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The relationship between pupil response and type 1 diabetes mellitus in children: A case-control study

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Abstract

Objective: This study aimed to compare pupil measurements obtained with the Sirius topography device in children with type 1 diabetes with the systemic and ocular findings of the subjects. *Methods:*This study involved 41 pediatric cases of type 1 diabetes mellitus (DM) and 41 control cases. Key outcome parameters included pupil diameter and the average rate of pupillary dilation. Both static and dynamic pupillometric assessments were conducted using the Sirius Topographer (CSO, Florence, Italy).These findings were further evaluated in relation to retinal nerve fiber layer thickness and ganglion cell layer thickness measurements. *Results:* A statistically significant negative correlation was identified between HbA1c levels and certain dynamic pupillometry parameters in the DM group. HbA1c was weakly and negatively correlated with 1st second pupil diameter (r=-0.204;p=0.006), moderately and negatively correlated with the 2nd second (r=-0.346; p = 0.001), 4th second (r -0.360;p= 0.001), and 6th second (r = -0.333;p=0.002), and weakly to moderately correlated with the 8th second (r=-0.297;p=0.007) and 10th second (r =-0.319;p=0.003). These findings indicate a negative relationship, meaning that as HbA1c levels increase, dynamic pupillometry measurements tend to decrease. A weak but statistically significant positive correlation was observed between ganglion cell count and the mesopic pupil diameter, a parameter of static pupillometry, in the DM group (r=0.219;p=0.049). No significant relationship was detected between retinal nerve fiber layer thickness (RNFLT) and pupillary response measurements in the DM group (p>0.05).
Conclusions: Although dynamic pupillometry measurements in children with diabetes were not associated with the duration of the disease, a significant correlation was observed with HbA1c levels.

Keywords: Diabetic autonomic neuropathy, pupil, pupillometry

INTRODUCTION

Although diabetic autonomic neuropathy (DAN) is frequently encountered among individuals with diabetes, it remains insufficiently investigated. This condition affects various organ systems -such as cardiovascular, gastrointestinal, genitourinary, sudomotor, and ocular pathways- and plays a critical role in the overall disease burden by elevating both morbidity and mortality rates.[1] Autonomic involvement of the pupil is considered one of the earliest manifestations of widespread autonomic neuropathy in diabetes. Sympathetic deficits have been reported to correlate with longer disease duration and with the presence of more widespread autonomic abnormalities. Notably, deviations in pupil size among individuals with diabetes have been documented in scientific literature since the 1980s.[2-4] In DAN, neuromuscular junctions and synaptic integrity may be compromised, leading to dysregulation of both sympathetic and parasympathetic control over the smooth musculature of the iris.[5] Currently, there are no imaging modalities capable of directly detecting autonomic nerve dysfunction or iris smooth muscle alterations in vivo in diabetic patients.

Although slit-lamp biomicroscopy remains a standard tool for anterior segment evaluation in clinical settings, it offers limited capacity for objective quantification. In recent years, advanced imaging modalities—including

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optical coherence tomography, ultrasound biomicroscopy, Scheimpflug imaging, scanning slit topography, and interferometry—have gained prominence for more precise assessment of anterior segment structures.[6] The Scheimpflug-based Sirius imaging system provides comprehensive evaluation of both anterior and posterior corneal surfaces, while also enabling precise measurement of anterior chamber depth, pupil size, chamber angle, and morphological features of the iris and lens.[7] Corneal topography is a useful and unique tool for the early diagnosis and management of corneal diseases such as keratoconus. It measures pupil diameter using the integrated pupillography measurement software. This software measures the scotopic pupil diameter at 0.4 lux, the mesopic pupil diameter at 4 lux, and the photopic pupil diameter at 40 lux light levels.[8]

This study aimed to compare pupil measurements obtained with the Sirius topography device in children with type 1 diabetes with the systemic and ocular findings of the subjects.

