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Evaluation of pentraxin-3 level in patients with diabetic retinopathy

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Objective
The aim of this study was to evaluate serum pentraxin-3 (PTX3) levels as an indicator of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).

Background
DR is responsible for 10.2% of worldwide visual loss. Pentraxin-3 is an acute phase protein secreted by different types of cells and correlates with the disease activity.

Patients and methods
A total of 80 individuals were included in the study. They were divided into three groups. Group 1 included 30, type 2 diabetic patients without retinopathy, group 2 included 30, type 2 diabetic patients with retinopathy, and group 3 included 20 apparently healthy individuals. Group 2 was subdivided into 20 patients with nonproliferative and 10 patients with proliferative DR. Serum glycated hemoglobin, C-reactive protein (CRP), lipid profile, liver function tests, renal function tests, serum PTX3 level, and fundus examination were measured in all the patients.

Results
Serum PTX3 was significantly elevated in T2DM with retinopathy than T2DM without retinopathy and control group. There is no statistical difference between proliferative and nonproliferative DR regarding PTX3. Serum PTX3 was significantly positively correlated with age and high-sensitivity CRP in the proliferative DR group and cholesterol, low-density lipoprotein and high-sensitivity CRP in the proliferative DR group.

Conclusion
PTX3 levels were significantly higher in T2DM with retinopathy than those without retinopathy and control group, and positively correlated with inflammatory marker. Thus, it might be used in the prognosis of DR.

Keywords:
diabetes mellitus, diabetic retinopathy, pentraxin-3, prognosis

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Introduction

Diabetes mellitus (DM) is an epidemic disease that accounts for high rate of morbidity and mortality. This is due to the high rate of occurrence of complications that lead to health burden both for patients and countries [1]. Death from cardiovascular complications affects nearly 50% of type 2 diabetes mellitus (T2DM) patients [2].

Diabetic complications include both microvascular and macrovascular. Retinopathy, nephropathy, and neuropathy are microvascular complications [3].

DM microvascular complications are caused by systemic inflammatory reaction [4,5]. The relationship between increased plasma concentration of acute phase biomarkers such as C-reactive protein (CRP) and T2DM has been reported by several studies [6,7].

Singh *et al.* [8] stated that diabetic retinopathy (DR) is a microangiopathy affecting all of the small retinal vessels, such as arterioles, capillaries, and venules. DR is characterized by increased vascular permeability, ocular hemorrhages, and lipid exudate. DR is responsible for a higher percentage of patients with visual loss [9]. Recently, DR is classified as either nonproliferative or proliferative [10].

Pentraxin-3 (PTX3) is an acute phase reactant released by peripheral tissues in response to endothelial dysfunction [11]. PTX3 promotes restenosis, inhibits angiogenesis, and increases the formation of advanced atherosclerotic lesions, typically by inhibiting the fibroblast growth factor (FGF2) reaction of angiogenesis [12,13]. Recently, PTX3 has been shown to be a sensitive biomarker of localized inflammatory reactions and innate immunity in cardiovascular and renal diseases [14–16].

Elevated levels of plasma CRP and short pentraxin are more frequently observed in both DM and DR patients [17,18].

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There are very few studies on PTX3 in DR [19], so the aim of our study was to determine the PTX3 level in T2DM patients with retinopathy and use it as a diagnostic and prognostic tool among those patients.

Patients and methods

This study was carried out at the Internal Medicine Department, Menoufia University Hospitals and Ahmed Maher Teaching Hospital. We divided the patients into three groups: group 1 included 30 T2DM patients without retinopathy (16 men and 14 women); group 2 included 30 T2DM patients with retinopathy (17 men and 13 women); and group 3 included 20 apparently healthy volunteers as a control (10 men and 10 women). Group 2 is subdivided into 20 patients with nonproliferative diabetic retinopathy (NPDR) and 10 patients with proliferative diabetic retinopathy (PDR).

All patients underwent full history taking and clinical examination was performed. Blood pressure measurements were taken using sphygmomanometer as a mean on three times at different occasions in sitting position: diastolic pressure (DP), systolic pressure (SP) measured, and mean arterial pressure = DP + 1/3(SP – DP), (normally 70–110 mmHg) [20]. Also, BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2) [21].

