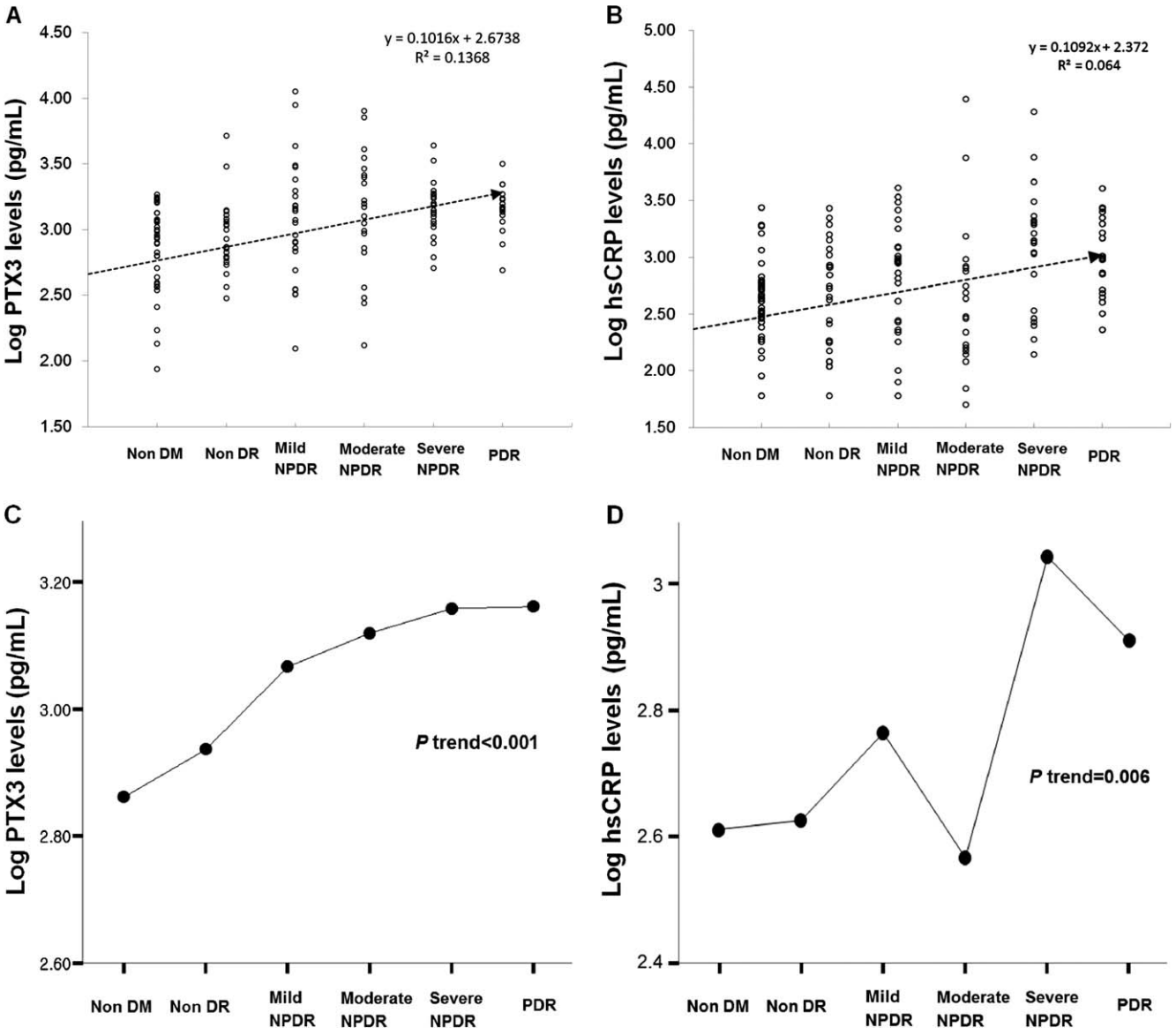

Figure 2. Correlation between log-transformed levels of plasma pentraxin 3 (PTX3) and high-sensitivity C-reactive protein (hsCRP) and subgroups of diabetic retinopathy ($R = 0.372$, $P < 0.001$). (**A**, **B**) Distributions and trends for PTX3 and hsCRP in each subgroup. (**C**, **D**) Changes and trends in the mean value of PTX3 and hsCRP in each subgroup. DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 3. Subgroups of Diabetic Retinopathy and Odds Ratios for Its Prevalence Based on Log PTX3 Quartiles in Patients With Type 2 DM

	Log PTX3 Quartiles			
	1: 2.1–2.87 pg/dL	**2: 2.88–3.12 pg/dL**	**3: 3.13–3.25 pg/dL**	**4: 3.26–4.05 pg/dL**
No DR	16	10	2	2
Mild NPDR	8	6	6	8
Moderate NPDR	6	4	3	8
Severe NPDR	2	7	7	7
PDR	1	4	11	4
ORs (95% CI)		1.85 (0.62–5.57)	9.53 (1.90–47.9)	9.53 (1.90–47.9)
P value for ORs		0.272	0.006	0.006
HbA1c and DM duration-adjusted multivariate ORs (95% CI)		2.59 (0.78–8.61)	8.69 (1.64–46.07)	8.47 (1.59–45.3)
P value for multivariate ORs		0.120	0.011	0.012

