BMC Ophthalmology

RESEARCH

Open Access

New marker for the detection of pre-retinopathy in patients with type 1 diabetes mellitus: systemic immuno-inflammation index

Hazan Gül Kahraman[1], Yusuf Ziya Güven[2*], Fahrettin Akay[2], Yusuf Üzüm[3] and Murat Aysin[4]

Abstract

Purpose This study aimed to investigate the relationships among urine parameters, systemic inflammation and retinal microvascular changes in patients with type 1 diabetes mellitus (T1DM) without clinical signs of diabetic retinopathy (DR), via optical coherence tomography angiography (OCTA) and the systemic immune-inflammation index (SII).

Methods A total of 64 participants, including 33 patients with T1DM and 31 healthy controls matched by age and sex, were examined. All the subjects underwent detailed eye assessments and OCTA imaging. Retinal and choroidal parameters were measured along with systemic markers such as C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), haemoglobin-A1C (HbA1c), spot urine tests and the SII. Relationships between systemic inflammation, renal and metabolic parameters, and ocular measurements were analyzed.

Results The T1DM group had significantly higher SII values (381.78 ± 57.30 vs. 284.86 ± 67.88, $p < 0.001$), HbA1c values (8.21 ± 1.80 vs. 5.15 ± 0.32, $p < 0.001$), spot microalbumin levels (13.50 ± 26.56 vs. 0.69 ± 0.57, $p = 0.009$), and albumin/creatinine ratios (0.13 ± 0.31 vs. 0.01 ± 0.01, $p = 0.031$). No significant differences in macular thickness, vascular density (VD), or foveal avascular zone (FAZ) area were detected between the groups. However, the mean retinal nerve fiber layer (RNFL) thickness and perifoveal ganglion cell complex (GCC) thickness were significantly lower in the diabetic group ($p < 0.05$). The SII was strongly positively correlated with choroidal thickness ($r = 0.686$, $p < 0.001$) and negatively correlated with parafoveal GCC thickness (r=-0.357, $p = 0.041$). HbA1c was negatively correlated with mean VD (r=-0.261, $p = 0.037$). No significant correlation was found between the SII and the FAZ or VD. Significant correlations were found between the mean vascular density and both the spot creatinine level (r = -0.527, $p = 0.002$) and the spot microalbumin level (r = -0.355, $p = 0.043$).

Conclusion This study highlights the potential of the SII as a biomarker for detecting early subclinical retinal and choroidal changes in T1DM patients before the onset of retinopathy. The observed correlations among spot urine tests, the SII and OCTA parameters support the role of systemic inflammation in the early microvascular alterations

*Correspondence:
Yusuf Ziya Güven
yusufziya777@gmail.com

Full list of author information is available at the end of the article

associated with diabetes. These findings may contribute to early diagnosis and novel preventive strategies in DR. However, given the limited sample size, these findings should be interpreted with caution. Larger, well-stratified prospective studies are warranted to validate these preliminary observations.

Keywords Choroid, Diabetic retinopathy, Inflammation, Optical coherence tomography, Retinal vessels, Type 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that begins in childhood and young adulthood. It develops as a result of autoimmune destruction of β-cells in the pancreas and is characterized by decreased endogenous insulin production [1]. T1DM is not only a disease that disrupts metabolic balance but also causes many systemic complications in the long term, negatively affecting the quality of life of patients. One of the most serious and common long-term complications of diabetes is microvascular damage, and diabetic retinopathy (DR) is the most common microvascular complication of diabetes, with DR being one of the leading causes of vision loss [2]. The incidence of DR in individuals with diabetes for more than 15 years has reached a very high level of 98% [3].

Chronic inflammation plays an important role in the pathophysiology of T1DM and the development of complications. Hyperglycemia triggers an inflammatory response in the retinal vascular endothelium by increasing the expression of proinflammatory cytokines (TNF-α, IL-1β, and IL-6) and adhesion molecules [4]. This process leads to microvascular damage by increasing leukocyte adhesion and accelerating retinal pericyte loss. In addition, inflammation-based oxidative stress contributes to the disruption of the blood–retinal barrier and the development of macular edema [5, 6]. The role of chronic inflammation in the pathogenesis of DR paves the way for the evaluation of anti-inflammatory agents as potential targets. Currently, the effectiveness of dexamethasone implants in resistant patients in addition to anti-VEGF agents in the treatment of DR demonstrates the role of inflammation in this process [7].

This strong relationship between T1DM and inflammation highlights the importance of systemic inflammation biomarkers in the diagnosis and treatment of this systemic disease. C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR) and the systemic immunoinflammatory index (SII) are among the parameters of systemic inflammation. The SII is calculated from the platelet, neutrophil and lymphocyte ratios and stands out as a comprehensive parameter that reflects not only inflammation but also the balance of the immune response. SII has been shown to be an important marker in various clinical conditions, such as cancer prognosis, cardiovascular diseases and sepsis, in addition to diabetes [8–10].

Optical coherence tomography angiography (OCTA) is a non-invasive technique that allows the examination of the microvascular structures of the retina and choroid. Some data obtained with fundus fluorescein angiography (FFA), which was previously an invasive method, can be evaluated quickly and quantitatively with OCTA. OCTA has become an important tool for revealing early changes in this disease through the examination of many parameters in the retina [11, 12]. It can enable us to detect pathologies in the early stages of DR, which is a microvascular complication of T1DM.

Although recent studies have suggested that the systemic immune-inflammation index (SII) may serve as a biomarker in diabetic macular edema (DME) and in later stages of diabetic retinopathy (DR), these studies have focused on patients with clinically evident disease. For example, Elbeyli et al. [13] demonstrated the diagnostic value of SII in DME, while Zhou et al. [14] reported associations between OCT parameters and systemic inflammation in treatment-naïve DR patients. However, the potential role of SII in identifying preclinical alterations has not been adequately investigated.

