· Clinical Research ·

Sex differences in retinal neurovascular changes in type 1 diabetes without retinopathy

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Abstract

● **AIM:** To investigate the sex-specific correlation between systemic factors and retinal neurovascular alterations in individuals with type 1 diabetes mellitus (T1DM) who do not exhibit signs of diabetic retinopathy (DR).

● **METHODS:** A cohort participant without DR diagnosed with T1DM, underwent comprehensive ophthalmologic evaluation, optical coherence tomography angiography retinal structural and microvascular density analysis, and systemic parameter assessment. Multiple linear regression analysis was used to investigate the impact of systemic parameters on retinal alterations in distinct gender groups.

● **RESULTS:** A total of 182 individuals were included, consisting of 85 males (mean age 23.28±12.75y) and 97 females (mean age 22.98±13.68y). Males exhibited significantly greater thickness in both the internal retinal layer and the entire retina compared to females ($P<0.01$), whereas females had higher densities of deep retinal vessels and choroidal capillaries ($P<0.05$). Additionally, glycemic control was found to have a notable influence on retinal thickness in males ($P<0.05$), while insulin function had a more pronounced impact on retinal structure in females ($P<0.01$). Furthermore, a significant correlation was observed between thyroid function markers and retinal parameters in both male and female ($P<0.05$).

● **CONCLUSION:** Sex differences in alterations in retinal structure and microcirculation are observed in individuals with T1DM prior to the development of clinical DR, with a noted association between these changes and systemic parameters.

● **KEYWORDS:** type 1 diabetes mellitus; diabetic retinopathy; gender differences; optical coherence tomography angiography

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) occurs because of autoimmune-mediated destruction of pancreatic beta cells, which are responsible for insulin production in the pancreas[1]. While autoimmune diseases are generally more prevalent in females, studies indicate that T1DM occurs more frequently in males between the ages of 15 and 39y, with no significant gender differences observed in other age groups[2]. Despite this, postmenopausal women with diabetes face a higher risk of all-cause mortality and vascular complications compared to men[3]. These disparities highlight the importance of examining the role of gender disparities on the development of complications associated with T1DM.

Even in the absence of clinical signs of diabetic retinopathy (DR), patients with diabetes can exhibit changes in retinal structure and microcirculation detectable by imaging techniques such as optical coherence tomography (OCT) and OCT angiography (OCTA)[4]. These early changes include thinning of the inner retinal layers, enlargement in the avascular area of the optic cup, a reduction in perfusion density of the superficial and deep capillary networks in the macula, and a decrease in radial perfusion density of perioptic capillaries[4]. Hemodynamic abnormalities, such as increased retinal blood flow velocities and microvascular changes like pericyte loss and capillary leakage and impaired perfusion often precede the onset of visible DR[5]. Furthermore, early neurodegeneration may occur before microangiopathy becomes evident in DR, with thinning of inferior temporal retinal nerve fiber layer (RNFL) around the peripapillary serving as an early marker[6]. Inadequate metabolic control in these patients may contribute to the thinning of the peripapillary RNFL, which tends to progress with the duration of diabetes mellitus[6].

Research has shown that female gender is an independent risk factor for the progression of DR[7]. However, few study have specifically examined the impact of gender on retinal structural changes before the clinical onset of DR. Study showed that boys may have a smaller foveal avascular zone and greater central retinal thickness compared to girls with T1DM[8]. Thus, this present study aims to investigate whether the similar phenomenon occurs in the preclinical phase of DR. Using multiple linear regression analysis, we seek to understand how these gender-related differences contribute to the alterations in retinal structure and microvasculature, along with systemic parameters in T1DM patients without DR. The ultimate goal is to inform gender-specific strategies for preventing and treating DR.

PARTICIPANTS AND METHODS

Ethical Approval The study adhered to the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all participants or their guardians for patients under 18 years of age. The study was conducted after approval from the Institutional Ethics Committee of the Second Xiangya Hospital of Central South University. Ethic number: NCT03610984.

From January 2016 to November 2019, A total of 182 patients (including 85 males and 97 females) diagnosed with T1DM at the Second Xiangya Hospital of Central South University were enrolled in this study. The diagnostic criteria followed were based on the guidelines provided by the American Diabetes Association (2014).

