Detection of Early Retinal Neurovascular Changes in Children and Adolescents with Type 1 Diabetes Mellitus Without Diabetic Retinopathy

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ABSTRACT

Purpose: To detect early retinal neurovascular structural changes in the macula and disc region using optical coherence tomography angiography before the development of diabetic retinopathy (DR) in children and adolescents with type 1 diabetes mellitus (T1DM).

Materials and Methods: Our prospective cross-sectional study was conducted between February 2021 and June 2021. The patient group consisted of 69 children and adolescents aged 7-18 who did not develop DR and vision loss, and the control group comprised 74 age and sex-matched healthy individuals. Foveal avascular zone (FAZ); vascular density (VD) analyses of the superficial capillary plexus (SCP), deep retinal capillary plexus (DCP) and radial peripapillary capillary plexus (RPCP); thickness analyses of the fovea (FT), parafovea (PFT) and peripapillary retinal nerve fiber layer (ppRNFL); were performed using optical coherence tomography angiography (OCTA) . The correlation of the changes detected in the participants with T1DM with the duration of diabetes and glycated hemoglobin (HbA1C) levels were evaluated.

Results: There was no statistically significant difference in FAZ areas, FT, ppRNFL values, DCP VD (except the inferior quadrant) and RPCP VD in children and adolescents with T1DM without clinical retinopathy, but there was a significant reduction in SCP parafoveal VDs and PFT . A high negative correlation was found between parafoveal region VD measurements, HbA1c levels and disease duration in DCP and SCP. In addition, PFT values also negatively correlated with disease duration. A high negative correlation was found between parafoveal region VD measurements, HbA1c levels and disease duration in DCP and SCP. In addition, PFT values were also negatively correlated with disease duration.

Conclusion: Microvascular structural changes may also occur in patients with T1DM without clinical retinopathy. These findings, detectable in OCTA, may be useful for the screening and management of patients with T1DM.

Keywords: Children; foveal avascular zone; optic coherence tomography angiography; vessel density; type 1 diabetes mellitus.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the third most common chronic disease in children and adolescents.[1]. Diabetic retinopathy (DR) that is mainly characterized by the destruction and degeneration of capillaries the most common microvascular complication of DM[2-4] In a multi-center study conducted in a pediatric population with T1DM, the prevalence of DR was reported as 11%.[5] The most important risk factors for the development of DR in children with T1DM are the duration of T1DM, adolescence, age at diagnosis, and the median glycated hemoglobin (HbA1c) level in the previous 12 months.[5] Although pediatric populations appear to be at low risk for DR, significant macular edema or even proliferative diabetic retinopathy may develop, especially in adolescents[6-9]. Diabetes causes microvascular damage, microglial cell activation, and ganglion cell loss, and neuronal apoptosis develops in various retinal layers.[10,11] These findings suggest that DR is both a neurodegenerative condition and a vascular condition.[11] Microvascular and neurodegenerative damages are known to occur before DR becomes evident with fundus examination or fundus photography.[12-15] Diabetic retinopathy (DR) is asymptomatic in its early stages. When patients present to the outpatient clinic with visual impairment, chronic and progressive pathology in the retinal microvascular structure has already developed. Therefore, screening programs designed to detect DR early are crucial to

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preserving vision in children and adolescents with T1DM.[5,16,17] The guidelines of the American Academy of Ophthalmology (AAO) (2017) do not recommend the examination of DR in children aged under 9 years or with a duration of illness less than 5 years. However, it has been shown that DR can also develop in children with a disease duration of 2-4 years or the 6-7 years age group. [18]

Fluorescein angiography (FA) is the gold standard in the diagnosis and classification of DR, but this method requires intravenous injection of substances and causes significant discomfort and stress[19,20]. Optical coherence tomography angiography (OCTA) is a rapid imaging modality that facilitates non-invasive examination of the different vascular plexuses in the retina [18]. Studies in adult populations have proved that OCTA and FFA have a good correlation and repetition.[21-23] Optical coherence tomography angiography (OCTA) uses the "motion contrast" principle to detect blood flow and noninvasively and reliably generates high-resolution cross-sectional images of the human retina. Microvascular damage due to diabetes in both the macular and optic disc regions can be quantitatively evaluated using OCTA.[2,18] A less common cause of vision loss in the absence of diabetic macular edema and proliferative DR is diabetic macular ischemia .Diabetic macular ischemia can be detected in the early stages of diabetes by detecting reduced retinal capillary density and widening in the foveal avascular zone (FAZ) in OCTA[24]. Considering that vision loss can be prevented in >90% of patients with early diagnosis and correct staging.[25,26] Optical coherence tomography angiography (OCTA) plays an increasing role in the diagnosis of DR and evaluation of treatment options.[27,28]