This study aims to address these gaps by evaluating the relationship between SII and retinal and choroidal microstructural changes in T1DM patients without any clinical signs of DR. To minimize the confounding hormonal influences of puberty on retinal development, we specifically included patients aged between 25 and 35 years.

In this study, the effects of inflammation-based pathophysiological processes on OCTA data in T1DM patients were investigated. In addition to the structural changes observed with OCTA, the relationships between systemic inflammation and metabolic parameters (hemogram, CRP, sedimentation, HbA1c, spot urine tests) were examined. Some previous studies suggest that the Systemic Immune-Inflammation Index (SII) may serve as a potential biomarker in different stages of diabetic retinopathy (DR) and in the development of macular edema; however, our study aimed to investigate the role of SII before the onset of DR and to evaluate this in patients with type 1 diabetes mellitus [13, 15]. By integrating systemic inflammatory markers with OCTA findings, we aim to contribute to the identification of early retinal changes and to clarify whether systemic inflammation could serve as a predictor of pre-retinopathic alterations in T1DM.

Methods

This research was conducted following the principles of the Declaration of Helsinki and with the approval of our hospital's clinical research ethics committee (Approval number: [2022-KAE-0043]). Written informed consent was obtained from all participants.

Patient selection

Thirty-three patients with type 1 diabetes mellitus who were over 25 years of age, had been diagnosed with type 1 diabetes mellitus for at least 5 years and were referred to the eye clinic for diabetic retinopathy screening were included in the study. A control group was formed by obtaining consent to participate in the study from 33 age- and sex-matched individuals, and only the right eyes of all the patients were included in the study. The subjects in the control group were volunteers who applied to the outpatient clinic for routine refraction examination, did not have any systemic disease, and did not have habits such as smoking or alcohol. All patients underwent anterior and posterior segment examinations by two ophthalmologists working in the retina clinic. Patients with any signs of DR on fundus examination were excluded. Patients with intraocular pressure (Goldman tonometry) greater than 21 mmHg were excluded.

Imaging protocol

All participants underwent OCTA imaging using SD-OCT (DRI-OCT Triton, Topcon, Inc., Tokyo, Japan). High-resolution imaging was performed using a system operating at an acquisition speed of 100,000 A-scans per second with a central wavelength of 1050 nm, achieving an axial resolution of 8 μm within tissue. For macular analysis, a 6.0 × 6.0 mm radial scan centered on the fovea was employed to evaluate macular thickness (MT), retinal nerve fiber layer (RNFL) thickness, and ganglion cell layer (GCL) thickness across the central, superior, inferior, temporal, and nasal sectors, in alignment with the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. The parafoveal region was defined as the annular area extending from 1 to 3 mm from the foveal center, while the perifoveal region spanned from 3 to 6 mm. GCL thickness measurements were obtained automatically by the device's software from the same macular scan and divided into two groups: parafoveal and perifovel region. Mean values of these regions analysed. Choroidal thickness was manually measured using the measurement tool, first at the subfoveal region, and then at points located 500 μm temporally and nasally from the subfoveal point.

Optical coherence tomography angiography (OCTA) was performed using a 4.5 × 4.5 mm scan area to evaluate the foveal avascular zone (FAZ) and quantify vessel density (VD) within the superficial capillary plexus (SCP). FAZ measurements were derived through manual delineation of the innermost capillary boundaries on the SCP images. Retinal vascular density in the SCP was quantified automatically using the device's integrated analysis tools. The SCP was delineated by the system's default segmentation algorithm, which defines it as the region extending from 2.6 μm below the internal limiting membrane to 15.6 μm beneath the boundary between the inner plexiform and inner nuclear layers (IPL/INL).

Patients with any pathology detected in the anterior or posterior segments during the examination, those with poor OCTA imaging quality, those with a refractive error greater than ± 3 diopters of spherical equivalent, and patients with any other systemic disease were excluded from the study. All patients were recorded at the same time of day, in the same lighting room, by the same technician to avoid affecting choroidal thickness.

Blood&urine collection and biomarker measurement

Blood and urine samples were collected immediately after the ophthalmological examination. HbA1c, hemogram, urea, creatinine, sedimentation, CRP, spot protein in urine, spot creatinine, and spot microalbumin were also examined. All blood cell counts were obtained from complete blood counts. The systemic immune-inflammation index (SII) was calculated via the following formula: SII= (neutrophil count×platelet count)/lymphocyte count.

Statistics

SPSS 22.0 was used for statistical analyses, and the normality of the data in the study was evaluated with the Kolmogorov–Smirnov test. The Mann–Whitney U test was used for non-normally distributed independent samples, and for normally distributed dependent samples, the independent sample t test was used to test whether there was a difference between the means. The results are presented as the means ± standard deviations, and $p < 0.05$ was considered statistically significant.

Correlation calculations were performed exclusively within the DM group; control cases were not included in these analyses.

Results

A total of 64 patients were included in this study (case group: $n = 33$; control group: $n = 31$), and no significant difference was found between the case and control groups regarding age ($p = 0.887$). Although the sex distribution differed between the groups, the difference was not statistically significant ($p = 0.061$) (Table 1).