Demographic and systemically data have been collected. It includes demographic data [age of onset, duration of disease, waist-to-hip ratio (WHR), systolic and diastolic blood pressure, body mass index (BMI)], glucose-metabolism-related paremeters (HbA1c, fasting C-peptide, C-peptide levels postprandial, fasting blood glucose), lipid profiles [triglyceride, high-density lipoprotein (HDL)], assessments of renal and liver function [including uric acid, urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR), glutamic oxalacetate transaminase (AST), glutamic-pyruvic transaminase, total protein and albumin (ALB) level], thyroid function [including thyrotropin, serum triiodothyronine (FT3), thyroid peroxidase antibody (TPO-Ab), thyroxine (FT4), thyroglobulin antibody (TGAb)]. The glucose metabolism-related parameters were obtained from medical records within three months prior to the ophthalmic examination.

The ophthalmological assessments included visual acuity testing and refraction, conducted by a senior optometrist, slit-lamp biomicroscopes (Topcon, Japan), fundus examination with additional lenses, and intraocular pressure measurement with a non-contact tonometer (Topcon, Japan). Color fundus photography and spectral-domain OCTA (RTVue-XR, Optovue Inc., Fremont, CA, USA) were also performed.

Each patient underwent a comprehensive ophthalmoscopic examination by two independent senior ophthalmologists, ensuring the absence of clinical signs of diabetic retinopathy, such as microaneurysms or other abnormalities, as determined by the Early Treatment Diabetic Retinopathy Study criteria using 7-field fundus photography[9]. Patients were excluded from the study if they had a history of intraocular surgery, high myopia or hyperopia (refractive errors exceeding ±6 diopters), intravitreal injections of anti-vascular endothelial growth factor (VEGF) or steroid, laser therapy, glaucoma, diabetic retinopathy, macular edema, kidney diseases, severe hypertension, or other systemic diseases affecting retinal thickness and capillary density.

For OCTA measurement, the automeasuring vascular density within a 6 μm×6 μm area centered on the fovea was assessed using the proprietary software Angio-Analytics TM (Verse 2016.100.0.0.35, Optovue Inc., Fremont, CA, USA). Three distinct layers of retinal capillary plexus were examined, including the superficial capillary plexus layer (SCP), deep capillary plexus layer (DCP), and choroid capillary plexus layer (CCP). Vessel density in the SCP, DCP, and CCP, was assessed in various regions based on the Early Treatment Diabetic Retinopathy Study chart centered on the fovea. The chart comprised two rings with diameters of 1 and 3 mm. The inner ring delineated the fovea (F), while the space between the two rings represented the parafovea (PF). The parafoveal region was further divided horizontally into the upper hemi (SH) and inferior hemi (IH) sections. Retinal structural parameters, including total retinal thickness (RT), inner retinal thickness (iRT), RNFL thickness, ganglion cell complex (GCC) thickness were assessed in the OCTA reports. The retina was defined as the area between the inner limiting membrane and retinal pigment epithelium in OCTA, while the inner retina was defined as the area between the ILM and inner plexiform layer in OCTA. RT, iRT, RNFL thickness, and GCC thickness were measured in all quadrants.

Statistical Analysis Kolmogorov-Smirnov test was used to assess the normality of the distribution of variables. Data in normal distribution is represented by mean and standard deviation and analyzed between different sexes, using SPSS 22.0 software (IBM Corp., Armonk, NY, USA), while those not conforming to normal distribution are represented by median (minimum, maximum). Depending on the normality and homogeneity of variances, either the Student's *t*-test or the Mann-Whitney test was employed, with a significance level set at $P<0.05$. Drawing upon existing research, the chosen variables were incorporated into the univariate regression analysis for retinal thickness and vessel densities, with an emphasis on those demonstrating statistical significance. Subsequently, variables with a *P*-value of less than 0.05 and a missing data rate of less than 50%, as well as the variable with the smaller *P*-value when both binary and continuous variables were available, were selected for inclusion in the multiple regression analysis. The final multiple regression model was adjusted for gender, duration of diabetes, and age. A *P*-value of less than 0.05 was considered indicative of statistical significance. For variables not conforming to normal distribution, the Mann-Whitney test was applied for intergroup comparisons.