METHODS

This single-center, cross-sectional, case-control study involved 41 pediatric cases of type 1 diabetes mellitus (DM) that were hospitalized between July 2022 and August 2024. Ethical approval was obtained from the Izmir City Hospital Ethics Committee in accordance with the Declaration of Helsinki (Approval No: 1747/1727 , Date: 14.08.2024). Written informed consent was obtained from all participants, with additional consent provided by a parent or legal guardian.

Cases of type 1 DM aged between 6 and 18 years were included in the study. Participants were excluded from the study if they had conditions that could potentially affect the accurate interpretation of the pupillometry results. The exclusion criteria included the following: patients with myopic, hyperopic, or astigmatic refractive errors exceeding ±1.0 D, a history of ocular trauma, congenital or acquired anomalies of the iris and pupil, previous ocular surgery, any ocular conditions that may impact pupil function, anterior or posterior synechiae, uveitis, corrected distance visual acuity of less than 20/50 on the Snellen chart, glaucoma, cataracts, a history of optic neuropathy, retinal diseases that could affect pupil function, permanent use of topical medications, systemic diseases that may influence pupil function, and patients with comorbidities that might impact autonomic functions,cases with poor quality of topography imaging. As a control group, 41 healthy individuals aged between 6 and 18 years were included in the study.

Clinical data

Variables recorded for each participant included age, sex, body mass index, and duration of diabetes. HbA1c levels were also documented. Blood samples were obtained from all participants after fasting. Comprehensive ophthalmological examination data for all participants were collected, which included best-corrected visual acuity (BCVA), intraocular pressure measured with the Canon TX20P (Tokyo, Japan), findings from slit-lamp biomicroscopy and dilated fundoscopy, as well as analyses of retinal nerve fiber layer thickness (RNFLT) and ganglion cell layer thickness (GCLT) in both eyes.

Initially, the eyelids were assessed for the presence of ptosis. Following this, pupil responses were evaluated using the automated pupillometry feature of the Sirius Topographer (CSO, Firenze, Italy) with Phoenix v2.1 software (Costruzione Strumenti Oftalmici, CSO, Firenze, Italy). All measurements were conducted by the same experienced clinician. All assessments were scheduled within a fixed afternoon window (14.00-16.00) to standardize potential circadian influences on pupil dynamics. Data from both eyes of each participant were included in the analyses. Throughout the measurement procedure, participants were instructed to maintain forward gaze while avoiding direct exposure to the light source to minimize accommodative reflexes. All recordings were obtained after a standardized dark adaptation period of five minutes. Pupil assessments were carried out under three distinct lighting conditions: scotopic (0.4 lx), mesopic (4 lx), and photopic (40 lx). The only illumination in the environment was provided by an LED light source, with light intensity levels verified and adjusted using a calibrated photometer. Pupillometry began under bright light exposure (500 lx), which was subsequently turned off to enable continued observation of pupillary dynamics during the transition from photopic to scotopic conditions. Pupil diameter and its variation over time were continuously monitored and recorded at baseline (0 seconds), at 1 second, and subsequently at 2-second intervals (see Figure 1). The following formula was used to quantify the rate of pupillary change. Here, ‘Vaverage’ (in mm/s) denotes the mean speed of diameter change up to a given time point, with