The mean systemic immune-inflammation index (SII) was significantly higher in the T1DM group (381.78 ± 57.30) than in the control group (284.86 ± 67.88, $p < 0.001$). Although no significant differences in CRP or

Table 1 Comparison of demographic data, urine and blood parameters between the T1DM and control groups

Parameter	Case Group (*n* = 33)	Control Group (*n* = 31)	*p* value
Gender			0.061[1]
Female	16 (48.5%)	8 (25.8%)	
Male	17 (51.5%)	23 (74.2%)	
Age (years)	33.6 ± 8.1	33.9 ± 8.7	0.887[2]
Diabetes mellitus duration(years)	7.0 (5.0–26.0)		
Urine spot microalbumin (mg/dL)	13.50 ± 26.56	0.69 ± 0.57	**0.009**[3]
Urine spot Creatinine (mg/dL)	128.06 ± 75.22	103.81 ± 88.60	0.244[2]
Spot albumin/Creatinine (mg/mg)	0.13 ± 0.31	0.01 ± 0.01	**0.031**[3]
Hemoglobin A1c (%)	8.21 ± 1.80	5.15 ± 0.32	**0.000**[2]
SII* (10^9/L)	381.78 ± 57.30	284.86 ± 67.88	**< 0.001**[2]

* SII: systemic immune-inflammation [1] : chi square test, [2] : t test, [3] : Mann Whitney U test

Table 2 Optic coherence tomography parameters of the patients

	Case Group (*n* = 33)	Control Group (*n* = 31)	*p* value
Central macular thickness (µm)	239.9 ± 26.8	232.4 ± 15.6	0.172[2]
Average Parafoveal retinal thickness (µm)	333.3 ± 106.5	311.0 ± 10.0	0.250[2]
Average Perifoveal retinal thickness (µm)	279.9 ± 18.5	273.8 ± 10.8	0.110[2]
Central VD*	20.5 ± 5.0	19.4 ± 4.6	0.362[2]
Superior VD*	44.5 ± 4.3	44.6 ± 8.1	0.935[2]
Temporal VD*	44.4 ± 4.1	45.8 ± 3.1	0.112[2]
Inferior VD*	43.4 ± 4.3	44.9 ± 3.7	0.129[2]
Nasal VD*	43.8 ± 3.5	44.4 ± 3.3	0.452[2]
FAZ area ($mm^{2)}$ **	322.8 ± 186.1	277.9 ± 105.8	0.237[2]
Central Choroidal Thickness (µm)	307.6 ± 61.2	296.8 ± 72.8	0.524[2]
Nasal Choroidal Thickness (µm)	310.7 ± 62.6	279.9 ± 69.1	0.067[2]
Temporal Choroidal Thickness (µm)	299.9 ± 65.9	277.8 ± 73.4	0.209[2]
Inferior RNFL (µm) ***	138.7 ± 14.7	144.9 ± 16.4	0.116[2]
Superior RNFL (µm) ***	128.4 ± 16.9	136.7 ± 15.7	**0.046**[2]
Nasal RNFL (µm) ***	83.9 ± 13.4	88.2 ± 14.8	0.227[2]
Temporal RNFL (µm) ***	84.7 ± 13.7	84.0 ± 10.5	0.808[2]
Mean (µm) RNFL***	108.9 ± 7.7	113.4 ± 9.7	**0.045**[2]
Average Parafoveal GCC thickness (µm) ****	117.3 ± 6.9	121.5 ± 10.9	0.068[2]
Average Perifoveal GCC thickness (µm) *****	105.2 ± 7.3	110.6 ± 8.6	**0.009**[2]

*VD: Vascular density, **FAZ: Foveal avascular zone ***RNFL: Retinal nerve fiber layer, ****Ganglion cell complex, [1] : chi square test, [2] : t test

ESR levels were detected between the groups ($p = 0.814$ and $p = 0.408$, respectively), spot microalbumin levels were notably elevated in the T1DM group (13.50 ± 26.56 vs. 0.69 ± 0.57, $p = 0.009$). Similarly, the albumin/creatinine ratio was significantly greater in T1DM patients (0.13 ± 0.31 vs. 0.01 ± 0.01, $p = 0.031$). HbA1c levels were also markedly higher in the T1DM group (8.21 ± 1.80 vs. 5.15 ± 0.32, $p < 0.001$). No significant differences were detected in the spot creatinine levels ($p = 0.244$).

In the evaluation of the macular and vascular structures, no significant differences were found between the case and control groups regarding central macular thickness, mean parafoveal macular thickness, mean perifoveal macular thickness, VD averages or FAZ area measurements (all p values >0.05) (Table 2)(Figure-1).

In terms of choroidal thickness measurements, although the subfoveal, nasal and temporal quadrant choroidal thicknesses were greater in the diabetic group than in the control group, this difference was not statistically significant ($p = 0.524$, $p = 0.067$, $p = 0.209$, respectively). A strong positive correlation was observed between the mean choroidal thickness and the systemic immune-inflammation index (SII) ($r = 0.686$, $p < 0.001$) (Table 3). Only statistically significant correlations ($p < 0.05$) were included in Table 3. No statistically significant correlations were observed between the remaining systemic biomarkers and the OCT/OCTA parameters.

In the retinal nerve fiber layer (RNFL) analysis, the superior quadrant RNFL thickness ($p = 0.046$) and the mean RNFL thickness ($p = 0.045$) were significantly lower in the diabetic group. When the ganglion cell thicknesses were compared, the perifoveal ganglion cell layer thickness was also found to be significantly lower in the diabetic group ($p = 0.009$).

