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The effectiveness of automatic pupillometry as a screening method to detect diabetic autonomic neuropathy

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Abstract

Purpose This study aimed to compare static and dynamic pupil responses of diabetic patients with and without nonproliferative diabetic retinopathy (DR) and normal healthy individuals under different lighting conditions via quantitative automated pupillometry.

Methods Forty patients with DM with nonproliferative DR (group 1), 40 patients with DM without DR (group 2), and 40 healthy controls (group 3) underwent a complete ophthalmologic examination. Static pupillometry [scotopic pupil diameter (PD), mesopic PD, low photopic PD, and high photopic PD] and dynamic pupillometry (resting PD, contraction amplitude, latency, duration, velocity of contraction, dilatation latency, and duration and velocity at rest) were measured via automatic quantitative pupillometry.

Results Analysis of variance revealed that scotopic PD [$F(2, 117) = 6.42$; $p = 0.02$], mesopic PD [$F(2, 117) = 3.20$; $p = 0.04$], and low photopic PD [$F(2, 117) = 4.86$; $p = 0.009$] were significantly different among the groups. Scotopic PD and low photopic PD were significantly lower in group 1 than in group 2 ($p = 0.03$ and $p = 0.03$, respectively). Meanwhile, the resting diameter, velocity of pupil contraction, and velocity of pupil dilatation were found to be significantly lower ($p = 0.02$, $p = 0.01$, and $p = 0.008$, respectively), and the duration of pupil contraction was significantly higher in group 1 than in group 3 ($p = 0.03$).

Conclusion Both DM patients with and without nonproliferative DR exhibited pupillary involvement. Automated pupillometry may be an easily applicable, noninvasive screening option for reducing mortality and morbidity rates associated with diabetic autonomic neuropathy.

Keywords Pupillometry · Diabetic retinopathy · Diabetic autonomic neuropathy

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Introduction

Diabetic retinopathy (DR), which affects more than 90 million people worldwide, remains the leading cause of vision loss in adults [1]. Early diagnosis and treatment of DR, which occurs as a complication of diabetes mellitus (DM), is crucial for the prevention of blindness [2, 3].

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Diabetic autonomic neuropathy (DAN), a subclinical and early outcome of DM, is a common diabetes complication that affects the cardiovascular, gastrointestinal, genitourinary, and ocular systems and causes significant morbidity and mortality [4–6]. As such, it is important to identify DAN patients early and take the necessary precautions.

The analysis of heart rate variability, which is mostly a noninvasive diagnostic method and is affected by variables, such as age, systolic pressure, plasma glucose, and myocardial ischemia, is used to detect DAN. However, the examination of pupillary dysfunction, which occurs earlier relative to cardiovascular autonomic dysfunction, is also a noninvasive method that can be used to detect DAN [7–9].

Pupillary light reflex (PIR) is the change in pupil diameter (PD) in response to light which is controlled by the autonomic nervous system. It can be used to assess the function of the visual system and optic nerve. During the process, pupil size is controlled by the circular muscle (sphincter, constriction) innervated by the parasympathetic nervous system (PNS) and radial muscles (dilatation) of the iris; here, the circular muscle is innervated by the PNS, whereas the radial muscle is innervated by sympathetic nervous system (SNS) fibers [10]. PNS dysfunction causes reduced pupil constriction with exposure to light, whereas dysfunction of the SNS causes a dilatation delay in the pupil in the dark.

It has been reported that pupil response, which can be used to evaluate the integrity of the neuronal pathways controlling the pupil size, can be impacted in many diseases, such as neurological errors, glaucoma, and retinal diseases [11–14].

Automatic pupillometry, which allows the measurement of pupil response via infrared pupillography, can be quantitatively measured by the objective, noninvasively reproducible PD. Both static and dynamic measurements can be made using a pupillometer. These measurements can be collected both statically and dynamically in the context of scotopic, mesopic, or photopic visual conditions [15, 16].

In this study, we aimed to compare the static and dynamic pupil responses of DM patients with and without nonproliferative DR (NPDR) and normal healthy individuals (control group) under different lighting conditions by using a quantitative automated pupillometry system.

Methods

Study design

This cross-sectional prospective study was conducted between January 2020 and February 2020 at the Dicle University Medical Faculty Hospital. This study included 40 patients with DM and NPDR, 40 patients with DM without DR, and 40 healthy patients. Approval was obtained from the ethics committee of Dicle University Faculty of Medicine (decision no. 2020/31). Our study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from all participants before measurements were performed.

Subjects and measurements

All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity, intraocular pressure measurement, and slit-lamp biomicroscopy. Patients with no systemic disease other than DM, patients not using systemic anticholinergic drugs, patients without iris or pupil anomalies, patients without pseudoexfoliation syndrome, patients with no history of intraocular surgery or previous inflammation, patients who did not use topical drops that could influence pupil reactions, and patients with no history of ocular trauma or glaucoma were included in this study. All measurements were performed by the same experienced clinician using an automatic quantitative pupillometry system (MonPack One; Metrovision, Perenchies, France). The white stimulus on the pupillometer consists of a combination of red, green, and blue light-emitting diode sources equipped with a high-resolution camera that allows accurate pupil measurement by the clinician. Both static pupillometry [scotopic PD (mm), mesopic PD (mm), low photopic PD (mm), and high photopic PD (mm)] and dynamic pupillometry [resting PD (mm), contraction amplitude (mm), latency (ms), duration (ms), velocity of contraction (mm/s), dilatation latency (ms), duration (ms), and velocity at rest (mm/s)] were conducted using the automatic pupillometry system for each patient. Results were recorded and evaluated, and all measurements were performed simultaneously to minimize the effect of circadian variation. The patient was asked to focus on the central area of the test area, and three consecutive measurements were taken; the

mean of these measurements was then adopted as the final measurement. The automatic release mode of the pupillometer was used to minimize any clinician-related errors.