The aim of this study was to determine early changes before clinically detectable retinopathy by measuring foveal retinal thickness (FT), parafoveal retinal thickness (PFT), peripapillary retinal nerve fiber layer (RNFL) thickness, FAZ area, vascular density (VD) analyses of the macular superficial capillary plexus (SCP), deep retinal capillary plexus (DCP), and radial peripapillary capillary plexus (RPCP) using OCTA in children with T1DM and by comparing them with healthy controls.

MATERIALS-METHODS

This prospective cross-sectional case-control study was conducted between June 2020 and February 2021 at a tertiary care training and research hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki for research involving human subjects. The study was approved by our hospital's local ethics committee and written informed consent was obtained from all participants and the parents of underage participants. The study group included 76 children and adolescents with T1DM, aged 7-18 years, who had no visual loss and were clinically diagnosed with DR.; seven patients were excluded from the study due to poor OCTA image quality. Analyses were performed on 138 eyes of 69 patients in the study group. 148 eyes of 74 age- and sex-matched participants were included in the control group.

The common inclusion criteria for all groups were best corrected visual acuity (BCVA) of 20/20 and spherical or cylindrical refractive error < 2 D. Those with a history of ocular surgery or trauma, glaucoma, amblyopia, any retinopathy, and optic nerve disease were excluded from the study. Those with any systemic disease in the control group, and patients with medically treated hypertensive nephropathy or clinically demonstrated microvascular complications, diabetes duration <1 year or any systemic disease other than diabetes in the study group were also excluded.

All participants underwent a detailed ophthalmologic examination including visual acuity and refraction, biomicroscopic examination, dilated fundus examination, and intraocular pressure (IOP) measurements. The disease duration of the patients with T1DM was recorded, and the average HbA1c value checked in the last 1 year was calculated. Imaging was performed after pupil dilation (1% cyclopentolate) using the OCTA device (Optovue RTVue XR Avanti; Optovue Inc., Fremont, CA) by the same technician who was trained in the use of the device.

Optical coherence tomography angiography (OCTA) (Optovue RTVue XR Avanti; Optovue Inc., Fremont, CA) is used to evaluate retinal vascularization. AngioVue noninvasively visualizes the retina and choroidal vasculature through motion contrast using a split-spectrum amplitude-decorrelation angiography (SS-ADA) algorithm to detect erythrocyte movement. Optical coherence tomography angiography (OCTA) examination was performed using the standard macular and peripapillary protocol. All eye scans were of a 3 × 3-mm scanning area centered on the fovea and a 4.5 × 4.5 mm scanning area centered on the papilla.

The foveal avascular zone (FAZ) is the retinal capillary free area located in the central fovea. The FAZ area (mm^2) was determined from the en face OCTA images. To calculate the VD, the AngioVue Analytical software was used to extract a binary image of blood vessels from the grayscale OCTA image, and then the percentage of pixels with a flow signal higher than the threshold in the defined region was calculated. Macular vessel densities were analyzed on a 1.5-mm wide parafoveal, with the circular ring centered on the macula. Parafoveal VD was calculated for the annular area between 0.3 and 1.25 mm radius from the center of the macula. The parafoveal region was divided into four sectors of 90 degrees

each (temporal, superior, nasal and inferior sectors) and the VD in each sector was calculated. Parafoveal VD, defined as the percentage of the total area occupied by the vessels and microvasculature, was also measured in SCP and DCP. Superficial capillary plexus (SCP) and deep capillary plexus (DCP) were created using an automated software algorithm. Then the "en face" image was segmented automatically to identify SCP and DCP with the segmentation algorithm. The "en face" images of the SCP were segmented between an inner border 3 mm below the internal limiting membrane and an outer border 15 mm below the inner plexiform layer (IPL). The "en face" images of the DCP were segmented under the IPL with inner and outer boundaries at 15 and 70 mm, respectively. Foveal thickness (FT) and parafoveal thickness (PFT) data were obtained from retinal maps, using the same device.