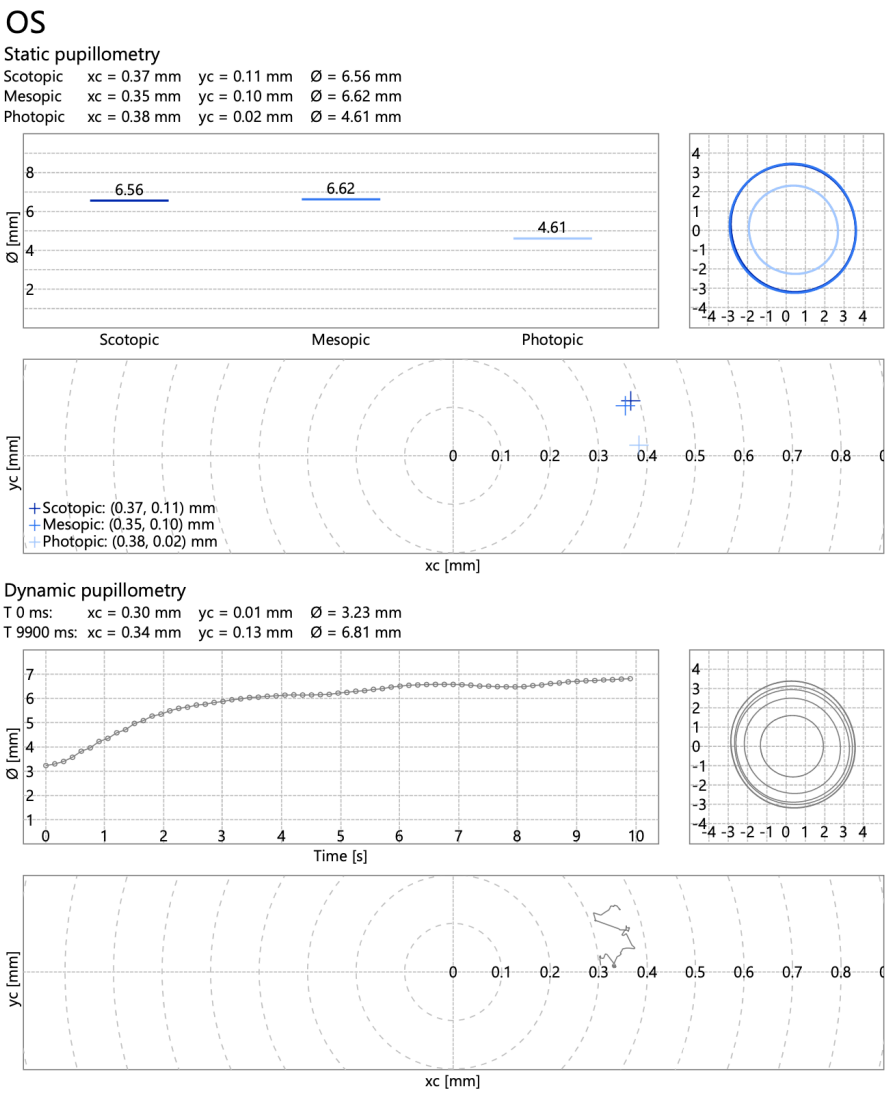

Figure 1. The Sirius Topographer (CSO, Italy) provides a comprehensive output of pupil metrics across varying illumination levels. The static analysis section displays pupil diameters along with centroid coordinates (x, y) on the left side of the graph. The dynamic pupillometry trace, presented on the right, illustrates temporal changes in pupil size, with corresponding centroid data and diameter values for each time point.

'ø' representing the pupil diameter in millimeters and 'Tx' indicating the specific time in seconds at which the rate is determined.

Vaverage(tx)= [øtx- øto]/ tx

Statistical analysis

Analyses were performed using SPSS (Statistical Package for the Social Sciences) v27. Continuous variables are summarized as mean±SD or median (min-max), as appropriate, and categorical variables as n (%). Normality was assessed with the Kolmogorov-Smirnov test. Group comparisons were conducted with the independent samples t test when distributional assumptions were met; otherwise, the Mann-Whitney U test was applied. Categorical variables were compared using the chi-square test. Associations between continuous variables were examined with Spearman's rank correlation. Statistical significance was set at $p<0.05$.