RESULTS

Demographic Characteristics between Different Sexes The demographic analysis revealed significant gender differences in several systemic parameters. Females exhibited significantly lower levels of urea nitrogen, glutamic-pyruvic transaminase, albumin, FT3, and FT4 compared to males. Conversely, females had longer duration of disease and higher serum creatinine, thyrotropin, TPO-Ab, and TGAb levels (Table 1).

Gender-Specific Differences in Retinal Thickness and Microvascular Density Males displayed a greater thickness in the retina and inner retina across all retinal quadrants compared to females (Figure 1A, 1B). The gender difference in GCC is not significant (Figure 1C). Additionally, males showed higher average and inferior thickness of RNFL compared to females (Figure 1D). There was no statistically significant difference between the two groups in terms of SCP (data not shown). In contrast, females demonstrated a higher density of DCP across most regions except in the fovea and exhibited increased density in the CCP, particularly in the superior hemisphere choroid regions (Figure 1E, 1F).

Gender-Specific Correlation of Systemic Factors with Neural Retinal Thickness The study examined how systemic factors associate with neural retinal thickness, showing gender-specific patterns (Figure 2). In males, higher HbA1c and postprandial blood glucose levels were correlated with reduced retinal thickness. Conversely, in females, lower C-peptide levels were significantly associated with reduced inner retinal thickness. In males, higher serum creatinine is linked to increased RT, whereas in females, it is associated with decreased retinal vessel density, especially in the CCP. Another critical aspect of the study was the significant correlation between insufficient thyroid function (indicative of decreased FT4 and TGAb) markers and retinal thinning in females. Additionally, several systemic factors elevated eGFR and AST in female were associated with retinal thinning, particularly in the outer retinal layers. Furthermore, low albumin levels and low total protein, young onset age, and high WHR were identified to be associated with a reduction in neural retinal thickness in male.

Gender-Specific Correlation of Systemic Factors and Microvascular Changes This study also investigates the gender-specific difference in microvascular densities in both retinal SCP and DCP (Figure 3). Increased HbA1c levels were associated with the decreased density of retinal capillary plexuses (both SCP and DCP) in both genders. While in the female patients, postprandial blood glucose levels are positively correlated with the choroidal vessel density. Insulin dependence, defined as the requirement for insulin therapy at the initial presentation of T1DM, exhibited a significant positive correlation with the vessel density in the SCP among male patients. The decreased postprandial C-peptide is significantly associated with the increased vascular density in both SCP and DCP only in the fovea in males (Figure 3A). While in the female patients, upregulated postprandial blood glucose levels are positively correlated with the choroidal vessel density. While upregulated postprandial C-peptide are associated with the decreased DCP and CCP in parafoveal area, with the exception of the fovea. Serum creatinine and intraocular pressure are negatively associated with choroidal vessel density (Figure 3B).

Gender-Specific Independent Risk Factors for Neural Retinal Thinning Revealed by Multiple Linear Model Analysis Multiple linear regression analysis was utilized to investigate the relationship between systemic variables and retina neurovascular changes focusing on gender differences. The β coefficients of systemic variables with a significance level of $P<0.05$ are presented in Figure 4. Among male patients, higher WHR was associated with decreased iRT, while lower ALB levels were also linked to reduced thickness only in the fovea. Additionally, higher HDL levels were correlated with thinner RNFL thickness. Thyroid-stimulating hormone (TSH) was negatively related to superficial retinal

Table 1 Demographic characteristics of the enrolled patients between different genders