Peripapillary capillary VD was measured in a 1.00-mm wide elliptical ring extending outward from the optic disc border in the radial peripapillary capillary (RPC) region. The VDs of the whole image, inside disc, and peripapillary areas were examined. Peripapillary RNFL thickness was evaluated as a 3.45-mm diameter circle around the optic disc in ONH mode.

All of the OCTA images reviewed to ensure the correct segmentation and identify poor-quality scans with motion artifacts or blurred images, or where the data were insufficient for proper analysis. The device included the projection artifact removal algorithm.

The data obtained were compared with the eyes of healthy controls. The correlation of these parameters with the duration of illness and HbA1c values of children with T1DM was examined.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed using the SPSS 21.0 package program. A normality check of the continuous variables was performed using the Shapiro-Wilk test. Student's t-test was used in the comparison of the groups for variables with normal distribution, and the Mann-Whitney U test was used in the comparison of the groups for variables without normal distribution. When examining the linear relationship between continuous variables, Spearman's Rho correlation coefficients were calculated because the data did not conform to normal distribution. The sex distribution was checked using the Chi-square test. The statistical significance level was accepted as 0.05.

RESULTS

In the study, 286 eyes of 143 patients were included. There were 69 children (138 eyes) in the T1DM group and 74 children (148 eyes) in the control group. The age and sex distributions of the participants are shown in Table 1. The age and sex distributions according to the groups were homogeneous (p>0.05). The average duration of illness in patients with T1DM was 54.83 ± 37.14 months. The mean HbA1c value in the last year was 8.56 ± 2.04% (Table 2). Retinal examinations of all participants were normal, their BCVA was 20/20.

When the OCTA data of the participants were examined, no statistically significant difference was found in children and adolescents with T1DM compared with the healthy controls in terms of FAZ size, FT, and superficial foveal vascular density (SFD) (p=0.129, p=0.251, and p=0.614, respectively). There was a significant decrease in parafoveal thickness

Table 1: *Demographic data of children and adolescents with type 1 diabetes mellitus and healthy controls*

	T1DM group (n=69)		Control group (n=74)		
	Mean±SD (min-max)	Median [IQR]	Mean±SD (min-max)	Median [IQR]	p
Age	12.54±3.12 (7-18)	13 [10-15]	12.54±3.23 (7-18)	12.5 [10-15]	*0.987
Sex					
Female	40	58.0%	48	64.9%	†0.397
Male	29	42.0%	26	35.1%	

p1: Mann Whitney U test, p2: Chi-square test. SD: standard deviation. IQR: Interquartile Range

Table 2: *Clinical characteristics of children and adolescents with type 1 diabetes mellitus*

	Mean±SD (min-max)	Median
DM Duration (month)	54.83±37.14 (12-145)	48 [24-84.5]
HbA1c (%)	8.56±2.04 (5.5-14.8)	8.4 [7.1-9.65]

DM: Diabetes mellitus, HbA1c: glycated hemoglobin. SD: Standard deviation

(PFT) values and all superficial parafoveal retinal quadrants' (nasal, temporal, superior, inferior) vascular density values . ($p<0.05$). . There was no significant difference between the groups in terms of deep foveal density (DFD), deep parafoveal density (DPD) and vascular density in the other deep retinal quadrants (superior, nasal, temporal) except for DID ($p>0.05$) (Table 3).

When the groups were examined in terms of ppRNFL, no significant difference was observed between the diabetic group and the control group in terms of the mean nerve fiber thickness and nerve fiber thickness in the superior and inferior quadrants. There was no significant difference between the groups in terms of RPCVD in the superior and inferior regions of the disc and inside the disc (Table 3).

When looking at the effect of OCTA values according to disease duration in patients with T1DM, no statistically significant change was observed in FAZ, SFD, FT, DFD, DSD, DND, DID values, PPRNL thicknesses, and RPCD values depending on the duration of the disease. A significant decrease was observed in all SCP VD values and PFT, except SFD, depending on the duration. In the deep retinal region, DPD and DTD values appeared to be significantly negatively correlated with disease duration (Table 4).