Table 1: Comparison of demographic data between groups

	Group		p
	Control (n=41)	DM (n=41)	
Sex, n(%)			
Male	21 (51.2)	19 (46.3)	0.659*
Female	20 (48.8)	22 (53.7)	
Age, Mean± Sd	11.78 ± 3.3	12.5 ± 3.15	0.430**
M (min-max)	12 (6-16)	13 (6-17)	
BMI, Mean± Sd	20.49 ± 2.22	21.18 ± 4.72	0.899**
M(min-max)	20.05 (15.0-24.3)	20.18 (12.31-34.4)	
HbA1c, Mean± Sd	5.06 ± 0.36	8.13 ± 1.99	**0****
M(min-max)	5.1 (4.1-5.9)	7.65 (5.8-14.2)	

*;p value for Chi-square test, **;p value for Mann Whitney U test

RESULTS

A total of 82 children were included and measurements from both eyes were analyzed. Among the participants, 54% of the children in the DM group and 49% of those in the control group were female. There was no statistically significant difference in sex distribution between the two groups (p= 0.659). The demographic characteristics of the participants are presented in Table 1.

The mean HbA1c level in the DM group was 8.13 ± 1.98, while it was 5.06 ± 0.39 in the control group. A statistically significant difference was observed between the groups in terms of HbA1c levels (p<0.001), indicating that HbA1c values were significantly higher in the DM group compared to the control group.

To assess whether the clinical parameters in the DM group followed a normal distribution, the Kolmogorov-Smirnov test was applied. The parameters Scotopic (mm), Mesopic (mm), and 0th second (mm) were found to be normally distributed (p> 0.05), whereas the remaining parameters did not conform to a normal distribution (Table 2).

The median duration of type 1 diabetes was 30 months (range, 9-144 months). No statistically significant association was found between the duration of diabetes and pupillary response measurements in children within the DM group (p> 0.05). Similarly, no significant correlation was observed between HbA1c levels and static pupillometry parameters in the DM group (p>0.05). However, a statistically significant negative correlation was identified between HbA1c levels and certain dynamic pupillometry parameters in the DM group. Specifically, HbA1c was weakly and negatively correlated with 1st second pupil diameter (r=-0.204; p = 0.006), moderately and negatively correlated with the 2nd second (r=-0.346; p = 0.001), 4th second (r=-0.360; p = 0.001), and 6th second (r=-0.333; p = 0.002), and weakly to moderately correlated with the 8th second (r=-0.297; p = 0.007) and 10th second (r = -0.319; p = 0.003). These findings indicate a negative relationship, meaning that as HbA1c levels increase, dynamic pupillometry measurements tend to decrease (Table 3).

There was no statistically significant difference in pupillary reaction changes between children in the DM and control groups (p>0.05) (Table 4).

The median GCLT was 83 μm (range: 60–94) in the DM group and 85 μm (range: 68–98) in the control group. A significant difference was found between the groups in terms of GCLT (p = 0.008), with the DM group demonstrating a lower count.

The RNFLT was 97.5 μm (range: 62–117) in the DM group and 100 μm (range: 83–119) in the control group. The difference in RNFLT between the groups was statistically significant (p = 0.001), indicating reduced RNFLT values in children with DM (Table 5). A weak but statistically significant positive correlation was observed between ganglion cell count and the mesopic pupil diameter, a parameter of static pupillometry, in the DM group (r = 0.219; p = 0.049). No significant relationship was detected between RNFLT and pupillary response measurements in the DM group (p> 0.05) (Table 6).

Table 2: Descriptive statistics of clinical parameters in the DM group

	Mean	SD	Median	Min	Max	p
Duration of DM (months)	43.67	37.43	30	9	144	0.001*
HbA1c	8.1	1.96	7.6	5.8	14.2	0.001*
Static Pupillometry						
Scotopic (mm)	6.52	0.64	6.53	4.85	8.47	0.513
Mesopic (mm)	6.23	0.77	6.19	4.29	8.16	0.880
Photopic (mm)	5.24	0.83	5.42	2.75	6.86	0.018*
Dynamic pupillometry						
0th second (mm)	3.54	0.52	3.5	2.1	5.1	0.181
1st second (mm)	4.33	0.49	4.2	3.0	5.3	0.019*
2nd second (mm)	5.08	0.51	5.0	3.8	6.2	0.002*
4th second (mm)	5.61	0.60	5.6	4.0	7.0	0.040*
6th second (mm)	5.88	0.63	6.0	4.1	7.2	0.012*
8th second (mm)	6.09	0.77	6.0	4.0	8.75	0.001*
10th second (mm)	6.17	0.62	6.1	4.4	8.0	0.002*

