Research Article

Pentraxin 3 (Ptx3) As A Novel Biomarker In Type 1 Diabetes With Diabetic Retinopathy

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Abstract

Background: Diabetic retinopathy (DR) remains a major microvascular complication of type 1 diabetes mellitus (T1DM), and inflammatory biomarkers such as pentraxin-3 (PTX3) have been proposed as potential indicators of retinal microvascular injury.
Objective: To investigates whether increased plasma PTX3 levels are associated with DR in patients with T1DM and assesses PTX3 as a candidate early biomarker for the detection of DR and for monitoring its progression.
Methods: This case–control analytical study was conducted over 18 months at Cairo University Pediatric Hospital and Kasr Al-Ainy Pediatric University Hospital (Cairo, Egypt). Thirty-six patients with confirmed T1DM were included and allocated into two equal groups based on ophthalmological assessment: DR (n=18) and no DR (n=18). Fundus assessment was performed by a specialized ophthalmologist, and plasma PTX3 was measured using a sandwich ELISA.
Results: Patients with DR were older (23.72±9.9 vs 14.42±3.03 years; p=0.001) and had longer diabetes duration (13.33±6.62 vs 8.22±3.03 years; p=0.017). Mean PTX3 was higher in the DR group (7.27±3.47 vs 5.78±2.81 pg/mL), but the difference was not statistically significant (p=0.282). Diagnostic performance of PTX3 for detecting DR was limited (AUC 0.605; 95% CI 0.414–0.795; p=0.282); at a cutoff of 8.62 pg/mL, sensitivity was 50% and specificity 83%.
Conclusion: In this cohort, plasma PTX3 alone showed limited ability to discriminate DR in T1DM and may be more useful as part of a combined risk-assessment panel rather than a standalone biomarker.

Keywords: Type 1 diabetes mellitus; diabetic retinopathy; pentraxin-3; inflammation; biomarker; ELISA.

INTRODUCTION

Diabetes mellitus (DM) is a major cause of morbidity and mortality around the world and is associated with numerous long-term complications [1]. Among them, diabetic retinopathy (DR) is a common microvascular complication and the major cause of blindness among working-aged persons [2]. Global prevalence estimates indicate that approximately 25.2 % of adults with diabetes develop DR, with regional differences ranging from 12.5 % in Southeast Asia to 36.2 % in the Western Pacific. DR prevalence is particularly high in individuals with type 1 diabetes mellitus (T1DM), with around 75 % of T1DM patients and 50 % of those with type 2 diabetes developing DR during their lifetime [3].

Although sight-threatening retinopathy is uncommon in childhood, early retinal changes are increasingly observed in children and adolescents with T1DM. A recent audit of British Pediatric Diabetes services (2022–2024) showed that background DR was detected in 6 of 68 screened children (8.9 %) aged ≥12 years, despite substantial improvements in glycemic control over the past decade, previously reported a 19.5 % prevalence of background DR in 2008, suggesting that early retinal changes remain a concern even with better glycemic management [4]. Children and adolescents have longer expected exposure to hyperglycemia, and microvascular complications can develop within a few years of diagnosis. The risk of earlier onset and faster progression of microvascular damage is particularly notable after puberty, yet these complications are often asymptomatic until significant damage has occurred [5]. Early detection through regular screening is therefore essential to prevent vision-threatening disease.

The pathogenesis of DR is multifactorial. Chronic hyperglycemia triggers immune cells to release cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1β, interleukin 6, and other mediators that promote endothelial injury and oxidative stress [6].

They are implicated in structural and functional alterations of retinal microvasculature, such as loss of pericytes, thickening of the basement membrane, and breakdown of the blood–retinal barrier [7]. With the advancement

of the disease, retinal ischemia induces the overexpression of the vascular endothelial growth factor (VEGF), leading to pathological neovascularization and proliferative DR [8]. Inflammation is central to DR, with elevated inflammatory markers in blood and ocular fluids supporting a role for chronic low-grade inflammation [9].

Pentraxin 3 (PTX3) belongs to the long pentraxin family and is produced locally at the inflammation site by various cell types, including endothelial cells, smooth muscle cells, and macrophages, following early pro-inflammatory cues [10]. PTX3 is secreted directly at the site of inflammation and therefore makes a valuable marker of localized vascular inflammation [11]. Higher PTX3 concentrations have been linked to a range of cardiovascular conditions and inflammatory diseases [10].