Patients with the following criteria were excluded: patients with a history of hypertension, patients with any form of chronic infection or current or past history of receiving any immune modulating drugs, patients with malignancy, renal impairment, intravenous drug abusers, patients with severe eye disease, and retinal detachment.

The protocol for this study followed the ethical standards and approved by the ethical committee of our institution and all patients gave informed consent to participate in this study.

Laboratory assessment

Blood samples for hematological and biochemical measurements were obtained from the forearm after overnight fasting. Serum glycated hemoglobin (HA1C), CRP, liver function tests, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and renal function tests (urea, creatinine) were measured by standard methods in the routine clinical laboratory.

Serum PTX3 levels were determined by an enzyme-linked immunoassay using PTX3 ELISA kits from Shanghai Sunred Biological Technology Company (Shanghai, China), according to the manufacturer's instructions.

Fundus examination

Fundus examination was carried out by slit lamp biomicroscope and indirect ophthalmoscopy, fundus color photograph centered on the macula and fundus fluorescein angiography wherever indicated.

Statistical analysis

Data were analyzed using the Program for Social Science, version 20.0 for windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc 13 for windows (MedCalc Software BVBA, Ostend, Belgium). Data were analyzed using statistical quantitative data and were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage. The following statistical tests were used as appropriate: χ^2-test, Student's *t*-test. Correlations between variables were done using Spearman's rank correlation coefficient (*r*). Values of *P* less than 0.05 were taken as statistically significant.

Results

Sixty diabetic patients were included in our study. They were divided into two groups; group 1 diabetic without retinopathy (30 patients), group 2 included 30 T2DM patients with retinopathy (17 men and 13 women); group 3 included 20 apparently healthy volunteers as a control (10 men and 10 women); besides group 2 was subdivided into NPDR (20 patients) and PDR (10 patients). Mean age of the groups were 55.03 ± 7.44,58 ± 6.68 and 66 ± 5.14 years, respectively, and the female: male ratios were 14: 16, 8: 12, and 5: 5, respectively (Table 1).

HA1C was highly significant in diabetes with normal fundus and retinopathy groups than in the control group (*P* = 0.000), whereas there was no significant difference between retinopathy group and diabetes with normal fundus group (*P* = 0.914) (Table 1).

As regards PTX3 and high-sensitivity C-reactive protein (hsCRP) levels, there were highly significant increase in NPDR group than in diabetes with normal fundus group (*P* = 0.000); there was also significant difference between PDR and diabetes with normal fundus group (*P* = 0.001 and 0.002, respectively) and no significant difference between PDR and NPDR (*P* = 0.891 and 0.981v) (Table 2 and Figs. 1 and 2).

In diabetes with normal fundus group PTX3 was positively correlated with hsCRP and age, significant with systolic blood pressure and not significant

Table 1 Comparison between studied groups according to demographic and clinical data