Correlation analysis using Pearson's coefficient revealed several statistically significant relationships between

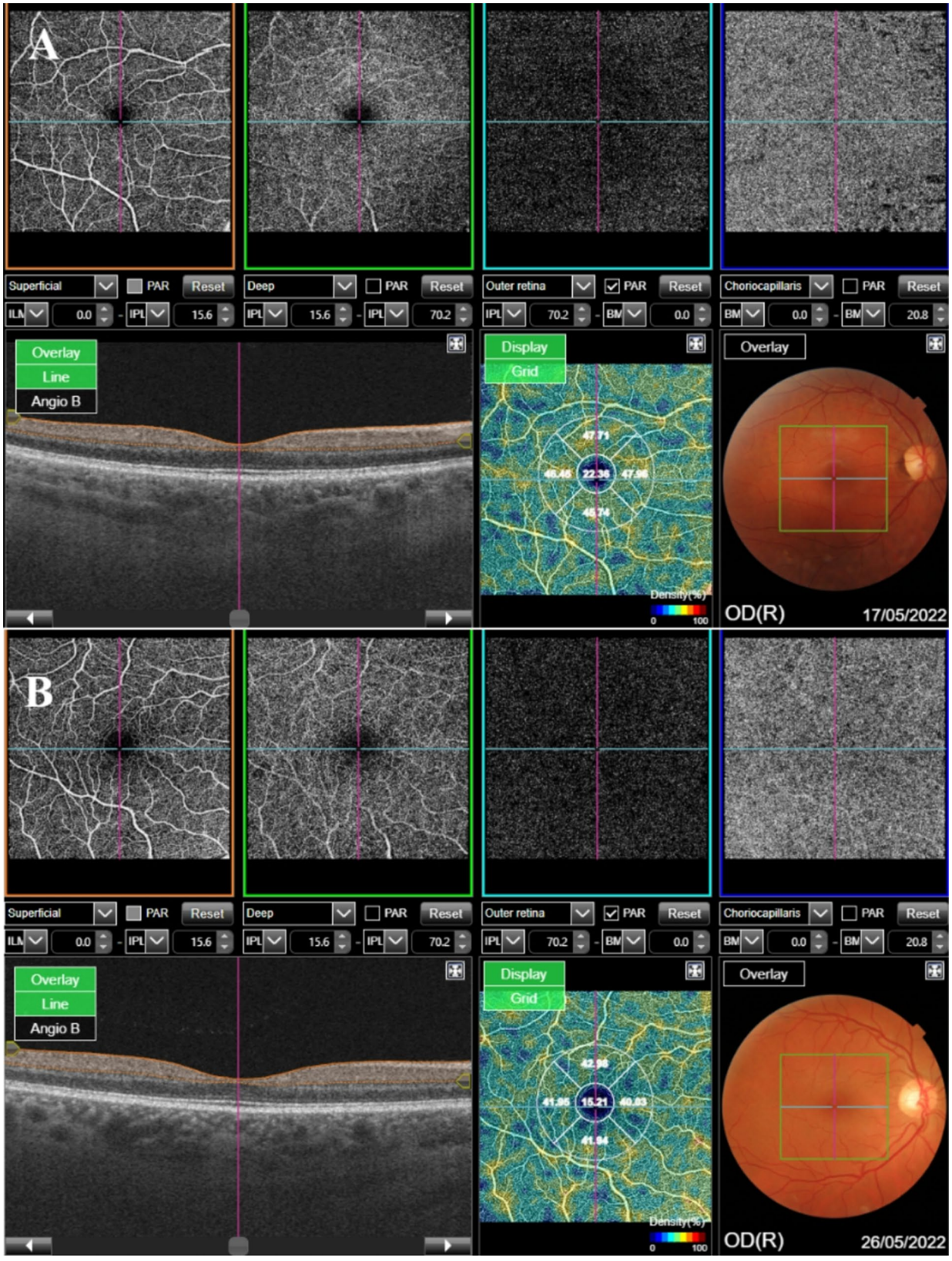

Fig. 1 OCTA images of a control **(A)** and a type-1 DM patient **(B)**

Table 3 Correlations between inflammatory and renal parameters and optic coherence tomography parameters

Parameter 1	Parameter 2	Pearson *r*	*p* value
Mean VD*	Spot Creatinine	-0.527	**0.002**
Mean VD*	Spot Microalbumin	-0.355	**0.043**
FAZ Area($mm^{2)}$ **	Spot Creatinine	0.348	**0.047**
FAZ Area($mm^{2)}$ **	Spot Microalbumin	0.371	**0.034**
Perifoveal Retinal Thickness(µm)	Spot Microalbumin	0.41	**0.018**
Perifoveal Retinal Thickness(µm)	Albumin/Creatinine Ratio	0.415	**0.016**
Parafoveal Ganglion Cell Layer(µm)	SII***	-0.357	**0.041**
Mean choroidal thickness(µm)	SII***	0.686	**< 0.001**

*VD: Vacular density

**FAZ: Foveal avascular zone

***SII: Systemic immune-inflammation index

inflammatory, renal, and retinal parameters. A moderate negative correlation was found between spot creatinine and mean vascular density (r = -0.527, p = 0.002) and between spot microalbumin and mean vascular density (r = -0.355, p = 0.043), suggesting that worsening renal marker levels may be associated with decreased retinal microvascular perfusion.

Additionally, the foveal avascular zone (FAZ) area was moderately positively correlated with both spot creatinine (r = 0.348, p = 0.047) and spot microalbumin (r = 0.371, p = 0.034), whereas perifoveal retinal thickness was positively correlated with spot microalbumin (r = 0.410, p = 0.018) and the albumin/creatinine ratio (r = 0.415, p = 0.016). A moderate negative correlation was observed between the systemic immune-inflammation index (SII) and parafoveal ganglion cell complex thickness (r = -0.357, p = 0.041), indicating a potential link between systemic inflammation and early neuroretinal thinning in T1DM patients without clinical retinopathy.