There is support that recent research has suggested an involvement of PTX3 in DR pathogenesis. High levels of PTX3 have been detected in diabetic and retinopathic patients, as opposed to non-retinopathic patients, supporting the suggestion that PTX3 might be a marker of inflammatory and vascular changes within the retina [12]. Evidence from currently available sources, particularly among T1DM patients, is unclear and limited, and further investigation is required.

Therefore, this study investigates whether increased plasma PTX3 levels are associated with DR in patients with T1DM and assesses PTX3 as a candidate early biomarker for the detection of DR and for monitoring its progression.

MATERIALS AND METHODS

Study Design and Setting

This case–control analytical study was conducted over 18 months at Cairo University Pediatric Hospital and the Ophthalmology Outpatient Clinic, Kasr Al-Ainy Pediatric University Hospital, Cairo, Egypt

Participants and allocation

Children and adolescents with confirmed T1DM were consecutively recruited from the Pediatric Endocrinology Outpatient Clinic. Participants were allocated into two equal groups based on ophthalmological assessment: cases (T1DM with diabetic retinopathy, DR) and controls (T1DM without DR), with 18 patients in each group.

Eligibility criteria

Eligible participants were older than 10 years, had a confirmed diagnosis of T1DM for at least 5 years, were receiving regular multiple daily insulin injections (MDI), and were attending regular follow-up for glycemic control and retinal assessment. Patients were excluded if they had other systemic illnesses (such as hypertension, systemic autoimmune diseases, renal dysfunction, or other metabolic disorders), acute or chronic infection, history of malignancy, use of immunomodulatory drugs, intravenous drug abuse, or severe ocular disease/retinal detachment due to non-diabetic causes.

Ethical approval and consent

Recruitment started after approval from the Ethics and Scientific Committees of the Pediatric Department, Faculty of Medicine, Cairo University, under REC code MD-7-2024. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from the legal guardians. Confidentiality, voluntary participation, and the right to withdraw without affecting care were assured.

Study procedures and visits

Each participant completed at least three core study visits. The first visit included detailed history-taking, a physical examination, and a review of glycemic control records. The second visit ensured referral for a comprehensive fundus examination if one had not been performed within the preceding 12 months. The third visit included retrieval of fundus findings and venous blood sampling for laboratory testing, including PTX3 measurement.

Clinical assessment

Clinical evaluation included demographic data and detailed diabetes history (age at diagnosis, duration, insulin regimen, frequency of self-monitoring of blood glucose, frequency of HbA1c testing, and history of fundus examinations), alongside past medical history (including associated autoimmune disorders) and family history. Physical examination included anthropometric measures, vital signs, and general systemic examination (including thyroid and skin assessment).

Ophthalmological assessment and retinopathy classification

Fundus assessment was performed by a specialized ophthalmologist using slit-lamp biomicroscopy and indirect ophthalmoscopy, with fundus color photography centered on the macula, and fluorescein angiography when

indicated. Diabetic retinopathy was classified as no DR, non-proliferative DR (NPDR), or proliferative DR (PDR). Ocular symptoms were recorded, including blurred vision, decreased visual acuity, and dark spots or peripheral night-vision loss.

Laboratory investigations

Complete blood count, erythrocyte sedimentation rate, C-reactive protein, albumin/creatinine ratio, renal function tests (urea and creatinine), liver enzymes (SGOT, SGPT), lipid profile (total cholesterol, LDL, HDL), and HbA1c were measured using standard laboratory procedures. Nouh MZ, Sonbol A, Mogahed M. Evaluation of pentraxin-3 level in patients with diabetic retinopathy. Menoufia Medical Journal. 2018 Jul 1;31(3):928.

Sample size calculation

The sample size was calculated using previously reported PTX3 values [13]. Using the higher SD (0.32 pg/mL), a minimum of 18 patients per group was required to achieve 80% power at a 5% significance level (two-sided Student's t-test). Calculations were performed using PS Power and Sample Size Calculations software (version 3.1.2, Vanderbilt University, Nashville, TN, USA).