Variables	Control group (*n*=20)	DM+retinopathy (*n*=30)	DM+normal fundus (*n*=30)	One-way ANOVA test		*Post-hoc* analysis		
				$F/\chi^{2*}/t$	*P*	P_1	P_2	P_3
Age								
Mean±SD	53.3±6.18	55.03±7.44	60.67±7.22	7.874	0.001	0.398	0.001	0.003
Range	41-64	42-72	50-75					
Sex (*n* [%])								
Female	10 (50.0)	14 (46.7)	13 (43.3)	0.218*	0.897	0.817	0.643	0.795
Male	10 (50.0)	16 (53.3)	17 (56.7)					
BMI								
Mean±SD	24.14±1.43	25.55±1.43	27.26±1.97	21.951	0.000	0.004	0.000	0.000
Range	21.5-26.4	23.2-29	23.1-31					
Duration								
Mean±SD	-	8.17±1.29	12.63±2.8	−7.943	0.000	-	-	-
Range	-	6-10	10-22					
Smoking (*n* [%])								
No	13 (65.0)	22 (73.3)	20 (66.7)	0.485*	0.785	0.529	0.903	0.573
Yes	7 (35.0)	8 (26.7)	10 (33.3)					
Systolic BP								
Mean±SD	121.75±11.27	128.17±15.45	125±11.45	1.468	0.237	0.093	0.391	0.351
Range	100-140	105-155	110-145					
Diastolic BP								
Mean±SD	73±6.37	77.67±9.71	74±5.15	2.900	0.061	0.033	0.643	0.060
Range	60-85	60-100	65-80					
AST (U/l)								
Mean±SD	33.35±20.7	24.37±14.93	27.87±17.82	1.566	0.215	0.081	0.283	0.443
Range	5-77	5-64	9-77					
ALT (U/l)								
Mean±SD	31.15±14.01	26±11.85	30.23±16.29	1.010	0.369	0.212	0.824	0.251
Range	13-53	13-60	8-74					
Creatinine (mg/dl)								
Mean±SD	0.75±0.22	0.89±0.29	1.08±0.39	6.844	0.002	0.117	0.001	0.025
Range	0.32-1.1	0.31-1.76	0.43-1.9					
Cholesterol (mg/dl)								
Mean±SD	180.4±56.14	198.87±44.31	206.33±52.93	1.599	0.209	0.211	0.080	0.570
Range	96-299	140-325	120-301					
Triglycerides (mg/dl)								
Mean±SD	118.55±36.58	147.27±29.79	138.73±39.96	3.973	0.023	0.007	0.053	0.356
Range	72-180	88-211	89-270					
HDL (mg/dl)								
Mean±SD	39.35±9.14	45.27±12.11	43.93±12.97	1.580	0.213	0.086	0.182	0.663
Range	25-55	28-78	22-75					
LDL (mg/dl)								
Mean±SD	110.9±49.41	125.83±43.08	135.63±46.48	1.735	0.183	0.264	0.066	0.412
Range	44-231	60-242	62-215					
HA1C								
Mean±SD	5.18±0.14	8.71±1.86	8.76±1.72	39.093	0.000	0.000	0.000	0.914
Range	5-5.4	6.5-12.6	6.7-12					
hsCRP (pg/ml)								
Mean±SD	2.6±0.35	2.76±0.33	3.09±0.2	18.537	0.000	0.062	0.000	0.000
Range	1.88-2.99	1.94-3.12	2.43-3.42					
PTX3 (pg/ml)								
Mean±SD	2.89±0.17	2.91±0.32	3.22±0.15	18.284	0.000	0.751	0.000	0.000
Range	2.6-3.13	2.23-3.26	2.75-3.45					

*Significant value *P* is less than 0.05. χ^2, χ^2-test. *t*, independent Student's t-test. Independent *t*-test: ANOVA, analysis of variance; BP, blood pressure; DM, diabetes mellitus; HA1C, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTX3, Pentraxin-3. P_1: Control group versus DM + normal fundus. P_2: Control group versus DM+retinopathy. P_3: DM + normal fundus versus DM + retinopathy.

with duration, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, cholesterol, diastolic blood pressure, LDL, HDL, and HA1C (Table 3).

Table 2 Comparison between diabetes without retinopathy group and retinopathy subgroups (nonproliferative diabetic retinopathy and proliferative diabetic retinopathy) according to demographic and clinical data

Variables	DM+normal fundus (*n*=30)	NPDR (*n*=20)	PDR (*n*=10)	One-way ANOVA test		Post-hoc analysis		
				F/χ^{2*}	*P*	P_1	P_2	P_3
Age	55.03±7.44	58±6.68	66±5.14	9.553	0.000	0.140	0.000	0.002
Sex (*n* [%])								
Female	14 (46.7)	8 (40.0)	5 (50.0)	0.337*	0.845	0.642	0.845	0.602
Male	16 (53.3)	12 (60.0)	5 (50.0)					
BMI	25.55±1.43	26.71±1.96	28.35±1.56	11.397	0.000	0.017	0.000	0.016
Duration	8.17±1.29	11.1±1.02	15.7±2.71	93.606	0.000	0.000	0.000	0.000
Smoking (*n* [%])								
Yes	22 (73.3)	12 (60.0)	8 (80.0)	1.587*	0.452	0.322	0.452	0.273
No	8 (26.7)	8 (40.0)	2 (20.0)					
Systolic BP	128.17±15.45	125.25±12.08	124.5±10.66	0.410	0.666	0.464	0.467	0.867
Diastolic BP	77.67±9.71	73.25±5.45	75.5±4.38	1.932	0.154	0.055	0.450	0.310
AST (U/l)	24.37±14.93	29±18.44	25.6±17.23	0.477	0.623	0.336	0.839	0.649
ALT (U/l)	26±11.85	27.95±18.35	34.8±10.49	1.447	0.244	0.636	0.095	0.256
Creatinine (mg/dl)	0.89±0.29	1.12±0.38	0.99±0.4	2.691	0.076	0.024	0.419	0.325
Cholesterol (mg/dl)	198.87±44.31	206.05±58.51	206.9±42.43	0.173	0.841	0.615	0.657	0.968
Triglycerides (mg/dl)	147.27±29.79	133.55±43.79	149.1±30.29	1.094	0.342	0.182	0.887	0.304
HDL (mg/dl)	45.27±12.11	44.6±14.74	42.6±8.97	0.167	0.847	0.856	0.566	0.661
LDL (mg/dl)	125.83±43.08	136.25±52.04	134.4±35.25	0.358	0.701	0.428	0.606	0.921
HA1C	8.71±1.86	8.69±1.81	8.89±1.61	0.045	0.956	0.964	0.790	0.704
hsCRP (pg/ml)	2.76±0.33	3.08±0.2	3.09±0.21	10.707	0.000	0.000	0.002	0.981
PTX3 (pg/ml)	2.91 ± 0.32	3.22 ± 0.17	3.23 ± 0.1	11.785	0.000	0.000	0.001	0.891