Table 3: *Optical coherence angiography values of children and adolescents with type 1 diabetes mellitus and healthy controls*

Location	T1DM group (n=138) Mean±SD	Control group (n=148) Mean±SD	P value
FAZ(mm^2)	0.26±0.09	0.29±0.1	0.129*
FT (µm)	210.93±14.77	213.93±16.24	0.251
PFT (µm)	278.24±10.8	283.11±11.59	**0.010**
SCP VD			
Fovea(%)	18.26±6.11	17.77±5.41	0.614
Parafovea (%)	50.86±2.46	52.25±1.78	**0.001***
Temporal (%)	49.2±3.17	50.49±2.25	**0.011***
Süperior (%)	52.42±2.49	53.73±1.86	**0.003***
Nasal(%)	50±2.8	51.4±1.97	**0.002***
Inferior(%)	51.7±2.99	53.42±2.03	**<0.001***
DCP VD			
Fovea (%)	35.62±7.03	34.7±6.87	0.433
Parafovea(%)	56.51±2.68	57.3±2.66	0.170*
Temporal (%)	56.44±3.2	57.35±2.24	0.126*
Superior (%)	56.58±3.2	57.33±2.93	0.330*
Nasal(%)	56.71±2.71	57.35±2.74	0.219*
Inferior(%)	56.08±3.06	57.22±3.31	**0.045***
ppPRNFL mean (µm)	99.2±9.65	102.28±10.74	0.106*
ppRNFL superior (µm)	99.57±10.35	102.59±10.67	0.088
ppRNFL inferior (µm)	98.8±9.95	101.79±12.17	0.203*
RPC VD			
Whole image (%)	48.76±1.97	49.52±1.77	0.056
Superior (%)	50.17±2.79	50.81±2.61	0.139*
Inferior (%)	49.78±2.47	50.4±2.62	0.144
Inside disk (%)	52.82±3.37	53.67±3.66	0.150

p: Student's t-test *Mann-Whitney U test. Values are given as mean ± standard deviation. FAZ = Foveal avascular zone, FT = foveal thickness, PFT = parafoveal thickness, VD=vascular density, SCP= superficial capillary plexus, DCP= deep capillary plexus, ppPRNFL = peripapillary retinal nerve fiber layer, RPCVD = radial peripapillary capillary . Values are given as mean ± standard deviation (SD)

Table 4: *Correlation of OCTA findings with disease duration and HbA1c values in the group with T1DM*

Region	Duration		Hba1c	
	r	p	r	p
FAZ (µm)	-0.018	0.885	-0.036	0.768
FT (µm)	-0.141	0.248	0.016	0.893
PFT (µm)	**-0.266**	**0.027**	0.045	0.711
SCP VD				
Foveal(%)	-0.042	0.731	-0.110	0.367
Parafoveal (%)	**-0.686**	**<0.001**	**-0.369**	**0.002**
Temporal (%)	**-0.577**	**<0.001**	**-0.352**	**0.003**
Süperior(%)	**-0.602**	**<0.001**	**-0.327**	**0.006**
Nasal(%)	**-0.676**	**<0.001**	**-0.362**	**0.002**
Inferior (%)	**-0.572**	**<0.001**	**-0.268**	**0.026**
DCP VD				
Foveal (%)	-0.124	0.310	-0.116	0.344
Parafoveal(%)	**-0.239**	**0.048**	**-0.330**	**0.006**
DTD (%)	**-0.307**	**0.010**	**-0.339**	**0.004**
DSD (%)	-0.165	0.177	**-0.295**	**0.014**
DND (%)	-0.215	0.076	**-0.248**	**0.040**
DID (%)	-0.229	0.058	-0.198	0.103
ppPRNFL mean (µm)	-0.004	0.972	0.050	0.685
ppPRNFL superior (µm)	-0.017	0.892	-0.044	0.720
ppPRNFL inferior (µm)	-0.036	0.770	0.125	0.307
RPC VD				
Whole image	-0.181	0.138	-0.194	0.110
Superior	-0.106	0.387	-0.122	0.317
Inferior	-0.098	0.425	-0.052	0.669
Inside disk	0.061	0.617	-0.146	0.230

p: Spearman Rho Correlation. FAZ = Foveal avascular zone, FT = foveal thickness, PFT = parafoveal thickness, VD=vascular density, SCP= superficial capillary plexus, DCP= deep capillary plexus, ppPRNFL = peripapillary retinal nerve fiber layer, RPC = radial peripapillary capillary, HbA1c:glycated hemoglobin

