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Comparison of Optical Coherence Tomography Angiography Findings between Healthy Children and Children with Type 1 Diabetes Mellitus and Autoimmune Thyroiditis

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What is already known on this topic?

There are rare studies regarding the impact of type 1 diabetes mellitus (T1DM) and autoimmune thyroiditis (AT) on impairment in retinal microcirculation in children.

What this study adds?

We demonstrated that in children with coexisting AT and T1DM but without clinically detectable diabetic retinopathy (DR), there is impairment in retinal microcirculation and irregularities at the foveal avascular zone margin compared to matched children with isolated T1DM. Impairment in retinal microcirculation and signs of onset of DR proliferative retinopathy can develop independently of AT in children with T1DM and AT.

Abstract

Objective: The aim of this study was to compare the development of early diabetic retinopathy (DR) findings, a microvascular complication, between patients with isolated type 1 diabetes mellitus (T1DM) (Group 1), concurrent T1DM and autoimmune thyroiditis (AT) (Group 2), and healthy controls (Group 3), who were matched for age, sex, number, and body mass index for comparison.

Methods: This was a prospective observational study that included individuals aged 10-20 years, and patients in Groups 1 and 2 had been followed up for ≥5 years. None of them developed clinical DR during the follow-up period. Optical coherence tomography angiography (OCTA) was used to evaluate the foveal avascular zone (FAZ) and parafoveal vascular density (PVD) for the development of early DR. OCTA findings were compared between patients and healthy controls.

Results: Thirty-five individuals were included in each of the groups. The mean FAZ and PVD differed significantly between the three groups (FAZ, $p = 0.016$; PVD, $p = 0.006$). The mean FAZ was higher in Groups 1 and 2 than in Group 3 ($p = 0.013$ and $p = 0.119$, respectively). The mean PVD was lower in Groups 1 and 2 than in Group 3 ($p = 0.007$, respectively). No significant difference was found between Groups 1 and 2 in terms of the mean FAZ and PVD ($p = 0.832$ and $p = 0.653$, respectively). The mean glycated hemoglobin (HbA1c) level was significantly correlated with FAZ and PVD (FAZ: $r = 0.496$, $p < 0.001$; PVD: $r = -0.36$, $p = 0.001$).

Conclusion: In patients with T1DM who did not develop clinical DR, OCTA findings revealed an increase in FAZ, which was associated with higher HbA1c levels. The mean PVD was significantly lower in the group with coexisting AT and T1DM than in the control group. These results suggest that the coexistence of AT and T1DM can contribute to the development of microvascular complications. However, studies with larger patient series are required.

Keywords: Autoimmune thyroiditis, diabetic retinopathy, foveal avascular zone, optical coherence tomography angiography, parafoveal vessel density, type 1 diabetes mellitus

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Introduction

Owing to the prevalence, associated complications, and cost of diabetes, it is recognized as the fastest growing global health issue. In 2021, over 1.2 million children and adolescents had type 1 diabetes mellitus (T1DM) (1). In the first nationwide report on diabetes in Turkey, the prevalence of T1DM was 0.75/1000 from January 2011 to December 2013, and the mean age of patients at diagnosis was 10.6 ± 4.6 years (2). In another study of children aged < 18 years from 2013 to 2015 in Northwest Turkey, 1773 patients (588, 592, and 593 in 2013, 2014, and 2015, respectively) were diagnosed with T1DM. The crude mean incidence was 8.99/100.000 (3).

The life expectancy of patients with diabetes is reduced by 10 years (4,5,6). In the majority of developed societies, DM is identified as a leading cause of blindness, renal failure, and lower limb amputation (4,5,6). Moreover, DM-related complications progress rapidly. Every day, 225 people undergo foot amputation, 120 people undergo dialysis, and 55 people lose their vision. Moreover, diabetic retinopathy (DR) is probably the most characteristic, easily identifiable, and treatable complication of DM but remains an important cause of vision loss in developed countries (7). The prevalence of DR in patients with T1DM ranges from 10.8% to 60.0% in clinic-based populations and from 14.5% to 79.0% in population-based studies (1).