*Significant values *P* less than 0.05. ANOVA, analysis of variance; BP, blood pressure; DM, diabetes mellitus; HA1C, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTX3, Pentraxin-3. P_1: DM + normal fundus versus NPDR group. P_2: DM + normal fundus versus PDR group. P_3: NPDR versus PDR.

Table 3 Correlation between log Pentraxin-3 and other measured laboratory parameters

Log PTX3	DM+normal fundus		NPDR		PDR	
	r	*P*	*r*	*P*	*r*	*P*
log hsCRP	0.778**	0.000	0.661**	0.002	0.661*	0.038
Age	0.902**	0.000	0.759**	0.000	0.607	0.063
BMI	0.050	0.795	0.122	0.607	−0.523	0.121
Duration	0.008	0.968	−0.299	0.201	0.291	0.415
Systolic BP	0.577**	0.001	0.061	0.798	0.124	0.732
Diastolic BP	0.321	0.084	0.244	0.301	0.113	0.757
AST	−0.066	0.727	0.191	0.421	−0.622	0.055
ALT	−0.045	0.811	0.058	0.808	−0.433	0.211
Creatinine	−0.213	0.259	0.319	0.170	0.527	0.117
Cholesterol	−0.036	0.851	0.182	0.442	−0.699*	0.024
Triglycerides	−0.134	0.479	0.067	0.779	−0.401	0.250
HDL	−0.171	0.368	0.030	0.899	−0.232	0.519
LDL	0.059	0.758	0.217	0.359	−0.657*	0.039
HA1C	0.304	0.102	0.220	0.351	0.043	0.907

*Significant values *P* less than 0.05, **Highly significant value with *P* less than 0.001. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; log hsCRP, log-transformed value of high-sensitivity C-reactive protein; log PTX3, log-transformed value of Pentraxin-3; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; *r*, Pearson's correlation coefficient.

In NPDR group, PTX3 did not correlate with duration, blood pressure, AST, ALT, creatinine, cholesterol, blood pressure, LDL, HDL, and HA1C. However, PTX3 is highly significant with age, with significant correlation with hsCRP (Table 3).

In the PDR group, PTX3 did not correlate with age, duration, blood pressure, AST, ALT, creatinine, cholesterol, blood pressure, HDL, and HA1C). In contrast, PTX3 was significant with (log hsCRP, cholesterol, LDL) (Table 3 and Fig. 3).

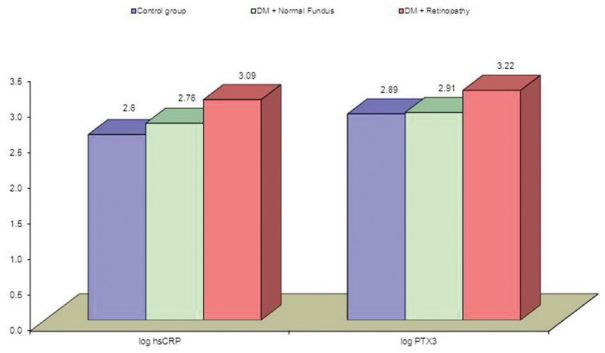
The cutoff point for PTX3 was 1150 pg/ml that has sensitivity 93.3% and specificity 72%, and cutoff point of CRP was 760 pg/ml has sensitivity 93.3% and specificity 68%. Combined use of PTX3 and CRP decrease sensitivity to 76.7%, but increase specificity to 90% (Fig. 4).