A post-hoc power analysis based on the correlation between the foveal avascular zone (FAZ) area and spot urine microalbumin levels (r = 0.371) yielded a statistical power of 0.88 (α = 0.05, two-tailed), indicating that the sample size was adequate to detect this moderate association with a high degree of reliability.

Discussion

The effects of type 1 DM on the retina and choroid prior to retinopathy have already been demonstrated in some previous studies. While some of these studies include pediatric cases, some also include patients with DR. Although examining the effects of type 1 DM on the retina in childhood is advantageous in terms of excluding the effects of systemic diseases, it may be misleading to examine only the effects of type 1 DM when it is considered that many hormones that are effective in puberty also have systemic effects [16]. To avoid the influence of pubertal hormonal changes on ocular structures, we focused on a relatively narrow adult age group (25–35 years), allowing a more isolated evaluation of diabetes-related effects.

The effect of systemic inflammation on choroidal thickness has been investigated in various studies. Changes in choroidal thickness have been observed, especially in systemic inflammatory diseases affecting vascular structures. A study conducted in individuals with Behçet's disease reported that subfoveal choroidal thickness increased even in patients without active ocular inflammation and that this could be an indicator of subclinical ocular and systemic immune response [17]. Similarly, studies conducted in patients with juvenile systemic lupus erythematosus have shown that choroidal thickness increases during the active phases of the disease and that this increase is associated with the active phases of systemic vasculitis [18]. These findings suggest that immune activation may have both increasing and decreasing effects on choroidal thickness and that choroidal thickness can be used as a biomarker of systemic immune response.

Previous studies investigating choroidal thickness in T1DM patients have reported conflicting results. Some have found increased thickness in patients without DR or with mild DR [19, 20, 21, 22, 23], while others reported significant thinning [24, 25, 26, 27]. Aksoy et al. [19] demonstrated increased choroidal vascularity index in T1DM patients without DR, suggesting early choroidal involvement. Duration of diabetes may be a contributing factor; for instance, Elvira et al. 28 observed thicker choroids in patients with diabetes duration < 24 years, while longer disease duration was associated with thinning. Our findings are novel in that we are the first to demonstrate a strong association between SII and choroidal thickness in T1DM patients without DR. Choroidal thickening may be multifactorial and reflect early inflammatory involvement. SII incorporates neutrophil, platelet, and lymphocyte counts; it is reasonable that the observed increase in choroidal thickness may be result of inflammatory-induced vascular dysregulation [8, 9]. One possible explanation is vascular dilation of the choroidal vessels

secondary, leading to increased choroidal blood flow [4, 16]. Alternatively, interstitial edema due to increased vascular permeability and disruption of the choroid's blood-retinal barrier may also contribute4, 17. The choroid's dense vasculature and high metabolic demand make it particularly susceptible to systemic inflammatory changes16, 17. These hypotheses suggest that choroidal thickness, although a nonspecific measure, may serve as a marker of early microvascular compromise in diabetes.

There are varying data in the literature on the effects of type 1 DM on VD rates in the SCP. While some studies have shown that there is no significant difference in VD when healthy controls are compared with type 1 DM patients without DR [29, 30, 31, 32, 33], some studies have reported that statistically significant difference [34]. Although the VD rate was low in type 1 DM patients in our study, this difference was not statistically significant. Our findings suggest that the mean VD values were negatively correlated with spot urine creatinine and microalbumin. Cankurtaran et al. [35] also examined the relationship between microalbuminuria and OCTA findings and demonstrated that there was a correlation between VD in the SCP and DCP layers and microalbuminuria even in the absence of retinopathy. These findings are consistent with the presence of microangiopathic changes in both the renal and retinal systems.

When the FAZ areas were examined in diabetic patients, there were studies with similar results to our study in which the difference was not statistically significant [29, 31, 36, 37, 38]. In some studies, it was statistically demonstrated that the FAZ area was wider in diabetic patients than in non-diabetic patients [23, 39]. When the relationship between the FAZ area and hbA1c in the cases was examined, Gołębiewska J et al. [40] reported that there was no statistically significant difference, similar to our study. Dm duration was also found to be correlated with the FAZ area in some studies [34].

The observed correlations between spot urine microalbumin and creatinine levels with both FAZ area and vascular density support the notion of a shared microvascular disease process in the retina and kidneys. Previous studies have demonstrated that FAZ enlargement correlates with systemic microvascular dysfunction, such as diabetic nephropathy, highlighting the utility of FAZ area as a sensitive indicator of microvascular impairment [41]. Given that both organs are highly sensitive to early capillary dysfunction, these findings may reflect a broader pattern of endothelial injury in T1DM. Retinal OCTA parameters may thus serve as noninvasive indicators of early renal microvascular stress, even in the absence of overt nephropathy.

When we examined the RNFL thicknesses of the groups, no significant differences were detected in the inferior, nasal or temporal quadrants, whereas the mean RNFL and superior quadrant thicknesses were lower in the diabetic group despite the absence of retinopathy. Chen et al. [42] also revealed thinning in the superior quadrant in the type 1 DM group, but unlike our study, it was not statistically significant. Marc et al. [24] reported significant thinning in the nasal quadrant. This thinning, which occurs before DR, suggests early neurodegenerative processes. Since both RNFL and GCC layers are composed of retinal ganglion cell axons and bodies respectively, these changes may reflect diabetic neurodegeneration [43]. The thinning in both layers supports the hypothesis that neuronal injury may precede microvascular impairment in diabetic retinal pathology [44]. These findings are consistent with prior studies suggesting that chronic hyperglycemia and systemic inflammation may lead to apoptosis of retinal neurons [8, 34, 44]. The observed negative correlation between SII and parafoveal GCC thickness shows the potential contribution of systemic immune response to early retinal neuronal damage in T1DM.