Indirect ophthalmoscopy is known as the primary approach for screening for DR, and it has high diagnostic accuracy (8). Currently, fluorescein angiography is considered the gold standard for the definitive diagnosis and grading of DR, but it needs an intravenous dye injection, which can cause nausea, vomiting, and hypersensitivity (9). Optical coherence tomography angiography (OCTA) is a quick, noninvasive procedure that may be performed without using a dye, making OCTA ideal for use in the pediatric population. Moreover, it is a potentially useful screening and follow-up tool for children with T1DM. Most OCTA studies have focused on adult patients with DR. In these studies, the mean foveal avascular zone (FAZ) in patients with DR was significantly greater than that of healthy controls. In addition, patients with DR had significantly lower parafoveal vascular density (PVD) (10,11,12). Several studies examined children with T1DM to assess FAZ and PVD but no consensus has been achieved to date (13,14,15). Thus, further studies are required to reach clear conclusions on this topic. Moreover, novel parameters such as FAZ and PVD, which can be subjected to automatic quantitative analysis using OCTA software, may help analyze early-onset T1DM without retinopathy screening and disease follow-up.

The aim of this study was to assess the retinal vessel density and FAZ area, as assessed using OCTA, in patients with isolated T1DM and those with concurrent T1DM and autoimmune thyroiditis (AT). Moreover, it aimed to compare potential pathological early changes in this population with those in healthy age-matched controls.

Methods

Patients with isolated T1DM (Group 1), patients with concurrent T1DM and AT (Group 2), and healthy volunteers (Group 3) were included. Participants in these three groups were matched for age, race, sex, number (n = 32), and body mass index. Patients with DM were consecutively enrolled from the outpatient clinic of the Clinic of Pediatric Endocrinology, University of Health Sciences Turkey, İzmir Dr. Behçet Uz Children's Training and Research Hospital, for routine follow-up. Inclusion criteria for patients with DM were aged between 10-20 years, diabetes duration of > 5 years, normotonia, body mass index less than the age- and sex-specific 95th percentile, absence of chronic diseases other than T1DM or AT, no other autoimmune diseases, and no history of smoking. None of the patients with DM took any medication other than insulin or levothyroxine on a daily basis. Moreover, patients with DM were selected based on a similar ratio for poor glycemic control, and they received the same dose of insulin. All patients with DM were undergoing conventional insulin therapy and had T1DM without complications, such as nephropathy or neuropathy. No severe hypoglycemic events that could cause coma and/or seizure were reported in patients with T1DM. Insulin pump or hybrid closed-loop therapy was not used for patients with T1DM. There were no differences between participants and all eligible diabetes hospital populations of the same age in terms of the clinical characteristics. The control group included healthy individuals matched for age, race, sex, number (n = 32), and body mass index.

The healthy controls included in the study were friends of the participants with DM and the participants treated at University of Health Sciences Turkey, İzmir Dr. Behçet Uz Children's Training and Research Hospital.

Written informed consent was obtained from the legal guardians of the participants. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol no: 679, date: 07.04.2022).

Blood Pressure Measurements

Blood pressure (BP) was measured in a quiet room during the regular 3-monthly follow-up visits. Notably, BP measurements were obtained using a conventional oscillatory measurement system positioned at the right-upper arm (DINAMAP; GE Healthcare, Munich, Germany). The cuff size was selected according to individual arm circumference, with the cuff bladder covering ≥40% and ≤100% of the arm circumference. Standard deviation (SD) values were calculated by adopting normal values from the study in the relevant literature (16).

Laboratory Methods

Blood samples were obtained at 8:00 a.m. after an overnight fast for ≤12 h during the patients' follow-up visit. Levels of fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured using standard laboratory methods. Each sample was processed immediately after the patient's visit with a maximum delay of one hour. Blood samples were obtained on the day of ocular examination in the DM group for measuring pre- and post-prandial blood glucose and 1-year mean glycated hemoglobin (HbA1c) levels. The duration of T1DM and levels of HbA1c were examined. The blood samples for HbA1c measurement were analyzed using the designated method of National Glycohemoglobin Standardization Program.