DM; Diabetes Mellitus, Ss; Standart deviation, Min; Minimum, Max; Maximum, M;Median, p: Kolmogorov-Smirnov test, *p<0,05

DISCUSSION

The microvascular alterations induced by diabetes are recognized contributors to the development of neuropathy. Among the numerous complications associated with diabetes mellitus, diabetic neuropathy stands out as both common and clinically significant.[9] Diabetic autonomic neuropathy may involve any organ or tissue regulated by the autonomic nervous system, with potential impairment of both sympathetic and parasympathetic pathways.[10] Pupillary autonomic neuropathy associated with diabetes typically presents as abnormally miotic pupils. This condition reflects a disruption in autonomic regulation, wherein sympathetic denervation leads to parasympathetic predominance.[11] Assessment of pupillary responses under varying standardized light intensities may serve as a non-

Table 3: Correlation between duration of DM and HbA1c with pupil reaction measurements in the DM group

	Duration of DM		HbA1c	
	r	p	r	p
Static pupillometry				
Scotopic (mm)	,050	0.654	-,169	0.130
Mesopic (mm)	,062	0.581	-,180	0.106
Photopic (mm)	-,142	0.204	-,071	0.527
Dynamic pupillometry				
0th second (mm)	-,134	0.229	-,173	0.121
1st second (mm)	-,141	0.206	**-,204**	0.006*
2nd second (mm)	,034	0.764	**-,346**	0.001*
4th second (mm)	,032	0.777	**-,360**	0.001*
6th second (mm)	,019	0.867	**-,333**	0.002*
8th second (mm)	,024	0.828	**-,297**	0.007*
10th second (mm)	,073	0.512	**-,319**	0.003*

*p<0,05; Statistically significant correlation between the variables, r:Spearman's rho correlation coefficient.

Table 4: Comparison of pupil reaction measurements between groups

	Control (n=82)	DM (n=82)	p
Static Pupillometry			
Scotopic (mm)	6.50 ± 0.79	6.52 ± 0.64	0.842[t]
Mesopic (mm)	6.37 ± 0.76	6.23 ± 0.77	0.215[t]
Photopic (mm)	5.28 (3.36-6.71)	5.42 (2.75-6.86)	0.602[m]
Dynamic pupillometry			
0th second (mm)	3.55 ± 0.57	3.54 ± 0.52	0.978[t]
1st second (mm)	4.2 (3.0-5.3)	4.2 (3.3-5.5)	0.811[m]
2nd second (mm)	5 (3.3-5.5)	5 (3.8-6.2)	0.606[m]
4th second (mm)	5.8 (3.95-7)	5.6 (4-7)	0.750[m]
6th second (mm)	6 (4.2-7.1)	6 (4.1-7.2)	0.447[m]
8th second (mm)	6 (4.5-7.5)	6 (4.0-8.75)	0.803[m]
10th second (mm)	6.15 (4.1-7.5)	6.1 (4.4-8)	0.748[m]

DM: Diabetes Mellitus; Mean ± standard deviation or median (range); [m]: Mann–Whitney U test, [t]: Independent samples t-test

invasive tool for identifying autonomic nervous system dysfunction.[12-13]

The present study sought to determine whether pupillometry could provide a simple, low cost and non invasive approach to explore autonomic related pupillary alterations in children with type 1 diabetes, without relying on laboratory based or invasive assessments.