Parameters	Male (*n*=85)	Female (*n*=97)	*P*	Reference values
Demographic characteristics				
Time of T1DM onset (y)	18.95±13.29	17.30±13.10	0.336	
Age (y)	23.28±12.75	22.98±13.68	0.648	
Waist-to-hip ratio	0.94±0.16	0.94±0.21	0.331	Male<0.9, female<0.85
Duration of disease (mo)	32.00±13.19	43.24±17.09	0.031	
Systolic blood pressure (mm Hg)	113.16±15.28	104.08±12.79	0.001	
Diastolic blood pressure (mm Hg)	69.25±11.65	67.96±10.84	0.544	
Weight (kg)	50.01±15.56	45.06±11.92	0.044	
BMI (kg/m²)	19.10±2.94	18.74±3.40	0.517	
Glucose-metabolism-related paremeters				
HbA1c (%)	8.40±2.54	7.96±2.07	0.573	4.0-5.6
Fasting C-peptide (pmol/L)	61.5 (5.5, 709.8)	31 (1.06, 631.8)	0.054	300-600
C-peptide 30min postprandial (pmol/L)	151.7 (5.02, 1628.8)	132 (5.5, 1729.9)	0.634	1200- 1800
C-peptide 2h postprandial (pmol/L)	133 (2.08, 1573.7)	137.5 (1.96, 1837.3)	0.052	400-1500
Blood glucose 30min postprandial (mmol/L)	11.545 (3.31, 21.23)	11.370 (3.84, 25.79)	0.834	<7.8
Lipid profiles				
Triglyceride (mmol/L)	0.84±0.53	0.74±0.48	0.235	0.56-1.70
HDL (mmol/L)	1.43±0.47	1.5±0.40	0.087	Male>1.0, female>1.3
Renal and liver function				
BUN (mmol/L)	4.56 (4.76, 5.37)	4.76 (2.66, 8.67)	0.033	3.2-7.1
Serum creatinine (μmol/L)	44.6 (20.3, 5416)	49.6 (26.6, 2669.0)	<0.001	Male 59-104, female 45-84
eGFR (mL/min·1.73 m²)	140.32 (0.42, 215.07)	134.44 (0.12, 190.39)	0.282	≥90
AST (U/L)	22.39±9.16	20.48±9.97	0.059	5-40
ALT (U/L)	19.80±12.11	15.49±12.77	<0.001	5-40
Total protein (g/L)	69.51±6.08	67.34±8.65	0.187	60-80
ALB (g/L)	43.66 (24.80, 50.80)	41.49 (29.20, 52.00)	0.009	35-55
Thyroid function				
TSH (μIU/L)	2.19±1.25	2.50±2.39	0.934	0.27-4.2
FT3 (pmol/L)	5.57±1.66	5.28±3.06	0.020	3.1-6.8
FT4 (pmol/L)	16.43±2.43	15.12±6.82	0.026	12-22
TPO-Ab (IU/mL)	17.4 (8.6, 1222.5)	23.3 (10.5, 1300)	0.013	<34
TGAb (IU/mL)	24.5 (2.6, 1300)	26.5 (4.6, 1327)	<0.001	<115
Best corrected visual acuity, logMAR	1.14±0.045	0.23±0.05	0.192	-1.0-0
Intraocular pressure (mm Hg)	16.54±2.70	16.51±3.10	0.931	10-21

Normal distribution is represented by mean±standard deviation, while those not conforming to normal distribution are represented by median (minimum, maximum). Postprandial glucose values were obtained 2h after a self-reported typical meal, standardization was not applied. T1DM: Type 1 diabetes mellitus; BMI: Body mass index; HDL: High-density lipoprotein; BUN: Urea nitrogen; eGFR: Glomerular filtration rate; AST: Glutamic oxalocetie transaminase; ALT: Glutamic-pyruvic transaminase; ALB: Albumin; TSH: Thyroid stimulating hormone; FT3: Serum triiodothyronine; FT4: Thyroxine; TPO-Ab: Thyroid peroxidase antibody; TGAb: Thyroglobulin antibody.

vascular density in foveal. These findings suggest that elevated WHR and HDL levels, as well as decreased ALB levels, are independent risk factors for thin retinal thickness in males.

Higher levels of TSH in female patients were linked to thinner inner retinal thickness, particularly in the inferior hemisphere regions, and parafoveal RT. Additionally, TPO-Ab levels were positively correlated with thicker RNFL in the superior hemisphere, and increased density of both superficial and deep retinal vessels.