OCTA and Ophthalmological Evaluation

Slit-lamp examination and indirect ophthalmoscopy were used to examine the clinical signs of DR in all patients. Patients with retinopathy findings, any ocular diseases, prior ocular surgery, myopia or hypermetropia higher than four diopters (D) were excluded from the study. Avanti RTVue XR AngioVue (Optovue, Inc., Fremont, CA, USA) was used to perform OCTA, and 3 × 3 mm pictures of the retina centered on the fovea were acquired. The AngioVue program was used to calculate the area of FAZ. In particular, the device software used in this study produced a vascular image of the retinal layer to a depth of 10 µm, from the inner limiting membrane to the outer plexiform layer. The FAZ boundary was determined using this method. For assessing PVD, the device automatically assessed the density of blood vessels in a 300-µm wide ring encircling FAZ (Figure 1).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). The mean ± SD or median (range), as appropriate, and percentage values were used to describe the obtained data. Subsequently, a stepwise multivariate linear regression model, including significant variables identified from univariate analyses, was used to determine the factors that independently explained a significant difference ($p < 0.05$) between dependent variables. Quantitative data were expressed as median (minimum-maximum). The Kruskal-Wallis and post-hoc Mann-Whitney U tests were used to compare values among the three groups. Spearman's rank correlation coefficient tests were used for the univariate analysis. A perfect correlation was considered to be indicated by a Spearman's rank correlation coefficient of 1, whereas a negative correlation was indicated by a Spearman's rank correlation coefficient of -1. A p value of < 0.05 was considered significant.

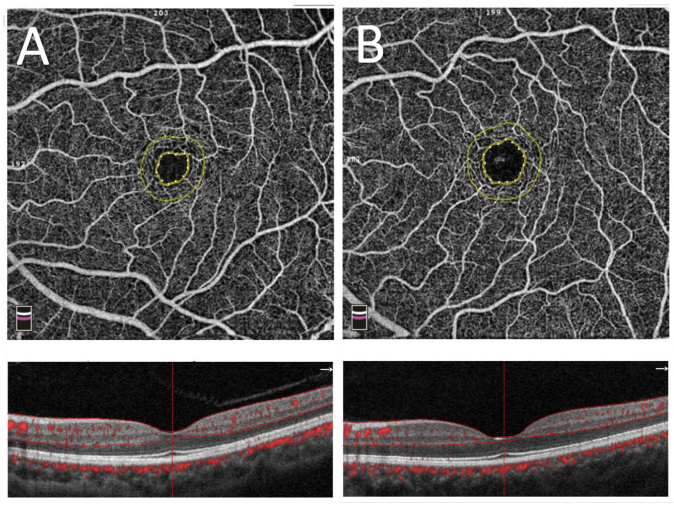

Figure 1. Examples of OCTA images with predicted foveal avascular zone area and parafoveal vessel density (A) a 14-year-old healthy boy's right eye with a foveal avascular zone area of 0.254 mm^2 and a parafoveal vessel density of 55.06, (B) a 15-year-old boy with T1DM has a foveal avascular zone area of 0.456 mm^2 and a parafoveal vessel density of 57.83

OCTA: optical coherence tomography angiography, T1DM: type 1 diabetes mellitus

Results

The characteristics of the study groups are presented in Table 1. The median DM duration was 8 (5.6-10.2) years. In the DM group, the 1-year median HbA1c level was 9.10% (6.3-15.2; reference range, 4.7-5.7%). The median daily insulin dose was 0.96 (0.80-1.10) IU/kg. No significant differences in age, sex, weight, and body mass index were found among the three groups. Groups 1 [172 (148-188) mg/dL] and 2 [168 (149-195) mg/dL] had higher serum

total cholesterol levels than Group 3 [150 (132-172) mg/dL; p = 0.011)], whereas no differences were found in terms of serum triglyceride, LDL, and HDL cholesterol levels among the three groups. Although no differences were found in the systolic BP among the study groups, Groups 1 (60.2 ± 7.69 mmHg) and 2 (65.33 ± 8.06 mmHg) had a higher diastolic BP than the control group (p = 0.020) (Table 1).