Statistical analysis

Statistical analyses were performed using SPSS version 29. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as median (interquartile range) due to non-normal distribution. Normality was evaluated using the Shapiro–Wilk test. Group comparisons were conducted using the chi-square test for categorical data, Fisher's exact test when expected counts were <5, and the Mann–Whitney U test for non-parametric continuous variables. Statistical significance was set at $p < 0.05$.

RESULTS

The analysis included 36 patients with T1DM, divided into two equal groups based on ophthalmological assessment: 18 patients with DR and 18 patients without DR.

Comparison of Demographic and Clinical Characteristics Between Groups

Patients with DR were significantly older than those without retinopathy (23.72 ± 9.9 vs. 14.42 ± 3.03 years, p = 0.001) and had longer diabetes duration (13.33 ± 6.62 vs. 8.22 ± 3.03 years, p = 0.017). Mean weight and height were also significantly higher in the DR group (58.73 ± 20.72 vs. 47.01 ± 14.46 kg, p = 0.018; and 157.25 ± 19.57 vs. 150.78 ± 14.42 cm, p = 0.043, respectively) (Table 1).

Table (1): Demographic and anthropometric comparison between the two groups

		No DR (n=18)	DR (n=18)	P-value
Sex	**Female**	8(42%)	11(58%)	0.317
	Male	10(59%)	7(41%)	
Age (years)	**Mean ± SD**	14.42±3.03	23.72±9.9	0.001
Diabetes Duration (years)	**Mean ± SD**	8.22±3.03	13.33±6.62	0.017
Weight (kg)	**Mean ± SD**	47.01±14.46	58.73±20.72	0.018
Height (cm)	**Mean ± SD**	150.78±14.42	157.25±19.57	0.043
BMI SD	**Mean ± SD**	0.1±1.31	0.35±1.8	0.367
Height **SD**	**Mean ± SD**	-0.85±1.27	-1.03±3.02	0.359

Data presented as n (%) for categorical variables and mean ± SD for continuous variables. BMI: Body Mass Index; DR: Diabetic Retinopathy; SD: Standard Deviation.

Associated Comorbidities and Diabetic Complications

Hashimoto thyroiditis was present exclusively in patients with DR (3 cases, 100% vs. 0%, p = 0.035). Diabetic nephropathy was diagnosed in 7 patients with DR compared to none without DR (p = 0.003). Diabetic neuropathy was found in 6 patients with DR and none without (p = 0.002) (Table 2).

Table (2): Associated comorbidities in patients with and without DR

Comorbidity	Status	No DR n (%)	DR n (%)	P-value
Fatty Liver	**No**	14 (52%)	13 (48%)	0.7
	Yes	4 (44%)	5 (56%)	
Hepatic Glycogenosis	**No**	15 (50%)	15 (50%)	1

	Yes	3 (50%)	3 (50%)	
Rheumatoid Disease	**No**	18 (53%)	16 (47%)	0.146
	Yes	0 (0%)	2 (100%)	
Hashimoto Disease	**No**	18 (55%)	15 (45%)	0.035
	Yes	0 (0%)	3 (100%)	
Celiac Disease	**No**	16 (47%)	18 (53%)	0.089
	Yes	2 (100%)	0 (0%)	
Diabetic Nephropathy	**No**	18 (62%)	11 (38%)	0.003
	Yes	0 (0%)	7 (100%)	
Diabetic Neuropathy	**No**	18 (60%)	12 (40%)	0.002
	Yes	0 (0%)	6 (100%)	
Hyperlipidemia	**No**	14 (54%)	12 (46%)	0.457
	Yes	4 (40%)	6 (60%)	

Data presented as n (%). DR: Diabetic Retinopathy.

Ocular Symptoms and Fundus Findings

Blurring of vision, decreased visual acuity, and dark spot or peripheral night vision loss were significantly more frequent among patients with diabetic retinopathy ($p = 0.001$, <0.001, and 0.009, respectively). Retinal findings also differed significantly, with normal fundus being more frequent in patients without retinopathy ($p < 0.001$), while NPDR was more common among those with retinopathy ($p < 0.001$) (Table 3).