DISCUSSION

Potential Mechanisms of Gender-Specific Differences in Retinal Structure This study revealed significant gender-specific variations in retinal thickness and microvascular density among T1DM patients without DR. Specifically, males demonstrated to have a notably thicker inner and overall retina compared to females, a finding consistent with previous studies that highlight gender differences in retinal anatomy[10]. The greater thickness in males might suggest a higher resilience to

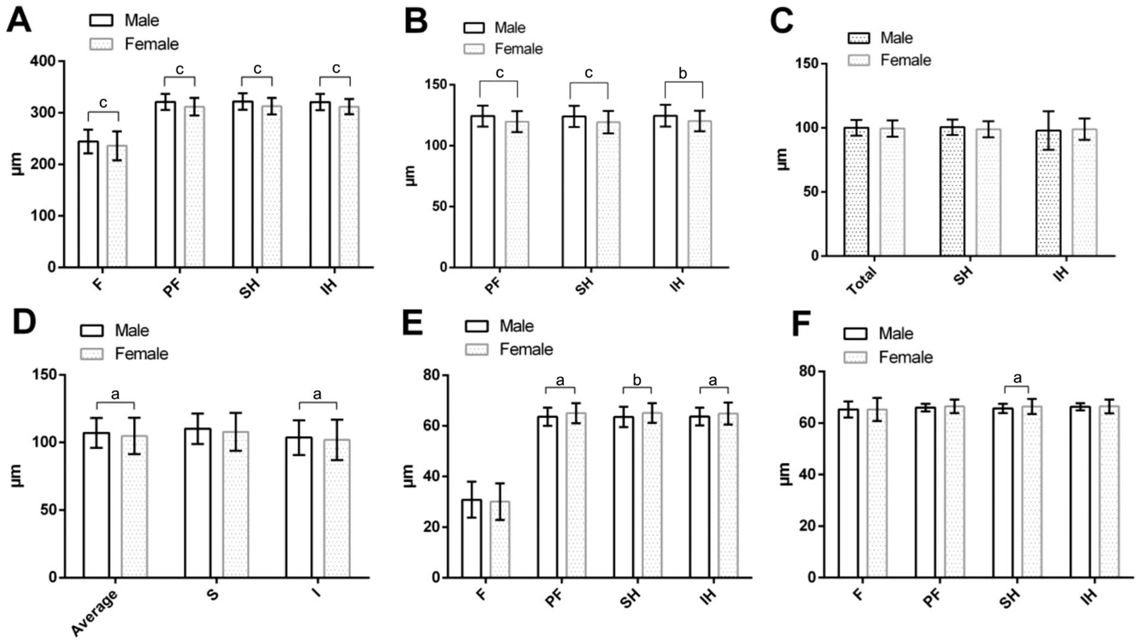

Figure 1 Gender-specific changes on retinal thickness and microvascular density Gender differences on the thickness of retina (A), the inner retina (B), the thickness of GCC (C), the thickness of RNFL (D), and vascular density on DCP (E) and CCP (F). DCP: Deep capilary plexus; CCP: Choroidal capilary plexus; GCC: Ganglion cell complex; RNFL: Retinal nerve fiber layer; F: Fovea; PF: Parafovea; SH: Superior hemisphere; IH: Inferior hemisphere; S: Superior; I: Inferior. [a]P<0.05, [b]P<0.01, [c]P<0.001.