In all subjects, the best corrected visual acuity was 20/20. The mean FAZ and PVD were significantly different between the three groups (p = 0.016 and p = 0.006, respectively). The mean FAZ was higher in Groups 1 and 2 than in Group 3 (p = 0.013 and p = 0.119, respectively) (Figure 2). The mean PVD was lower in Groups 1 and 2 than in Group 3 (p = 0.007, respectively) (Figure 3). No significant difference was found between Groups 1 and 2 in terms of the mean FAZ and PVD (p = 0.832 and p = 0.653, respectively).

The correlations between risk factors and FAZ and PVD are shown separately for Groups 1, 2 and 3 in Figures 4 and 5. A significant correlation was found between mean HbA1c levels and FAZ and PVD (FAZ: r = 0.496, p < 0.001; PVD: r = -0.36, p = 0.001), whereas no correlation was found between other parameters and FAZ and PVD. Moreover, no correlation was found between thyroid-stimulating hormone (TSH) levels and FAZ and PVD. The correlations between FAZ and HbA1c and PVD and HbA1c persisted in multivariate linear regression analyses (both p < 0.001).

Discussion

Many researchers have suggested that early DR in T1DM is associated with an increased risk of poor glucose control, high HbA1c level, hypertension, and dyslipidemia (17,18,19,20). However, the effects of T1DM and AT on capillary endothelial structure and retinal microcirculation remain unclear. Based on the results of our study, we suggest that the coexistence of AT and T1DM is associated with a detrimental effects on the capillary endothelial function because of impaired glucose control in patients with T1DM. To the best of our knowledge, this is the first study to assess the potential early pathologic changes of DR in children with isolated T1DM, children with concurrent AT and T1DM, and healthy controls matched for age, race, sex, and body mass index. Notably, no confounding factors such as BP and lipid

Table 1. The characteristics of the study groups

	AT + T1DM (n = 32)	T1DM (n = 32)	Healthy children (n = 32)	p
Age (years)	15.6 (14.0-18.7)	15.4 (13.7-17.2)	15.3 (14.2-18.2)	0.851
Male (n, %)	9 (28.1%)	9 (28.1%)	9 (28.1%)	1
Weight SDS	0.15 (-1.1-1.2)	0.21 (-0.7-0.8)	0.22 (-1.0-1.2)	0.975
Height SDS	-0.47 (-1.0-0.1)[a]	-0.09 (-0.6-0.6)	0.22 (-0.2-1.1)[a]	0.004
BMI SDS	0.41 (-0.6-1.3)	0.46 (-0.3-0.8)	-0.21 (-1.1-1.0)	0.289
SBP (mmHg)	120 (115-128)	120 (111.8-127.8)	119.5 (100.8-128.8)	0.73
DBP (mmHg)	80 (74.3-87)[b]	79.5 (65.8-85)[a]	69 (66.3-75.8)[a,b]	< 0,001
T1DM duration (years)	8.1 (5.9-9.7)	8.0 (5.4-11)	-	0.941*
Insulin dose (IU/kg/day)	0.9 (0.8-1.1)	1.0 (0.9-1.2)	-	0.434*
PGC (n, %)	14 (43.8%)	17 (53.1%)	-	0.617
FBG (mg/dL)	217 (155-289)[b]	263 (177-301)[a]	89 (84-95)[a,b]	< 0.001
Mean HbA1c (%)	9.4 (6.3-15.2)[b]	9.05 (6.8-12.8)[a]	5 (4.9-5.4)[a,b]	< 0.001
Triglyceride (mg/dL)	92 (64-130)	88 (64-110)	85 (62-99)	0.315
HDL (mg/dL)	57 (49-64)	61 (53-69)	56 (47-63)	0.122
LDL (mg/dL)	89 (78-105)	89 (68-102)	84 (65-92)	0.064
TC (mg/dL)	168 (149-195)[b]	172 (148-188)[a]	150 (132-172)[a,b]	0.011
fT4 (ng/dL)	1.24 (1.13-1.35)	1.23 (1.14-1.36)	1.27 (1.17-1.38)	0.621
TSH (μIU/mL)	3.13 (2.20-4.58)[a]	2.34 (1.79-3.46)	2.14 (1.57-2.98)[a]	0.004
Anti-TG (IU/mL)	68 (31-149)[a,b]	16 (14-20)[a]	17 (15-21)[b]	< 0.001
Anti-TPO (IU/mL)	144 (23-271)[a,b]	11 (10-13)[a]	11 (10-13)[b]	< 0.001
FAZ	0.301 ± 0.05	0.303 ± 0.05	0.270 ± 0.03	0.006**
PVD	52.0 ± 3.2	52.9 ± 2.7	54.6 ± 1.2	0.016**