DISCUSSION

Before the first typical DR symptoms are detected on retinal examinations, substantial neural retinal damage and subclinical microvascular changes have already begun.[21,29] We thought that OCTA measurements could be useful detection of this changes before permanent damage devolops in children with diabetes. Many studies are showing a decrease in vascular density in the superficial and deep capillary plexuses in adults with diabetes without DR.[30-38] Adolescents with T1DM may have a more rapid onset and progression of vision-threatening retinopathy compared with adults with T1DM.[39,40] It has been shown that early retinal capillary closure can be temporary and reversible, tight metabolic control seems very important to prevent vision loss in young individuals with T1DM due to the expected long disease duration.[41] There are only a few OCTA studies on children and adolescents with T1DM.[42-46] In this study, we aimed to detect early neurovascular structural changes in the macular and disc region in children and adolescents with T1DM who did not develop DR using non-invasive OCTA, performing quantitative analysis.

There are different results in studies evaluating the FAZ area in patients with diabetes. Some studies found that the FAZ surface area in SCP was wider in adults with DM without clinical DR than in healthy controls.[34,38,47] Tam et al.[36] found no difference in terms of FAZ between control eyes and diabetic eyes in adults with diabetes. Again, Carnevali et al.[31] and Sacconi et al.[12] found no significant change in FAZ area in patients with T1DM compared with controls. In children and adolescents with T1DM without diabetic retinopathy,

Ortiz et al.[43] showed that the FAZ area was significantly larger, whereas other studies[16,43-45] showed that there was no significant difference in the FAZ area compared with healthy controls. Similarly, in our study, there was no significant difference in terms of FAZ between the groups.

Studies performed in adult eyes with early DM showed a significant decrease in macular VD in OCTA.[31,48,49] This change may result from cellular degeneration in the retina, basement membrane thickening, and endothelial cell proliferation due to hyperglycemia, destroying the capillary structure by disrupting the capillary integrity.[16] Mameli et al[50] found a significant decrease in SPD, STD, SND, and SSD values in children, adolescents and young adults with T1DM, but they found no significant difference in SFD. Also, they found a significant decrease in DFD, DPD, and DTD values. In our study, although a significant effect was observed in SCP, there was no significant difference in VD in DCP except for DID. In the study conducted by Demir et al.[44], no significant difference was observed in children and adolescents with T1DM without DR in terms of FAZ, retinal thickness, vascular density in SCP, DCP, and RPCP (except inside the disc and superior temporal disc region) compared with healthy controls. Golebiewska et al.[43] found no significant difference in terms of VD in both SCP and DCP in children with T1DM compared with healthy controls. In contrast, Kara et al.[45] a significant decrease was found in VD in SCP, DCP and RPC regions (except inside disc). In the study conducted by Li et al.[16] on children with T1DM without retinopathy, a significant decrease was found in VD in the inner and outer macular rings, but no significant difference was observed in the disc region. In the study by Koca et al[46], a significant decrease in VD was found in all macular regions in both SCP and DCP in the T1DM group, but no significant difference was observed in optic disc radial peripapillary capillary (RPC) VD when compared with the control group. Similarly, in our study, no significant change was observed in VDs in the disc region. The macula is an area where photoreceptor cells are denser and the cells here have a greater metabolic need. It can be said that the metabolic needs of cells in the peripapillary region are relatively lower compared with the macular region; therefore, changes in the peripapillary region are relatively less in the eyes of children with early DM. On the contrary, Vujosevic et al.[10] reported that VDs inside the disc and in the peripapillary region of adults with DM without DR decreased earlier than the VD in the SCP in the macular region.

Histopathologic studies performed in patients with DM have described pericyte and endothelial cell loss that disrupted the blood-retinal barrier. [10] These changes cause decreased blood flow and capillary occlusion.[51] Hyperglycemia also causes microglial cell activation, ganglion cell loss, and the development of neuronal apoptosis in both inner and outer retinal layers. [6,10] In our study, RT and RNFL values and VDs in the disc region were thinner than normal in children and adolescents with T1DM without DR, but this did not reach statistical significance. This may be attributed to the younger age of the patients, the short duration of diabetes, and low HbA1c levels , which indicates good metabolic control. A significant reduction in the SCP region may indicate that this region is more susceptible to the vascular effect of hyperglycemia.