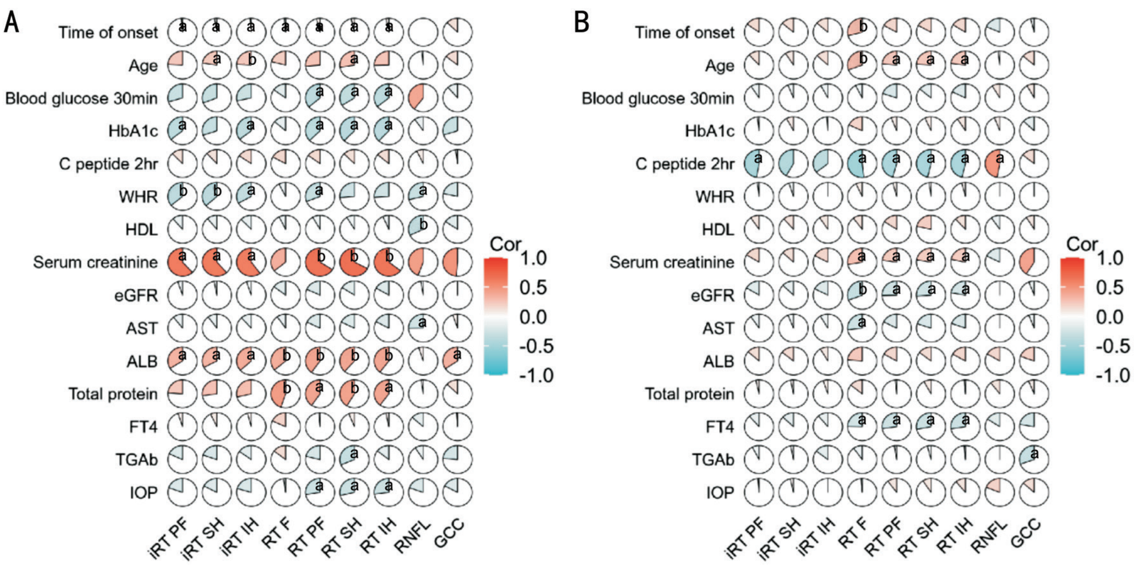

Figure 2 The pie charts indicates correlation of systemic variables and retinal neural structure in male (A) and female (B) [a]P<0.05, [b]P<0.01. Cor: Correlation value; WHR: Waist-to-hip ratio; HDL: High-density lipoprotein; eGFR: Estimated glomerular filtration rate; AST: Glutamic oxalocetie transaminase; ALB: Albumin; FT4: Thyroxine; TGAb: Thyroglobulin antibody; RBC: Red blood cell; IOP: Intraocular pressure; RT: Retinal thickness; iRT: Inner retinal thickness; RNFL: Retinal neural fibrotic layer; GCC: Ganglion cell complex; F: Fovea; PF: Parafovea; SH: Superior hemisphere; IH: Inferior hemisphere.

early retinal thinning, which is often a precursor to DR[11]. In contrast, males in our study exhibit a greater focal loss volume in the ganglion cell complex compared to females, showing the opposite trends to be prone to neural degeneration.

Conversely, females exhibited a significantly higher vessel densities of the DCP and CCP, particularly outside the macula and in the superior choroid. This increased vascular density could imply a protective adaptation, potentially compensating for the lower retinal thickness. The higher density might also reflect gender-specific responses to systemic conditions, such as sex hormonal variations[12] or differences in insulin sensitivity[13], which could influence microvascular health.

Sex-Specific Regulatory Network of Metabolism and Systemic Factors The systemic parameters evaluated in this study were selected due to their well-documented roles in diabetic microvascular complications. Factors such as

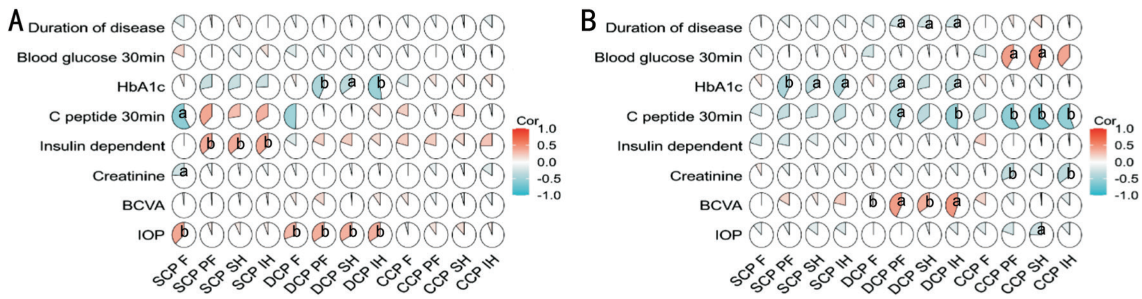

Figure 3 The pie charts indicates correlation of systemic variables and retinochoroidal microvessel denstiy in male (A) and female (B) [a]P<0.05, [b]P<0.01. Cor: Correlation value. Insulin-dependent: The necessity of insulin therapy at the initial onset of the condition; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CCP: Choroidal capillary plexus; F: Fovea; SH: Superior hemisphere; IH: Inferior hemisphere.