Variables are shown as median (interquartile range), p < 0.05. *Mann-Whitney U test. [a,b]Post-hoc analysis p < 0.0167.
AT: autoimmune thyroiditis, BMI: body mass index, SDS: standard deviation score, SBP: systolic blood pressure, DBP: diastolic blood pressure, T1DM: type 1 diabetes mellitus, PGC: poor glucose control, FBG: fasting bood glucose, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TC: total cholesterol, ft4: free thyroxine, TSH: thyroid stimulating hormone, Anti-TG: thyroglobulin antibody, Anti-TPO: thyroid peroxidase antibody, FAZ: foveal avascular zone, PVD: parafoveal vascular density

abnormalities that may have affected capillary endothelial structure were identified in our study. This cohort was not studied in terms of retinal capillary endothelial dysfunction owing to the fact that diabetes is an endothelial disease.

Impaired capillary endothelial function can be attributed to increasing age, male sex, smoking, BP, body mass index, serum cholesterol and triglyceride levels, and the presence of DM with poor glycemic control (17,18,19,20). In patients with T1DM whose HbA1c level is >7%, microvascular complications, such as retinopathy, nephropathy, and neuropathy are significantly increased (17,18,19,20). Wysocka-Mincewicz et al. (21) compared the FAZ of 84 children with T1DM to that of 20 children with T1DM and AT, and they found no difference between the two groups in terms of FAZ. However, children with T1DM had a greater foveal thickness, global loss volume, and parafoveal thickness than children with T1DM and AT. Notably, Wysocka-Mincewicz et al. (21) did not evaluate confounding factors, such as BP and lipid abnormalities, that could affect the capillary endothelial structure. Ulaş et al. (22) reported a potential association between central serous chorioretinopathy and hypothyroidism, but the effect of the mean arterial pressure and blood glucose abnormalities on capillary endothelial dysfunction were not considered by them. Moreover, they did not consider lipid abnormalities and peroxidation caused by hypothyroidism. Wysocka-Mincewicz et al. (21) did not find a relationship between FAZ and TSH. Similarly, our results did not reveal a correlation between TSH and FAZ or PVD. Onoe et al. (14) compared the FAZ of 29 children with T1DM to that of 24 healthy children and found that FAZ was