Discussion

The most common microvascular complication of DM is DR that leads to preventable visual loss in diabetic patients [22,23]. The percentage of DR in T2DM after a duration of 20 years is estimated at about 60% [24]. The increased incidence of DR is due to many factors such as poor glycemic control and long duration of diabetes, associated hypertension, hyperlipidemia, nephropathy, pregnancy, and anemia [10].

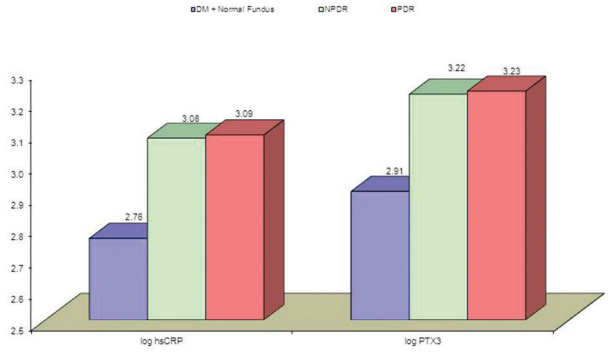
Many factors have involved in the pathogenesis of DR such as chronic hyperglycemia, increased polyol and protein kinase C pathway activity [25,26], increased vascular endothelial growth factor [25], production

Figure 1



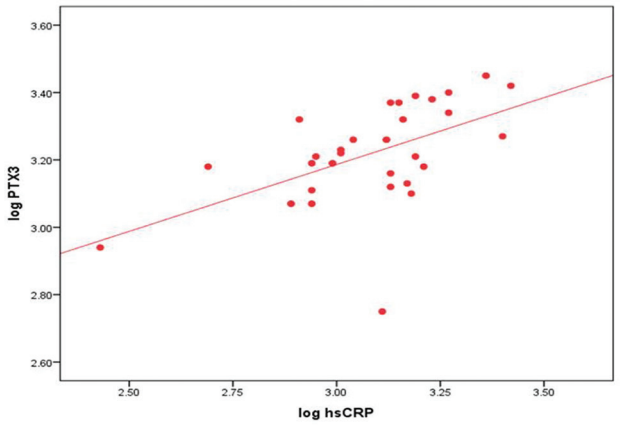
Comparison between log PTX3 and log hsCRP in the studied groups. DM, diabetes mellitus; log hsCRP, log-transformed value of high-sensitivity C-reactive protein; PTX3, Pentraxin-3.

Figure 2



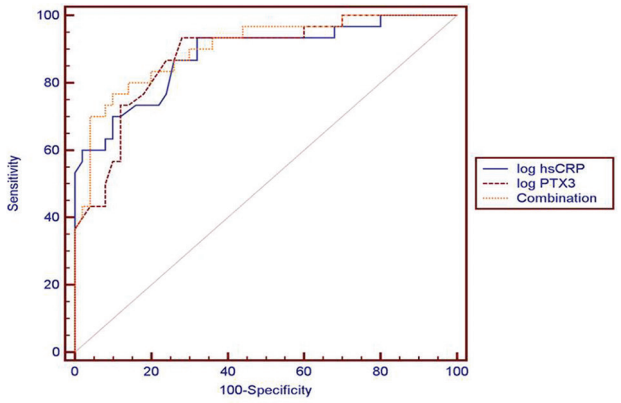
Comparison between levels of log hsCRP and log PTX3 in the patient group. DM, diabetes mellitus; log hsCRP, log-transformed value of high-sensitivity C-reactive protein; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PTX3, Pentraxin-3.

Figure 3



Correlation between log hsCRP and log PTX3 in diabetes with retinopathy. log hsCRP, log-transformed value of high-sensitivity C-reactive protein; PTX3, Pentraxin-3.