Table (3): Ocular symptoms and retinal signs in the two groups

Finding	Status	**No DR n (%)**	**DR n (%)**	P-value
Blurring vision	**No**	18 (62%)	11 (38%)	0.001
	Yes	0 (0%)	7 (100%)	
Decrease Visual Acuity	**No**	18 (67%)	9 (33%)	<0.001
	Yes	0 (0%)	9 (100%)	
Dark Spot/Peripheral night loss	**No**	18 (58%)	13 (42%)	0.009
	Yes	0 (0%)	5 (100%)	
Normal Fundus	**No**	0 (0%)	18 (100%)	<0.001
	Yes	18 (100%)	0 (0%)	
NPDR	**No**	18 (90%)	2 (10%)	<0.001
	Yes	0 (0%)	16 (100%)	
PDR	**No**	18 (53%)	16 (47%)	0.089
	Yes	0 (0%)	2 (100%)	

Data presented as n (%). DR: Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy.

Laboratory Investigations

Plasma PTX3 levels showed a trend toward higher values in the retinopathy group (7.27 ± 3.47 vs. 5.78 ± 2.81 pg/mL), but this difference did not reach statistical significance ($p = 0.282$) (Table 4).

Table 4: Comparison of Laboratory Parameters in T1DM Patients with and Without DR

Variable	**No** DR **(n=18)**	**Yes (n=18)**	**P-value**
Hemoglobin (g/dL)	11.36 ± 1.87	10.16 ± 1.59	0.053
FT4 (ng/dL)	1.14 ± 0.24	1.29 ± 1.46	**0.021**
TSH (µIU/mL)	2.32 ± 1.19	2.58 ± 1.08	0.288
Albumin/Creatinine Ratio (mg/g)	17.73 ± 6.92	25.42 ± 9.21	0.066
Creatinine (mg/dL)	0.63 ± 0.15	0.66 ± 0.14	0.638

PTX3 (pg/mL)	5.78 ± 2.81	7.27 ± 3.47	0.282
HbA1c (%)	9.79 ± 1.88	10.07 ± 1.63	0.367
Total Cholesterol (mg/dL)	177.61 ± 31.64	193.89 ± 28.52	0.125
LDL (mg/dL)	86.82 ± 27.78	80.5 ± 10.48	0.962
HDL (mg/dL)	53 ± 14.34	51.5 ± 11.12	0.924
ALT (U/L)	32.03 ± 31.14	31.11 ± 25.16	0.669
C-Reactive Protein			0.063
Negative	17 (57%)	13 (43%)	
Positive	1 (17%)	5 (83%)	
Anti-Thyroid Antibodies			0.035
Negative	15 (45%)	18 (55%)	
Positive	3 (100%)	0 (0%)	

Data presented as mean ± SD for continuous variables and n (%) for categorical variables. DR: Diabetic Retinopathy; FT4: Free Thyroxine; TSH: Thyroid Stimulating Hormone; PTX3: Pentraxin 3; HbA1c: Glycated Hemoglobin; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; ALT: Alanine Aminotransferase.

Diagnostic Performance of PTX3

Receiver operating characteristic curve analysis demonstrated poor diagnostic performance of plasma PTX3 for detecting diabetic retinopathy, with an area under the curve of 0.605 (95% CI: 0.414–0.795, p = 0.282). At an optimal cutoff value of 8.62 pg/mL, PTX3 showed 50% sensitivity and 83% specificity, with a positive predictive value of 75% and a negative predictive value of 62.5% (Table 5, Figure 1).

Table (4): Diagnostic Performance of Plasma PTX3 for Detection of Diabetic Retinopathy

PTX3	AUC	P-Value	95% CI	Cut-off	Sensitivity	Specificity	PPV	NPV
	0. 605	**0.282**	**0.414-0.795**	**8.62**	**50%**	**83%**	**75**	**62.5**

PTX3, pentraxin-3; AUC, area under the ROC curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; ROC: receiver operating characteristic.