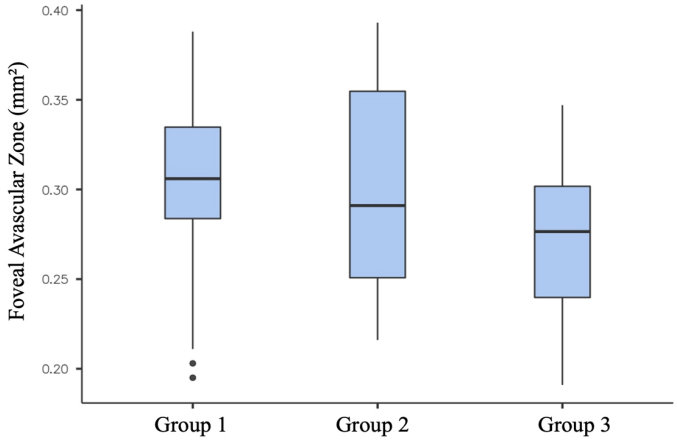

Figure 2. The average foveal avascular zone areas of the three groups

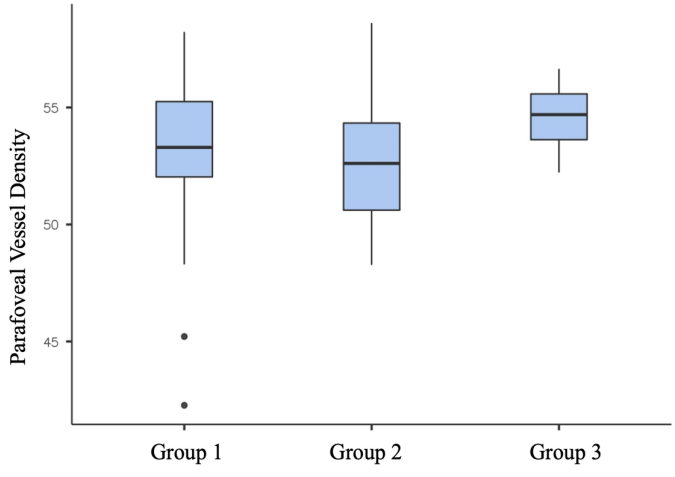

Figure 3. The average parafoveal vessel density of the three groups

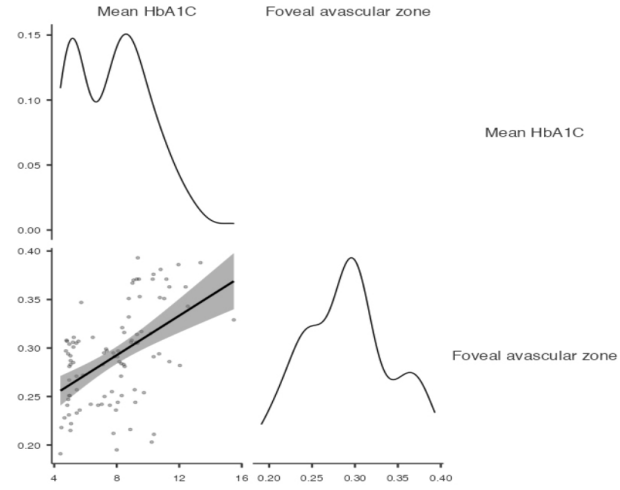

Figure 4. Correlation between mean HbA1c and FAZ

HbA1c: glycated hemoglobin, FAZ: foveal avascular zone

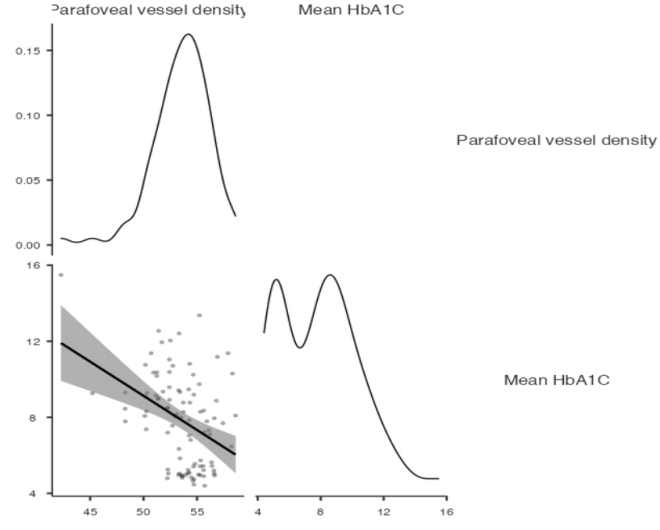

Figure 5. Correlation between mean HbA1c and PVD

HbA1c: glycated hemoglobin, PVD: parafoveal vascular density

greater in patients with T1DM, but there was no difference in terms of PVD. Gołębiewska et al. (23) compared the OCTA parameters of 94 children with T1DM to those of 36 healthy children and found no difference between the two groups. However, elevated HbA1c levels were found to be correlated with reduced parafoveal superficial vessel density and parafoveal thickness. Inanc et al. (13) compared the onset of DR between 60 children with T1DM and 57 age-matched controls, and they found a greater FAZ in children with T1DM. In the present study, the mean FAZ and PVD differed between children with DM and healthy children. Moreover, we found that DR changes started early in children with DM and were related to poor glucose control. These findings suggested that AT had no effect on the development of DR in cases of no lipid abnormalities and peroxidation. Hence, we hypothesized that early DR signs may develop independently of AT in children with T1DM and AT.