In the present study, the ganglion cell layer thickness in perifoveal region was significantly thinner in the diabetic group than in the control group, which was similar to the results of most studies [44, 45, 46]. Our study revealed a negative correlation between the parafoveal ganglion cell layer thickness and the SII. These findings indicate that neurodegenerative loss may occur due to the inflammatory process. Immune activation may trigger neuroretinal damage through oxidative stress, cytokine-mediated neurotoxicity (e.g., TNF-α, IL-6), and mitochondrial dysfunction, all of which contribute to retinal ganglion cell apoptosis before vascular signs of DR appears [8, 43].

Elevated SII was associated with both inner retinal neurodegeneration, reflected by GCC thinning, and microvascular compromise, indicated by reduced vessel density and enlarged FAZ. These findings support the hypothesis that inflammation contributes to parallel retinal neuronal and microvascular injury. Correlations between SII and choroidal vascularity may show that SII may influence ocular microcirculation beyond the retina. Taken together, SII appears to act as a systemic marker of neurovascular stress, potentially linking systemic immune dysregulation to early subclinical changes in both retinal and choroidal structures.

In subclinical retinal changes, neurodegeneration may precede overt microvascular alterations. Several studies have reported that neuronal loss can be detected before microvascular abnormalities occur in OCTA or fundus examination [44, 45]. Oxidative stress, mitochondrial dysfunction, and activation of proinflammatory and apoptotic pathways are triggered as a result of chronic hyperglycemia, which affect retinal neurons even in the absence of vascular compromise [8, 43].

OCTA may have limited sensitivity in detecting capillary dropout in preclinical diabetic retinopathy, especially within the superficial capillary plexus (SCP), due to segmentation variability and projection artifacts. In contrast, structural parameters such as RNFL and GCC thickness can be quantitatively and reproducibly measured, making them more sensitive indicators of early damage [44, 46].

The observed correlations between retinal, choroidal, and systemic inflammation markers suggest that such combined evaluations may support the early diagnosis of DR in T1DM patients and contribute to future targeted treatment approaches.

Since patients without DR were included in our study, the relationship between DR stage and the SII could not be examined. This relationship can be examined in more detail with a larger case group and patients with different DR stages, and perhaps new treatments can be developed by targeting these values in DR treatment. Another limitation of this study is the absence of axial length measurements. Due to the cross-sectional nature of our study, we cannot establish all causal relationships. Longitudinal studies with larger cohorts and functional assessments are needed to confirm whether these imaging and laboratory findings can serve as reliable early indicators of microvascular damage and progression. Given its accessibility from routine blood counts, the SII could serve as a practical and cost-effective tool for early DR risk evaluation in clinical settings. However, further studies are needed to define clinically meaningful cutoff values for this biomarker.

Conclusion

Since there are no publications in the literature that include all choroidal and inflammatory markers and urine markers in type 1 DM patients, this feature distinguishes our study from others. This study highlights that the systemic immune-inflammation index (SII) may reflect early retinal and choroidal microstructural changes in patients with type 1 diabetes mellitus before clinical signs of DR appear.

Author contributions

YZG, HGK, and YÜ were responsible for data collection.HGK and YZG drafted and revised the manuscript.FA contributed to the conception and design of the study.HGK, YZG, MA, and YÜ were involved in data processing and analysis. All authors reviewed and approved the final version of the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

The authors declare that the data supporting the findings of this study are available upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from İzmir Katip Çelebi University Ethics Committee] (Approval number: [2022-KAE-0043]). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Ophthalmology, İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital, İzmir, Turkey
[2]Department of Ophthalmology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey
[3]Department of Internal Medicine, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey
[4]Department of Public Health, Balikesir University Faculty of Medicine, Balikesir, Turkey

Received: 30 March 2025 / Accepted: 13 May 2025
Published online: 19 May 2025

References

1. Kulkarni A, Muralidharan C, May SC, Tersey SA, Mirmira RG. Inside the B cell: molecular stress response pathways in diabetes pathogenesis. Endocrinology. 2022;164(1). https://doi.org/10.1210/ENDOCR/BQAC184.
2. Lundeen EA, Burke-Conte Z, Rein DB, et al. Prevalence of diabetic retinopathy in the US in 2021. JAMA Ophthalmol. 2023;141(8):747. https://doi.org/10.1001/JAMAOPHTHALMOL.2023.2289.
3. Barrett EJ, Liu Z, Khamaisi M, et al. Diabetic microvascular disease: an endocrine society scientific statement. J Clin Endocrinol Metab. 2017;102(12):4343–410. https://doi.org/10.1210/jc.2017-01922.
4. Eshaq RS, Harris NR. The role of TNF-α and IFN-γ in the hyperglycemia-induced ubiquitination and loss of PECAM-1 in rat retinal endothelial cells. Microcirculation. 2021;28(7):e12717. https://doi.org/10.1111/MICC.12717.
5. Akkaya S, Açikalin B, Asilyazici E et al. *Diyabetik Retinopatinin Tanı ve Tedavisi Diagnosis and Treatment of Diabetic Retinopathy*.
6. Uğurlu N, Taşlıpınar AG, Yülek F, Özdemir D, Ersoy R, Çakır B. Evaluation of retinal microvascular structures in type 1 diabetic patients without diabetic retinopathy. Ankara Med Journal Published Online Dec. 2018;26. https://doi.org/10.17098/amj.501136.
7. Berhuni M, Yılmaz EB, Soysal GG, Özcan ÖZ, Doğan L. Efficacy and safety of intravitreal dexamethasone implant in Treatment-Resistant diabetic macular edema: Six-month results. Cesk Slov Oftalmol. 2025;81(Ahead of Print):1–6. https://doi.org/10.31348/2025/4.
8. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822–32. https://doi.org/10.1038/S41591-019-0675-0.
9. He L, Xie X, Xue J, Xie H, Zhang Y. Association of the systemic immune-inflammation index with all-cause mortality in patients with arteriosclerotic cardiovascular disease. Front Cardiovasc Med. 2022;9:952953. https://doi.org/10.3389/FCVM.2022.952953/FULL.
10. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212–22. https://doi.org/10.1158/1078-0432.CCR-14-0442.
11. Shin Y, Il, Nam KY, Lee SE et al. Peripapillary microvasculature in patients with diabetes mellitus: An optical coherence tomography angiography study. *Scientific Reports 2019 9:1*. 2019;9(1):1–10. https://doi.org/10.1038/s41598-019-52354-8
12. Li T, Jia Y, Wang S, et al. Retinal microvascular abnormalities in children with type 1 diabetes mellitus without visual impairment or diabetic retinopathy. Invest Ophthalmol Vis Sci. 2019;60(4):990–8. https://doi.org/10.1167/IOVS.18-25499.