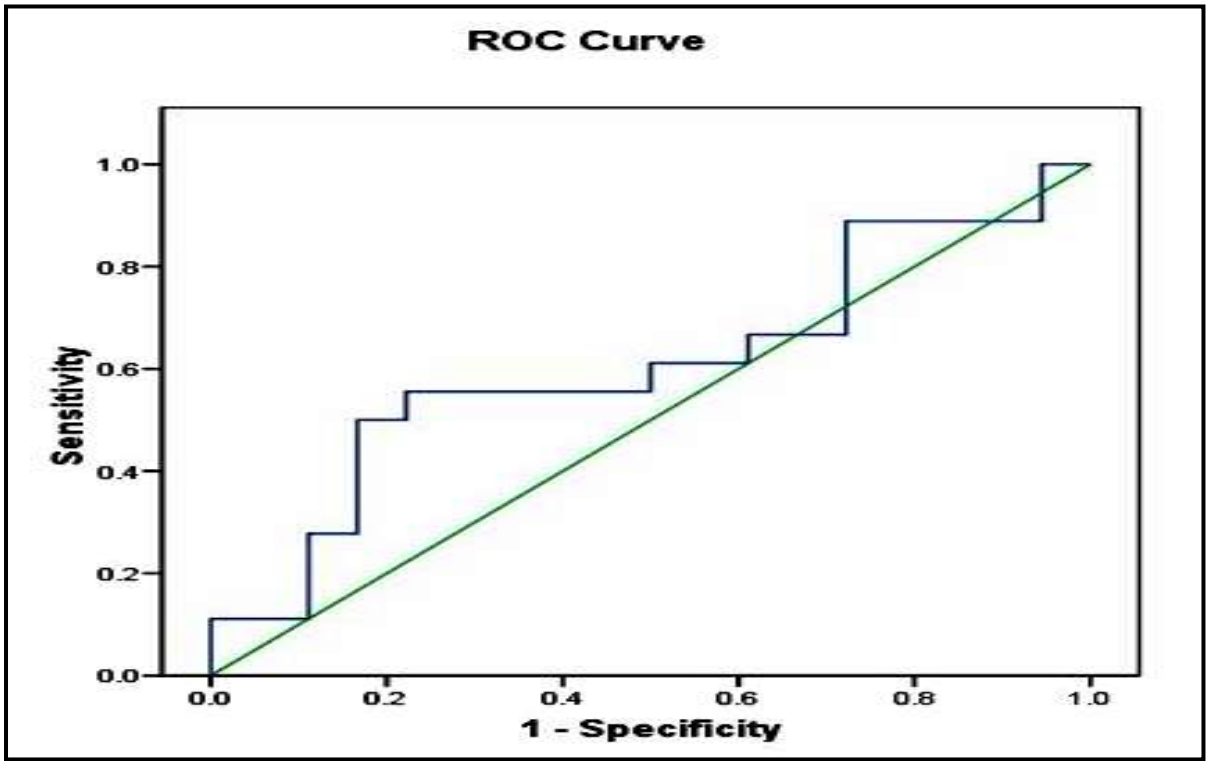

Figure (1): ROC Curve of Plasma PTX3 for Detection of Diabetic Retinopathy

DISCUSSION

The present study evaluated plasma PTX3 as a potential biomarker for DR in T1DM and examined clinical and biochemical differences between cases and controls. Consistent with previous epidemiological work [14], patients with retinopathy were older and had a longer duration of diabetes than those without DR. Longer exposure to hyperglycemia promotes the accumulation of advanced glycation end products and sustained activation of inflammatory pathways, leading to retinal microvascular damage [15]. The higher frequency of microvascular complications among the DR group further supports the notion that chronic hyperglycemia drives systemic endothelial dysfunction [16]. This aligns with a large recent Mendelian randomization analysis, which found that genetically predicted DR increased the odds of diabetic nephropathy (overall OR≈1.32), suggesting a causal link rather than mere confounding [17]. Similarly, in a 2024 multicenter study from Ethiopia (n=1,219), peripheral neuropathy independently tripled the odds of PDR, while nephropathy more than doubled the odds after multivariable adjustment [18].

The symptom pattern in our sample fits the biology of early DR: blurred vision and reduced acuity are typically driven by macular edema and/or macular ischemia, which degrade central vision even when vascular changes are still "non-proliferative" (i.e., microaneurysms, dot-blot hemorrhages) rather than neovascular; contemporary reviews and guidelines consistently note macular edema as the leading cause of visual loss in NPDR [19, 20].

Night-vision complaints also make sense because rod-mediated function and dark adaptation are among the earliest retinal processes to falter in diabetes; experimental and clinical work shows rod pathway dysfunction and nocturnal hypoxia can precede or accompany mild NPDR, which explains scotopic symptoms even when fundus signs are limited [20, 21].