The duration of T1DM and HbA1c are the most effective risk factors for DR[3]. Diabetes mellitus duration is the only predictor of DR in children in the AAO guidelines. However, a recent large study in the United States of America[52] showed an increase of 20% risk for DR for every 1 point increase of HbA1c in children with T1DM. In our study, it was seen that vascular densities in both SCP and DCP showed a significant negative correlation with HbA1c levels. It can be said that children are more sensitive to metabolic changes and early diagnosis may be beneficial[52]. In the study conducted by Koca et al.[46] VD in SCP was found negatively correlated with mean HbA1c. Virk et al.[53] showed that change in HbA1c was predictive for DR risk in adolescents with T1DM. In the study of Demir et al.[44] no significant relationship was found between RPCVD and RNFL values, duration of diabetes, and HbA1c levels. They found a significant negative correlation between diabetes duration and HbA1c levels and central FT, inner retinal thickness, FAZ area, and foveal region VD. Parafoveal thickness (PFT) values were only negatively correlated with HbA1c levels, while DSD, DID and DND values were only negatively correlated with disease duration. Inanc et al.[54] found no correlation between disease duration and HbA1c levels or microvascular changes of the macular region in children with T1DM without DR. Golebiewska et al.[43] found a negative correlation between HbA1c levels and SPD and PFT, and between T1DM duration and DPD. Fayoumi et al.[55] found a negative correlation between PFT and HbA1c levels, but no significant correlation between ppRNFLs and the duration of DM or HbA1c levels. Li et al.[16] reported that the duration of T1DM was not significantly correlated with FAZ diameter or VDs. Again, Durbin et al.[56] found no correlation between HbA1c and OCTA parameters in adults with diabetes. Gołębiewska et al.[43] reported a negative correlation between HbA1c levels and SPD and between the duration of T1D and DPD. Kara et al[45] found that SCP VD was negatively correlated with both disease duration and HbA1c levels. Takese et al.[33] observed no correlation between FAZ parameters and DM duration. When we looked at the correlation between disease duration and OCTA parameters in our study, there was a high negative correlation between vascular densities in superficial regions and disease duration,

and there was no significant correlation in terms of disc parameters and ppRNLF.

The different results obtained in all these studies support that the development of DR is multifactorial. Although DM duration and HbA1c levels appear to be the most important parameters affecting microvascular changes detected using OCTA, genetic predisposition and lifestyle are also important factors. Our study had some limitations. This cross-sectional study determined the retinal vascular status of patients over a specific period. Insulin is a vasoactive substance. [57] Some deviation in measurement values may be possible depending on the amount and timing of the treatment taken by the patients. Likewise, the current blood glucose concentration itself may have a significant vascular effect. [58,59] Also, OCTA technology has not yet been optimized for these functional analyses, and this technology measures perfused vessel densities, not absolute blood flows. Another factor is that the HbA1c values of the patients only reflect the diabetic control at a certain point. It is not a reliable indicator of long-term diabetic control. Another factor, the incidence of DR development in children and adolescents, as in adults, is time-dependent, but it is not linear. The time before puberty contributes less to the development of DR, but significantly increases the risk of DM complications in adolescence. [44,60] For this reason, how much of the calculated diabetes periods are in times of puberty will affect the results. In addition, a possible delay between the onset of the disease and diagnosis may lead to inaccurate estimations of disease duration. However, the common point across all studies is that retinal neurovascular structural changes begin before retinopathy develops in children and adolescents with T1DM.

As a result, in our study, we observed that microvascular structures in SCP were affected earlier than those in the DCP and disc region before DM findings developed clinically in children and adolescents with T1DM. Decreased VDs in the SCP can be a biomarker that can be used for the early detection of DR. More studies with larger series are needed on this subject. Detection of such early pathologies before the sequelae of DR can direct treatment for optimization of diabetic control before any complications that threaten vision develop. This may prevent the onset of DR or extend the period before its development and contribute to the long-term prognosis.

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