13. Elbeyli A, Kurtul BE, Ozcan SC, Ozarslan Ozcan D. The diagnostic value of systemic immune-inflammation index in diabetic macular oedema. Clin Exp Optom. 2022;105(8):831–5. https://doi.org/10.1080/08164622.2021.1994337.
14. Nie Y, Zhou H, Wang J, Kan H. Association between systemic immune-inflammation index and diabetes: a population-based study from the NHANES. Front Endocrinol (Lausanne). 2023;14:1245199. https://doi.org/10.3389/FENDO.2023.1245199/BIBTEX.
15. Zhou J, Song S, Zhang Y, Jin K, Ye J. OCT-Based biomarkers are associated with systemic inflammation in patients with Treatment-Naïve diabetic macular edema. Ophthalmol Ther. 2022;11(6):2153. https://doi.org/10.1007/S40123-022-00576-X.
16. Demir ST, Ucar A, Elitok GK, et al. Evaluation of retinal neurovascular structures by optical coherence tomography and optical coherence tomography angiography in children and adolescents with type 1 diabetes mellitus without clinical sign of diabetic retinopathy. Graefe's Archive Clin Experimental Ophthalmol. 2020;258(11):2363–72. https://doi.org/10.1007/S00417-020-04842-1/METRICS.
17. Chung YR, Cho EH, Jang S, Lee SY, Lee ES, Lee K. Choroidal thickness indicates subclinical ocular and systemic inflammation in eyes with behçet disease without active inflammation. Korean J Ophthalmol. 2018;32(4):290. https://doi.org/10.3341/KJO.2017.0139.
18. Ru L, Xu J, Lin Z, Cao L, Zhang L. Analysis of choroidal thickness in juvenile systemic lupus erythematosus and its correlation with laboratory tests. BMC Ophthalmol. 2023;23(1):1–10. https://doi.org/10.1186/S12886-023-02906-4/TABLES/7.
19. Aksoy M, Simsek M, Apaydın M. Choroidal vascularity index in patients with Type-1 diabetes mellitus without diabetic retinopathy. Curr Eye Res. 2021;46(6):865–70. https://doi.org/10.1080/02713683.2020.1846755.
20. Duran M, Cevher S, Kendirci HNP. Choroidal thickness and choroidal vascularity index changes in children with type 1 diabetes mellitus without retinopathy. Photodiagnosis Photodyn Ther. 2023;43. https://doi.org/10.1016/J.PDPDT.2023.103706.
21. Pilotto E, Cosmo E, Torresin T, et al. Outer retinal and choroidal changes in adolescents with Long-Lasting type 1 diabetes. J Clin Med 2024. 2023;13(1):229. https://doi.org/10.3390/JCM13010229.
22. Wu Y, Xiao Y, Cui L et al. Association between the onset of diabetic retinopathy and thickness changes in the retina and choroid of children with type 1 diabetes: A three-year longitudinal study. Ophthalmic Physiol Opt. Published online 2025. https://doi.org/10.1111/OPO.13439
23. Niestrata-Ortiz M, Fichna P, Stankiewicz W, Stopa M, DETERMINING THE EFFECT OF, DIABETES DURATION ON RETINAL AND CHOROIDAL THICKNESSES IN CHILDREN WITH TYPE 1 DIABETES MELLITUS. Retina. 2020;40(3):421–7. https://doi.org/10.1097/IAE.0000000000002420.
24. Carbonell M, Alonso N, Castelblanco E, et al. Assessment of inner retinal layers and choroidal thickness in type 1 diabetes mellitus: A Cross-Sectional study. J Clin Med 2019. 2019;8(9):1412. https://doi.org/10.3390/JCM8091412.
25. Esmaeelpour M, Brunner S, Ansari-Shahrezaei S, et al. Choroidal thinning in diabetes type 1 detected by 3-Dimensional 1060 Nm optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(11):6803–9. https://doi.org/10.1167/IOVS.12-10314.
26. Yolcu U, Çağıltay E, Toyran S, Akay F, Uzun S, Gundogan FC. Choroidal and macular thickness changes in type 1 diabetes mellitus patients without diabetic retinopathy. Postgrad Med. 2016;128(8):755–60. https://doi.org/10.1080/00325481.2016.1210475.
27. Bilici S, Gultekin Erol T, Bilici ME, Canturk Ugurbas S, Ugurbas SH. Evaluation of choroidal structures in children with newly diagnosed Type-1 diabetes mellitus. Beyoglu Eye J. 2024;9(3):144–8. https://doi.org/10.14744/BEJ.2024.36036.
28. Orduna-Hospital E, Perdices L, Sanchez-Cano A, Acha J, Cuenca N, Pinilla I. Choroidal changes of long-term type 1 diabetic patients without retinopathy. Diagnostics. 2020;10(4). https://doi.org/10.3390/diagnostics10040235.
29. Eid P, Creuzot-Garcher C, Aho LS, et al. Early retinal microvascular changes assessed with Swept-Source OCT angiography in type 1 diabetes patients without retinopathy. J Clin Med. 2023;12(7). https://doi.org/10.3390/jcm12072687.