The stage distribution we observed nearly all cases being NPDR with only two PDR mirrors recent cohorts, especially in youth or earlier disease duration: for example, a 15-year New Zealand T1DM cohort reported that most positive screens were minimal or mild DR with only a handful of moderate–severe grades [14], and population studies in 2024 likewise show NPDR is far more common than PDR (e.g., NPDR ≈27.5% vs PDR ≈7.3% in one European sample [22]; PDR ≈3.1% in an East African multicenter series [18].

Contrary to our hypothesis, plasma PTX3 levels did not differ significantly between patients with and without retinopathy (median 7.27 vs 5.78 ng/ml, p = 0.282). The ROC analysis yielded an area under the curve of 0.605, with a sensitivity of 50 % and specificity of 83 % at a cut-off of 8.62ng/ml. These findings suggest that plasma PTX3 alone is a poor discriminator of DR in T1DM. Our results diverge from several studies. In most studies, PTX3 was significantly elevated in DR and even showed predictive value. For example, in a Korean cohort, plasma PTX3 levels were significantly higher in patients with DR compared to diabetics without DR (average ~1.82 vs 1.09 ng/mL). PTX3 levels also rose with greater DR severity. The ROC analysis showed PTX3 had an AUC of ~0.72 for distinguishing DR status, indicating moderate diagnostic accuracy [23]. In an Egyptian study, serum PTX3 level significantly increased in patients with DR more than in patients without DR, with a cut-off point of 1150 pg/ml, sensitivity 93.3%, and specificity 72%, suggesting PTX3 as a strong potential biomarker for DR in this population [24]. In another Egyptian cohort focusing on early DR, patients with non-proliferative DR had significantly higher PTX3 levels than diabetics without, and positively correlated with DR and emerged as an independent predictor of NPDR in logistic models (OR ~16 for DR when PTX3 was elevated) [25]. This reinforces that PTX3 (and related inflammation) is strongly linked to DR development. Additionally, one meta-analysis of 15 studies (1,339 participants) reported higher serum or plasma PTX3 levels in patients with DR compared with diabetic controls, although differences between NPDR and PDR were not statistically significant [26].

Several factors may account for this discrepancy. First, our sample size was small (n = 36), reducing the power to detect moderate differences. Second, most of our cases had non-proliferative DR, whereas PTX3 upregulation may become more pronounced in advanced proliferative stages. Third, local production of PTX3 within ocular tissues may better reflect retinal inflammation; concentrations in aqueous humor correlate strongly with DR severity [26], whereas systemic levels may be diluted or influenced by other inflammatory sites. Fourth, most previous studies recruited patients with type 2 diabetes, who often have more pronounced systemic inflammation and obesity; PTX3 levels correlate positively with HbA1c and body mass index [26], whereas our T1DM cohort had similar HbA1c values between groups and relatively low body mass. Finally, ethnic differences and genetic variants of PTX3 could modulate its expression; studies in European and Asian populations may not generalize to Egyptian cohorts. However, one Polish study (43 patients) aligned with our findings and observed no direct association between plasma PTX3 concentration and the presence of DR. PTX3 levels were similar in patients with and without retinopathy [27].

While most evidence points to higher plasma PTX3 in DR (supporting its role as an inflammation-linked marker of DR), there is some variability across populations. Differences in patient characteristics, diabetes type/duration, and study methodologies likely explain why a few studies (and our results) did not find PTX3 to discriminate DR; nevertheless, the prevailing trend is that systemic PTX3 rises in the presence of diabetic retinopathy, highlighting both its promise and the need for further standardization in its clinical use.

The present study has several limitations. the small sample (n=36) may reduce power to detect modest PTX3 differences; the single-center design limits generalizability; and the case–control design cannot establish temporality or causality between PTX3 elevation and DR onset. Fourth, PTX3 was measured at a single time point, without evaluating longitudinal changes in relation to DR progression. Finally, we did not measure PTX3 in ocular fluids or assess genetic polymorphisms that might influence PTX3 expression.

CONCLUSION

In this case–control study, serum PTX3 was higher in T1DM patients with DR than in those without, but the difference was not statistically significant and its diagnostic accuracy was limited. DR was significantly associated with older age, longer diabetes duration, more frequent ocular symptoms, and higher rates of diabetic nephropathy, neuropathy, and autoimmune thyroid disease. Overall, PTX3 does not appear suitable as a standalone early marker, but it may add value when combined with established clinical and laboratory predictors to enhance risk stratification and screening in this high-risk group.

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