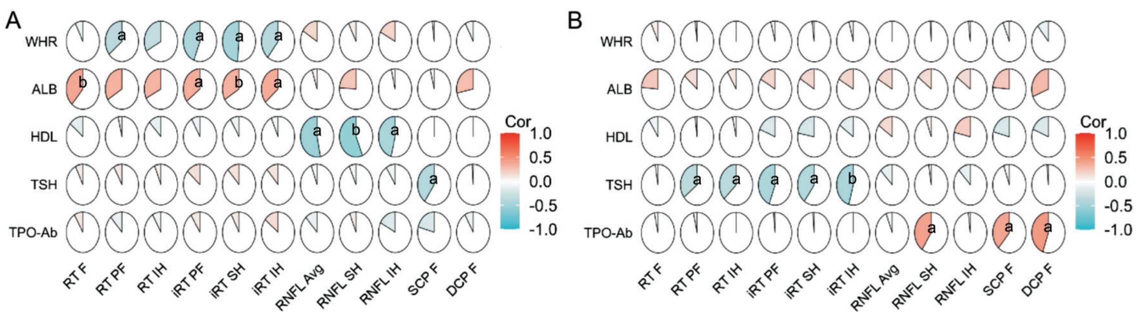

Figure 4 The pie charts indicates β coefficient in male (A) and female (B) [a]P<0.05, [b]P<0.01. Cor: β coefficient value; WHR: Waist-to-hip ratio; ALB: Albumin; HDL: High-density lipoprotein; TSH: Thyroid stimulating hormone; TPO-Ab: Thyroid peroxidase antibody; RT: Retinal thickness; iRT: Inner retinal thickness; RNFL: Retinal neural fibrotic layer; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; F: Fovea; PF: Parafovea; SH: Superior hemisphere; IH: Inferior hemisphere; Avg: Average.

the duration of diabetes, WHR, and triglyceride levels are recognized as risk factors for DR in patients with T1DM[14]. Additionally, ALB levels serve as indicators of systemic endothelial integrity and have been associated with the progression of DR[15]. Elevated HbA1c levels have been linked to greater RNFL thinning in preclinical stages of DR[6]. Furthermore, preclinical studies suggest that a sustained reduction in thyroid hormone signaling may exacerbate the progression of DR[16]. This study identified significant gender differences in the impact of glycemic control (HbA1c) and insulin function (C-peptide) on the retina. Specifically, in male subjects, the glycotoxic effects predominated, as evidenced by a negative correlation between retinal thickness and HbA1c levels. This finding aligns with previous research[17], and implies that hyperglycemia may directly harm retinal neurons and pericytes through the formation of advanced glycation end products[18]. In females, reduced C-peptide levels in females correlate with increased DCP and CCP, potentially indicating the activation of hypoxia-inducible factors as a consequence of insulin deficiency[19]. This activation may drive angiogenesis to sustain retinal oxygenation[20]. Clinically, these findings suggest that males should prioritize enhancing glycemic control to mitigate retinal thinning, whereas females should carefully consider the timing and dosage of insulin replacement therapy to prevent excessive angiogenesis.

Association of Serum Creatinine and eGFR with Parafoveal Retinal Parameter Our study found that in T1DM males without DR, elevated creatinine was linked to increased retinal thickness, especially in the parafoveal region, possibly due to renal dysfunction related fluid retention[21] or altered blood flow[22]. Nevertheless, in females, higher creatinine levels correlated with reduced vessel density in the parafoveal CCP, suggesting that increased creatinine may serve as a marker for underlying microvascular changes in the eye.

In females, up-regulated estimated eGFR was inversely correlated with down-regulated retinal thickness, probably in the outer retina. This finding is in contrasts with other studies that a moderately reduced eGFR is associated with severe DR[23] or diabetic macular edema[24]. In our study, we suggest that higher eGFR in early diabetes might lead to early retinal thinning and degeneration in those without DR. The progression of retinal thickness from preclinical stages to DR is not well understood, complicating its link to systemic factors like high serum creatinine and low eGFR.