TABLE 4. Multivariate Logistic Analysis With Stepwise Selection to Determine the Influence of Clinical Factors for Predicting the Progression From Non-DR to DR in Patients With Type 2 DM

Factor	*P* Value	ORs	95% CI
Duration of DM, y	0.014	1.144	0.027–1.275
Log PTX3, pg/mL	0.025	5.253	1.227–22.483
Statin use	0.058	0.380	0.140–1.033
HbA1c, %	0.121	1.329	0.928–1.903
Hosmer–Lemeshow test	0.561		

group 3 ($P = 0.057$). In contrast, PTX3 showed significantly elevated values in DM patients with DR compared to DM patients without DR and normal subjects ($P < 0.001$). Pentraxin 3 also showed a significant correlation with DR development as revealed by multivariate logistic analysis ($P = 0.025$). Furthermore, although direct comparison of log PTX levels did not detect differences in the four subgroups of group 3 ($P = 0.761$), trend analysis in group 3 showed a significant correlation between PTX 3 levels and severity of DR ($P < 0.001$). Hence, in the present study, PTX3 levels appear to be more closely related to the development and progression of DR than hsCRP.

Regarding a possible cause for this relationship, DR is largely thought to be a result of diabetes-induced retinal microvascular dysfunction and is characterized by capillary leakage or closure, resulting in ischemia. Leukocyte–endothelial interactions play an important role in the early phase of the development of DR. Activated leukocytes such as neutrophils, which act as part of the innate immune system, can cause damage in diseases such as DR by adhering to the endothelium and inducing local vascular and tissue injury.[50] Pentraxin 3 is known to be produced by both activated neutrophils and injured endothelial cells, and the leukocyte–endothelial interaction might stimulate PTX3 as well as the systemic vascular inflammation that causes DR. Pentraxin 3 is believed to be involved in innate immunity and tissue remodeling, which might explain its elevated levels in DM patients with microvascular complications.[51] In this context, previous prospective data also support a possible role of inflammation in diabetogenesis, since they support the hypothesis that type 2 DM may be a manifestation of ongoing cytokine-mediated acute-phase response, initiated by the innate immune system.[52] Hence, PTX3 is a good candidate biomarker to detect diabetic complications in the retina, as well as DR progression. However, the AUC was lower than expected (AUC = 0.721). Since DM and DR are multifactorial diseases, several factors, including age, BMI, DM duration, and HbA1c, could all affect the aggravation of DR, reducing the AUC. However, localized ocular treatments using intravitreal anti-VEGF and PRP did not seem to affect PTX3 levels. Therefore, PTX3 can be an important risk factor for DR development and progression, especially if combined with factors such as HgA1c, DM duration, age, BMI, antioxidant uptake, and hsCRP levels. However, the exact mechanism of DR development and progression is still unclear and must be further studied.

One of the strengths of this study was the inclusion of patients who were carefully selected according to strict criteria by retinal subspecialists (HSY and JMW), who were blinded to the patients' clinical information during DR grading. In addition, the present study focused on the effect of PTX3 on DR development in type 2 DM patients with and without DR. Despite these strengths, this study also has certain limitations. A selection bias due to nonrandomized selection might have occurred, since none of excluded patients agreed to provide