30. Raffa L, Alosaimy R, Babaker R, Ezzat S. Optical coherence tomography angiography evaluation of retinal and optic disc alterations in children with type 1 diabetes without retinopathy. Indian J Ophthalmol Published Online August. 2024;14. https://doi.org/10.4103/ijo.ijo_3357_23.
31. Rego-Lorca D, Mateu-Salat M, Chico A, Molina-Montero A, Díaz-Cascajosa J, Vela-Segarra JI. OCTA and microperimetry changes preceding the appearance of diabetic retinopathy in patients with type 1 diabetes. Curr Eye Res Published Online. 2024. https://doi.org/10.1080/02713683.2024.2435357.
32. Koca SB, Akdogan M, Koca S. Evaluation of early retinal vascular changes by optical coherence tomography angiography in children with type 1 diabetes mellitus without diabetic retinopathy. Int Ophthalmol. 2022;42(2):423–33. https://doi.org/10.1007/S10792-021-02059-7.
33. Cutruzzolà A, Carnevali A, Gatti V, et al. Continuous glucose Monitoring-Derived metrics and capillary vessel density in subjects with type 1 diabetes without diabetic retinopathy. J Diabetes Res. 2023;2023. https://doi.org/10.1155/2023/9516059.
34. Kara O, Can ME. Evaluation of microvascular changes in retinal zones and optic disc in pediatric patients with type 1 diabetes mellitus. Graefe's Archive Clin Experimental Ophthalmol. 2021;259(2):323–34. https://doi.org/10.1007/s00417-020-04935-x.
35. Cankurtaran V, Inanc M, Tekin K, Turgut F. Retinal microcirculation in predicting diabetic nephropathy in type 2 diabetic patients without retinopathy. Ophthalmologica. 2020;243(4):271–9.
36. Augustin AJ, Atorf J. The value of optical coherence tomography angiography (OCT-A) in neurological diseases. Diagnostics (Basel). 2022;12(2). https://doi.org/10.3390/DIAGNOSTICS12020468.
37. Carnevali A, Sacconi R, Corbelli E, et al. Optical coherence tomography angiography analysis of retinal vascular plexuses and choriocapillaris in patients with type 1 diabetes without diabetic retinopathy. Acta Diabetol. 2017;54(7):695–702. https://doi.org/10.1007/S00592-017-0996-8/METRICS.
38. Simonett JM, Scarinci F, Picconi F, et al. Early microvascular retinal changes in optical coherence tomography angiography in patients with type 1 diabetes mellitus. Acta Ophthalmol. 2017;95(8):e751–5. https://doi.org/10.1111/AOS.13404.
39. Korkmaz HA, Dogan B, Devebacak A, Değirmenci C, Afrashi F. The relationship of serum diabetes antibodies with the development of early diabetic retinopathy findings in children with type 1 diabetes mellitus. J pediatr ophthalmol strabismus. Published Online Dec. 2024;30:1–8. https://doi.org/10.3928/01913913-20241121-03.
40. Gołębiewska J, Olechowski A, Wysocka-Mincewicz M, et al. Optical coherence tomography angiography vessel density in children with type 1 diabetes. PLoS ONE. 2017;12(10):e0186479. https://doi.org/10.1371/JOURNAL.PONE.0186479.
41. Yao H, Li Z. Is preclinical diabetic retinopathy in diabetic nephropathy individuals more severe? Front Endocrinol (Lausanne). 2023;14. https://doi.org/10.3389/FENDO.2023.1144257.
42. Chen L, Feng Y, Zhang SS, Liu YF, Lin P. Quantifying peripapillary vessel density and retinal nerve fibre layer in type 1 diabetic children without clinically detectable retinopathy using OCTA. Int J Ophthalmol. 2024;17(2):278–81. https://doi.org/10.18240/ijo.2024.02.08.
43. Chen Y, Li J, Yan Y, Shen X. Diabetic macular morphology changes May occur in the early stage of diabetes. BMC Ophthalmol. 2016;16(1). https://doi.org/10.1186/S12886-016-0186-4.
44. van Dijk HW, Verbraak FD, Kok PHB, et al. Early neurodegeneration in the retina of type 2 diabetic patients. Invest Ophthalmol Vis Sci. 2012;53(6):2715–9. https://doi.org/10.1167/iovs.11-8997.
45. Jonsson KB, Frydkjaer-Olsen U, Grauslund J. Vascular changes and neurodegeneration in the early stages of diabetic retinopathy: which comes first?? Ophthalmic Res. 2016;56(1):1–9. https://doi.org/10.1159/000444498.
46. Karti O, Nalbantoglu O, Abali S, et al. Retinal ganglion cell loss in children with type 1 diabetes mellitus without diabetic retinopathy. Ophthalmic Surg Lasers Imaging Retina. 2017;48(6):473–7. https://doi.org/10.3928/23258160-20170601-05.

Publisher's note