Systemic Variables on Retinal Neurovascular Changes in Men and Women Revealed by Multiple Linear Regression Analysis HDL, typically considered protective in cardiovascular health, shows a paradoxical relationship with retinal parameters in this study. In males, higher HDL levels are associated with decreased RNFL, particularly in the parafoveal region. This result is consistent with the research conducted by Shi *et al*[25] which indicated a negative association between high HDL levels and peripapillary RNFL thickness, a marker for early retinal neurodegeneration[6]. This result suggested that the protective role of HDL might be less effective or even detrimental in the context of retinal health in T1DM. This could be due to HDL's complex role in modulating inflammation and lipid metabolism at the microvascular level[26]. WHR, an indicator of central obesity, has been reported to have detrimental effects on arterial retinal microcirculation[27]. In our study, WHR was negatively correlated with retinal thickness, suggesting that prolonged adiposity may contribute to retinal thinning and elevate the risk of diabetic retinopathy, especially among males.

Moreover, our study revealed significant correlations between thyroid function markers and retinal parameters specifically in women. The stronger association between thyroid markers and retinal parameters in women may stem from sex-specific hormonal modulation since estrogen enhances immune reactivity and thyroid autoantibody production[28], potentially amplifying autoimmune damage to the retinal microvasculature. Hypothyroidism may impair retinal energy metabolism, exacerbating hypoxia and neurodegeneration in diabetic patients[16], in our cohort, elevated TSH in females correlated with inner retinal thinning, possibly reflecting cumulative metabolic stress in a hypothyroid state. The elevated TPO-Ab and TGAb levels observed in female patients may indicate subclinical autoimmune thyroiditis, a condition prevalent in women with T1DM due to shared autoimmune susceptibility[29]. TPO-Ab has been linked to endothelial dysfunction and leukocyte adhesion[30], which may contribute to pericyte loss and capillary dropout in the diabetic retina.

Our study has several limitations. First, the lack of a healthy, age- and sex-matched control group constrains our capacity to ascertain whether the neurovascular alterations observed are specific to T1DM or if they represent normal physiological differences based on sex. To more accurately delineate diabetes-related changes, future research should incorporate healthy control groups. Second, although we accounted for certain systemic factors in our multiple regression models, we recognize that retinal structural parameters, such as RT, iRT, and GCC, may confound OCTA-derived vascular density metrics. Not all analyses were fully adjusted for these structural variables, and this potential confounding effect should be considered when interpreting the vascular findings. Thirdly, the cross-sectional design of our study limits the ability to draw causal inferences. Although we identified significant associations between systemic factors and retinal parameters, these should be interpreted as correlational rather than causal. Longitudinal studies are necessary to ascertain whether the observed retinal alterations precede or are a consequence of systemic dysregulation in T1DM. Furthermore, the mean duration of diabetes was notably longer among female participants compared to male participants. Although we adjusted for duration in our multivariate analyses, this discrepancy may have influenced sex-related differences in retinal outcomes and could represent a potential source of residual confounding. Additionally, the detailed subdivision of retinal layers and regions increases the risk of false-positive findings due to multiple comparisons. While we attempted to address this issue by adjusting for key covariates and focusing on clinically relevant variables, some associations may still be attributable to chance or residual confounding. Therefore, future validation in larger, prospective cohorts is essential.

In conclusion, our study underscores the significance of incorporating gender-specific systemic factors in the analysis of early retinal neurovascular changes associated with T1DM. The findings reveal notable associations between various parameters, including ALB, HDL, WHR, thyroid function, and retinal alterations. The gender-specific correlations identified in this research suggest that the integration of glycemic control, ALB levels, HDL, and WHR into routine clinical evaluations may enhance personalized risk stratification, particularly for male patients. Conversely, the impact of thyroid dysfunction and insulin management, which disproportionately affects female patients, necessitates careful consideration within comprehensive diabetes care, as these factors may indirectly influence retinal microvascular stability. Future research should investigate how interventions targeting glycemic control, lipid profiles, or thyroid function may differentially influence retinal outcomes in men and women.

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