Figure 4



Receiver operating characteristic curve for detection of the best cutoff point of serum PTX3 and hsCRP in diabetic retinopathy. log hsCRP, log-transformed value of high-sensitivity C-reactive protein; PTX3, Pentraxin-3.

of advanced glycation end products [27], chronic oxidative damage [28], increased activation of the renin angiotensin system, and chronic inflammation and leukostasis [10].

PTX3 is a 200 amino acid protein that is secreted from the endothelium, macrophages, myeloid cells, dendritic cells, and many other cells in response to cytokines and endotoxins such as bacterial products, interleukin-1, and tumor necrosis factor [29].

PTX3 plays many biological roles such as in the regulation of inflammatory reaction, innate immunity, and female fertility [11]. The expression of PTX3 is increased in acute coronary syndromes [30], and it is a predictor of poor outcome in congestive heart failure patients [31]. PTX3 is also increased in many other diseases such as sleep apnea syndrome [32], pulmonary infection [33], rheumatoid arthritis, progressive systemic sclerosis, and in other rheumatologic diseases [34].

Both PTX3 and CRP are acute phase reactants known to be involved in inflammation, endothelial dysfunction, and atherosclerosis [35–39]. As they are increased in DM, they can be used as prognostic factors for vascular complications such as DR [5,38,39].

In our study, plasma levels of PTX3 and CRP were significantly higher in both NPDR and PDR than in diabetes with normal fundus group and with normal individuals, whereas there was no significant difference between both groups of diabetic retinopathy. This reflects that DR in T2DM is an inflammatory process associated with increase inflammatory reactants.

PTX3 and CRP, in our study as well as in the study by Zhou *et al.* [19] and Yang *et al.* [40], showed significant increase in their levels with the development and progression of DR, with a cutoff value of 1150 pg/ml and sensitivity 93.3% and specificity 72% for PTX3, and with a cutoff value of 760 pg/ml and sensitivity

93.3% and specificity 68% for CRP. The combined use of PTX3 and CRP decreases the sensitivity to 76.7%, but increases specificity to 90%.

Similar results regarding elevated PTX3 and CRP in DR were documented by Yang *et al.* [40] and Woo *et al.* [40,41], who reported that the retinal pigment epithelium and vascular tissues can express PTX3 locally reflecting that it can be used as a biomarker of vascular inflammation. Yang *et al.* [40] stated that PTX3 levels are associated with the development and progression of DR in Korean patients with T2DM. This was a case–control study which recruited 163 individuals – 92 diabetic patients with DR, 30 diabetics without DR, and 41 healthy controls whose plasma levels of PTX3 and hsCRP were measured and compared. The proportion of higher-degree retinal complications increased in direct correlation with log PTX3 levels with a *P* trend less than 0.001 whereas a similar analysis based on log hsCRP values had a *P* trend of 0.006. On the basis of the PTX3 and hsCRP levels selected based on receiver operating curves, the diagnostic sensitivity of PTX3 for DR was 53.3% and the sensitivity was 91.7% while for hsCRP it was 51.1 and 70.8%, respectively. The authors therefore suggested that PTX3 may be a more accurate predictor of DR development than hsCRP. The presence of elevated PTX3 levels from early disease and its progressive elevation with increasing disease severity seem to suggest it has potential as a screening marker.

Nowak *et al.* [17] reported similar results regarding CRP whereas other studies such as that of Cai *et al.* [42] and Nguyen *et al.* [43], did not show significant association between CRP and DR. Few studies have reported lower serum levels of CRP in T2DM with DR compared with those without DR as in Lim *et al.* [44] and Tsunoda *et al.* [45]. Yang *et al.* [40] assumed that this discrepancy could be due to differences in the sites of inflammation and production of inflammatory cytokines or the effects of confounding factors such as drugs or liver disease.

Possible explanations of this association are that DM microangiopathy is associated with endothelial dysfunction and neutrophil adhering to the damaged endothelium and inducing local vascular and tissue injury [46].This leukocyte–endothelial interaction produces PTX3 that is believed to be involved in innate immunity and tissue remodeling. [47]. This supports the hypothesis that T2DM may be a manifestation of ongoing cytokine-mediated acute-phase response, initiated by the innate immune system [48].

Conclusion

PTX3 as well as CRP are acute phase reactants that can be used as markers of progression of retinopathy in T2DM and they are increased with disease duration. Moreover, poor glycemic control was significantly associated with higher incidence and severity of diabetic retinopathy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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