HbA1c levels in patients with DM indicate high blood glucose levels during the day. Further, high serum glucose levels are associated with microvascular complications, such as DR (17,18,19,20). Notably, even a 1% reduction in HbA1c levels in patients with DM leads to a 32% reduction in microvascular complications. The increased plasma glucose in patients with T1DM is metabolized via four main metabolic pathways, including polyol pathway flux, increased advanced glycation end-product (AGE) formation, activation of protein kinase C (PKC) isoforms, and increased hexosamine pathway flux, as an adaptation mechanism (24,25). In patients with DM, high serum glucose levels increase glycosylation and AGE formation. Further, in the vascular endothelium of all organs, an increase in AGE levels causes binding to receptors for AGEs (RAGEs). As RAGEs are present in eye blood vessels, they bind to the capillary endothelium, which further leads to the development of retinopathy. In patients with hyperglycemia, serum glucose must be metabolized by any available pathway, and this activates the beta and gamma isoforms of PKC via the diacylglycerol (DAG) pathway. Increased PKC levels activate NADPH oxidases and increase reactive oxygen radicals. An excessive increase in reactive oxygen radicals leads to complications. Similarly, increased glucose may be metabolized via the polyol pathway by aldose reductase. The activation of the polyol pathway increases the use of hydrogen. Hydrogen is required for the production of nitric oxide (NO) from arginine. Although hydrogen is not directly involved in the synthesis of NO, it is involved in the polyol pathway as a compensatory mechanism; this decreases NO synthesis. Vasoconstriction and ischemia caused by the reduction in NO and the activation of DAG PKC pathways cause provocations in the bloodstream (24,25). In addition, increasing vascular endothelium hypoxia increases growth factors, such as vascular endothelial growth factor, which in turn leads to an increase in nuclear factor kappa B, which suppresses inflammatory genes and promotes irreversible acceleration. This further leads to vasoconstriction, oxidation, and inflammation. Given that DM is an endothelial disease, defense against oxidation is poor in patients with DM, and signs of early DR are attributed to proliferation, as observed in our cohort. We found a relationship between HbA1c levels and FAZ and PVD but we did not find a relationship between thyroid function tests and FAZ and PVD.

Study Limitations

This study has some limitations. First, this was a single-center study with a relatively small sample, and our post-hoc analysis included children with T1DM and AT. Second, the study was cross-sectional and could not describe the long-term effects of the disease and its treatment. However, we believe that the study is meaningful as it provides data on the retinal microcirculation using OCTA parameters in the analyzed subgroup. Third, all OCTA parameters examined in the study were influenced by age. Therefore, the results should be interpreted taking into account the potential effect of poor glucose control on early DR changes in children with AT and T1DM. Quantitative assessments in OCTA may be impacted by axial length. The fact that the children's axial length was not assessed is one of the study's shortcomings. However, it is feasible to assume that when groups of similar ages and without distinct refractive errors are compared, the difference between the axial lengths of the groups will be limited.

Conclusion

Our data suggest that the coexistence of AT and T1DM in children without clinically detectable DR leads to impaired retinal microcirculation and FAZ margin irregularities, similar to children with T1DM matched for age, race, sex, number, body mass index, BP, and plasma lipid levels. Impairment in retinal microcirculation and signs of DR can develop independently of AT in children with concurrent T1DM and AT. Further studies are needed to evaluate the role of OCTA in early disease detection and treatment counseling in children with both AT and T1DM. Early monitoring of microvascular risk factors may be required.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital of Clinical Research Ethics Committee (protocol no: 679, date: 07.04.2022).

Informed Consent: Written informed consent was obtained from the legal guardians of the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Hüseyin Anıl Korkmaz, Ali Devebacak, Behzat Özkan, Design: Hüseyin Anıl Korkmaz, Ali Devebacak, Behzat Özkan, Data Collection or Processing: İbrahim Mert Erbaş, Cumali Değirmenci, Nilüfer Uyar, Analysis or Interpretation: Ali Devebacak, Cumali Değirmenci, Filiz Afrashi, Literature Search: Ali Devebacak, Cumali Değirmenci, Filiz Afrashi, Writing: Hüseyin Anıl Korkmaz, Behzat Özkan.

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