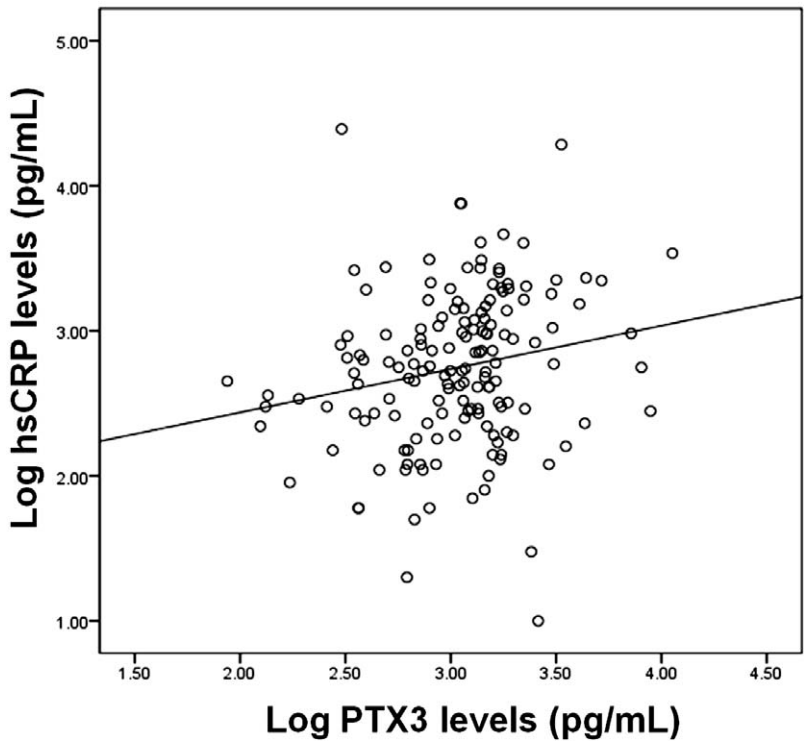

FIGURE 3. Correlation between log pentraxin 3 (PTX3) and log high-sensitivity C-reactive protein (hsCRP) levels in normal and type 2 diabetic patients ($R = 0.196$, $P = 0.014$).

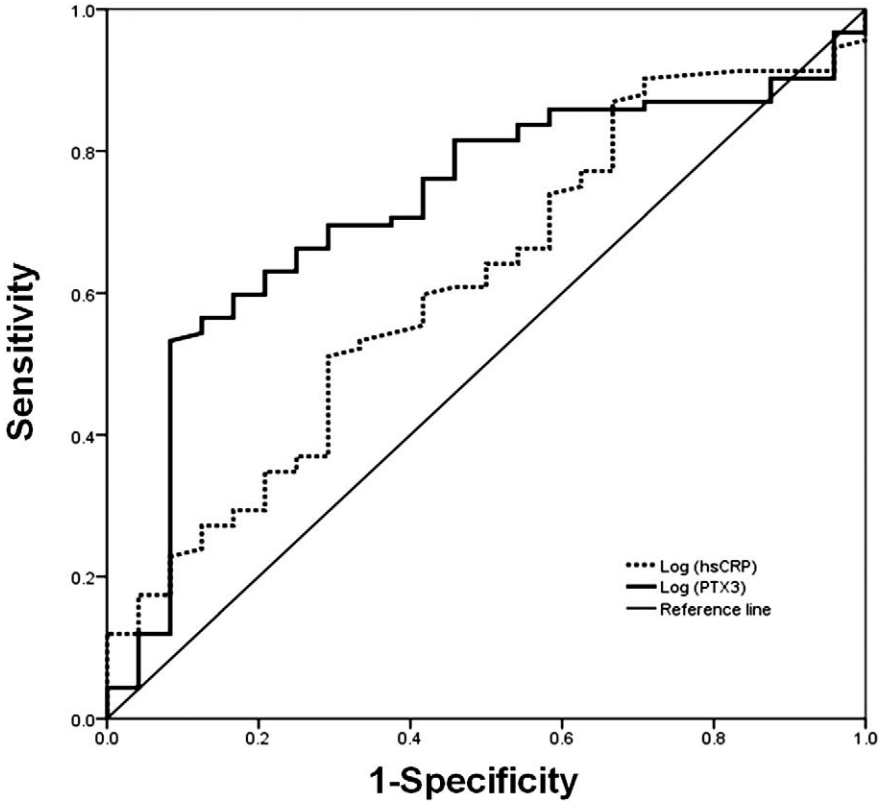

FIGURE 4. Receiver operating characteristic (ROC) curves for log pentraxin 3 (PTX3) and log high-sensitivity C-reactive protein (hsCRP) for predicting the presence of diabetic retinopathy in type 2 diabetic patients.

TABLE 5. AUC and Cutoff Values for Plasma PTX3 and hsCRP for Predicting the Progression From Non-DR to DR in Patients With Type 2 DM

	Cutoff Value	AUC	Sensitivity	Specificity	95% CI	*P* Value
Log PTX3, pg/mL	3.14, PTX3 = 1406.0	0.721	0.533	0.917	0.606–0.835	0.001
Log hsCRP, pg/mL	2.91, hsCRP = 841.7	0.614	0.511	0.708	0.491–0.737	0.087

their blood samples or other information, and study patients were selected only from visitors to the university hospital. In addition, the sample size was relatively small and was based solely on Korean patients. One study, examining kidney dysfunction patients, has reported that black and Chinese patients have lower levels of PTX3 than white and Hispanic patients,[53] and therefore our results may not generalize to all patients. Moreover, although we compared age- and BMI-matched groups, the use of statins, which was shown to affect PTX3 levels in an earlier study, was still frequent in our DR patients and could bias our results as described above.[54] However, subgroup analysis showed that the relationship between statin use and DR development ($P = 0.058$; multivariate logistic regression analysis) and DR progression ($P = 0.084$; χ^2 test) was not significant.

In conclusion, our study suggests that plasma PTX3 is closely associated with DR development and progression, and may be a better predictor for DR development than hsCRP in DM patients. Future studies should address validation of the role of PTX3 and its mechanism of action.

Acknowledgments

Disclosure: **H.S. Yang**, None; **J.E. Woo**, None; **S.J. Lee**, None; **S.H. Park**, None; **J.M. Woo**, None

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