In our cohort, HbA1c showed a statistically significant inverse association with pupil diameters at several time points during dynamic pupillometry, suggesting that poorer metabolic control may coincide with a less pronounced dilation profile. Given that the dynamic assessment primarily reflects the dilatation phase under low-light conditions, the observed pattern is compatible with altered autonomic contribution to pupillary control; however, attributing this finding a specific branch (sympathetic vs parasympathetic) should be considered interpretative and requires confirmatory autonomic testing. While some reports have questioned the accuracy and diagnostic reliability of this technique, others have emphasized its potential as a valuable screening modality, particularly for identifying high-risk diabetic patients. In one study, reduced pupil diameters and attenuated reflex amplitudes were observed in both diabetic individuals with and without cardiac autonomic neuropathy, prompting the suggestion that pupillary alterations may occur in parallel with, or potentially precede, clinically evident systemic autonomic involvement; however, this interpretation should be regarded as preliminary in the absence of longitudinal confirmation. In a separate investigation, it was similarly hypothesized that pupillary changes could manifest before the onset of overt ocular symptoms.[14-17]

Compared with controls, participants with subclinical and non proliferative diabetic retinopathy in a previous study showed significant alterations in multiple pupillometry parameters, particularly pupil size during dark

Table 5: Comparison of pupil reaction measurements between groups

	Control (n=82)	DM (n=82)	p
GCLT	85 (68-98)	83 (60-94)	0.008[m]
RNFLT	100 (83-119)	97.5 (62-117)	0.001[m]

RNFLT: Retinal nerve fiber layer thickness. GCLT: ganglion cell layer thickness. Data are presented as median (range); m: Mann–Whitney U test.

Table 6: Correlation between ganglion cell layer thickness and retinal nerve fiber layer thickness and pupil reaction measurements in children with DM

	GCLT		RNFLT	
	r	p	r	p
Static Pupillometry				
Scotopic (mm)	,068	0.546	-,101	0.365
Mesopic (mm)	**,219**	0.049*	-,041	0.717
Photopic (mm)	,175	0.115	-,123	0.271
Dynamic pupillometry				
0th second (mm)	,089	0.427	,097	0.385
1st second (mm)	,061	0.587	,020	0.859
2nd second (mm)	,138	0.216	,090	0.419
4th second (mm)	,197	0.076	,102	0.360
6th second (mm)	,097	0.385	-,020	0.862
8th second (mm)	,094	0.402	,002	0.986
10th second (mm)	,119	0.286	,053	0.638

DM: Diabetes mellitus, RNFLT: retinal nerve fiber layer thickness, GCLT: ganglion cell layer thickness, *p < 0.05; statistically significant correlation.

adaptation, pupil size after pharmacological dilation, and the corresponding constriction and dilation ratios. In line with these findings, it was concluded that pupil diameters and pupil constriction and dilatation ratios under mesopic and pharmacologically dilated conditions may provide supportive information when autonomic involvement is suspected in type 2 diabetes, but the strength and reproducibility of these parameters vary across protocols and populations.[18]

In the study by Erdem *et al*., it was shown that static pupil diameters were significantly reduced in patients with non-proliferative diabetic retinopathy (NPDR), especially at scotopic, mesopic and low photopic illumination levels. When dynamic pupil parameters were examined, a significant decrease in resting pupil diameter, contraction velocity and dilation velocity and a prolongation in contraction duration were found in these patients. In addition, scotopic and low photopic pupil diameters were significantly reduced compared to diabetic individuals without diabetic retinopathy (DR), while no significant difference was found between the two groups in terms of dynamic pupil responses. Unlike this study, which observed a statistically significant change in pupillary response measurements with diabetes duration, in our study no statistically significant association was found between the duration of diabetes and pupillary response measurements in children within the DM group.[19]

In this cohort, pupillary response measures did not differ significantly between the diabetes group and the control group. This finding may be attributable to the relatively younger age of the type 1 diabetes cohort, their shorter disease duration, and the likely presence of only mild autonomic involvement of the iris. Similar to our findings, the study conducted by Cui *et al*., which included both children with type 1 diabetes and healthy peers, reported no statistically significant difference in pupil diameter between the groups.[20] In line with the findings of Cui *et al*., Schwingshandl and colleagues also observed that, at rest, children with type 1 diabetes exhibited a slightly reduced pupil diameter compared to healthy controls; however, this difference did not reach statistical significance.[4] Although previous research has explored microscopic alterations in the iris smooth muscle of individuals with diabetes and proposed a potential link between such structural damage and irregularities in pupil size, the association between iris smooth muscle function and pupillary dilation has yet to be investigated under in vivo conditions.[21]

In their investigation involving children with type 1 diabetes, Yu *et al*. suggested that early neural alterations in the retina may occur prior to the development of microvascular damage. They also observed that, even in the absence of visual impairment or other ocular conditions, a reduction in peripapillary RNFL thickness -particularly in

the nasal quadrant-could be detected. Similarly, in our study, the mean ganglion cell layer thickness and RNFL thickness were statistically significantly lower in diabetic children without diabetic retinopathy or vision loss compared to the control group.[22] There are other studies that reported a thinning of these layers in children without signs of diabetic retinopathy, compared to healthy controls.[23,24] These studies highlight that retinal neurodegeneration may begin earlier than diabetic retinopathy.

A review of the existing literature reveals that alterations in ganglion cell and RNFL thickness -recognized as markers of retinal neurodegeneration- have not yet been systematically examined in relation to pupillary changes, indicating a gap in current research in children. In the diabetic cohort, a modest yet statistically meaningful positive association emerged between the ganglion cell layer thickness and mesopic pupil diameter, one of the static pupillometry indices. Although the strength of the correlation was limited, it aligns with the concept of parallel neurodegenerative and autonomic alterations in diabetes. In particular, the positive relationship between the number of ganglion cells and the mesopic pupil diameter raises the hypothesis of a shared or parallel process linking retinal neurostructural measures and pupillary behavior; however, the directionality and underlying mechanism cannot be inferred from cross-sectional correlations. Further longitudinal and mechanistic studies are warranted to clarify this association. However, no notable correlation was found between RNFLT and any pupillary response parameters within the same group. Several studies describe blunted pupillary constriction parameters in diabetes in the context of autonomic impairment. However, the timing and the reproducibility of these findings are not consistent, largely because measurement devices, lighting protocols, and analytic definitions differ between studies. Moreover, a concurrent association between RNFL thickness and static pupillometry metrics in diabetic individuals points to a parallel progression of retinal neurodegeneration and autonomic neuropathy within the same disease continuum.[25]

This study has certain methodological limitations that should be acknowledged. Primarily, the pupillometry device employed lacked the capability to quantify the velocity of pupillary constriction, which may have restricted the depth of physiological interpretation. Because both eyes were included in the dataset, the assumption of independent observations may not be fully met; therefore, the results should be interpreted while considering potential correlation between fellow eyes. In addition, we did not obtain parallel systemic autonomic neuropathy markers; therefore, the observed pupillometric associations should be interpreted as indirect signals of autonomic involvement rather than definitive evidence of generalized autonomic neuropathy. The limited number of participants is another drawback that may have influenced the robustness of the outcomes. Because the study was carried out at a single center and employed a cross-sectional approach, the generalizability of the findings to other populations may be limited.

In conclusion, in our study, although dynamic pupillometry measurements in children with diabetes were not associated with the duration of the disease, a significant correlation was observed with HbA1c levels. These findings align with the known vulnerability of autonomic pathways to chronic hyperglycemia and support the hypothesis that early signs of autonomic dysfunction, specifically involving the sympathetic innervation of the iris dilator muscle, may be detectable through dynamic pupillometry even in pediatric diabetic populations.These findings suggest that abnormal pupillary responses may represent a non-invasive, easily applicable screening tool for the early detection of DAN as an indicator of metabolic control, thereby potentially reducing diabetes-related morbidity and mortality. Future large-scale studies with higher sample sizes will contribute valuable insights to the existing literature.

DISCLOSURE

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