Statistical analysis

We performed all statistical analyses using the Statistical Package for the Social Sciences software (version 26.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to calculate demographic data. Data were expressed as means ± standard deviations. The Kolmogorov–Smirnov test was employed to assess the normal distribution of variables. One-way analysis of variance was conducted to determine whether there was a significant difference among the three groups. In addition, post hoc tests were conducted for pairwise comparisons. Categorical variables were compared using an independent *t* test and Chi-square test. All results were accepted to be statistically significant at $p < 0.05$.

Results

The mean ages of the patients included in the study were 54.80 ± 4.46, 52.62 ± 3.88, and 52.52 ± 4.40 years in group 1, group 2, and group 3, respectively. The mean disease durations of patients with DM with and without DR were 10.45 ± 3.20 and 6.05 ± 1.56 years, respectively. Of the patients included in this study, 57 (47.5%) were female and 63 (52.5%) were male (Table 1).

In the analysis of variance, it was found that scotopic PD [$F(2, 117) = 6.42$; $p = 0.02$], mesopic PD [$F(2, 117) = 3.20$; $p = 0.04$], and low photopic PD [$F(2, 117) = 4.86$; $p = 0.009$] were significantly different among the groups. According to the pairwise comparison of static pupillometry measurements of the groups, scotopic PD was significantly lower among both patients with DM with DR than among healthy patients [− 0.522; 95% confidence interval (CI) − 0.880 to − 0.164; $p = 0.002$] or patients with DM without DR [− 0.382; 95% CI − 0.740 to − 0.024; $p = 0.03$], whereas low photopic PD was also significantly lower among patients with DM with DR than among healthy patients [− 0.305; 95% CI − 0.562 to − 0.047; $p = 0.016$] or patients with DM without DR [− 0.280; 95% CI − 0.537 to − 0.022; $p = 0.03$]. Also, mesopic PD was significantly lower among patients with DM with DR than among healthy patients [− 0.300; 95% CI − 0.597 to − 0.002; $p = 0.04$] (Table 2).

In the analysis of variance, it was found that the resting diameter [$F(2, 117) = 3.65$; $p = 0.029$], duration of pupil contraction [$F(2, 117) = 3.33$; $p = 0.039$], velocity of pupil contraction [$F(2, 117) = 4.60$; $p = 0.012$], and velocity of pupil dilatation [$F(2, 117) = 4.86$; $p = 0.009$] were significantly different among the groups. While the resting diameter [− 0.315; 95% CI − 0.600 to − 0.029; $p = 0.02$], velocity of pupil contraction [− 0.993; 95% CI − 1.788 to − 0.199; $p = 0.01$], and velocity of pupil dilatation [− 0.315; 95% CI − 0.561 to − 0.069; $p = 0.008$] were significantly lower among patients with DM compared with the control group, the duration of pupil contraction [26.175; 95% CI

Table 1 Demographic and clinical characteristics of the study participants

Characteristic	Group 1 (with DM with DR)	Group 2 (with DM without DR)	Group 3 (control)	*p*-value
Age (years) (mean ± SD)	54.80 ± 4.46	52.62 ± 3.88	52.52 ± 4.40	0.02
Sex (n, %)	17 (42.5)	20 (50.0)	20 (50.0)	> 0.05
Female	23 (57.5)	20 (50.0)	20 (50.0)	
Male				
DM duration (years) (mean ± SD)	10.45 ± 3.20	6.05 ± 1.56	–	< 0.001

Table 2 Static pupillometry measurements of the groups

Pupil diameter (mm)	Group 1 (with DM with DR)	Group 2 (with DM without DR)	Group 3 (control)	Analysis of variance among groups**		Pairwise comparisons (post hoc analysis ***)
				F	*p*-value	*p*-value
Scotopic	3.09 ± 0.52	3.47 ± 0.62	3.61 ± 0.83	6.42	0.002*	GR 1 − GR 2 = 0.03*
						GR 1 − GR 3 = 0.002*
						GR 2 − GR 3 = 0.62
Mesopic	2.75 ± 0.53	2.99 ± 0.48	3.05 ± 0.64	3.20	0.044*	GR 1 − GR 2 = 0.13
						GR 1 − GR 3 = 0.04*
						GR 2 − GR 3 = 0.88
Low photopic	2.70 ± 0.55	2.98 ± 0.37	3.00 ± 0.50	4.86	0.009*	GR 1 − GR 2 = 0.03*
						GR 1 − GR 3 = 0.016*
						GR 2 − GR 3 = 0.97
High photopic	2.42 ± 0.32	2.46 ± 0.24	2.45 ± 0.29	0.21	0.783	

*$p < 0.05$, **analysis of variance, ***Tukey's test

2.067–50.282; $p = 0.016$] was significantly higher (Table 3).

Duration of DM was positively correlated with scotopic PD, mesopic PD, low photopic PD, and duration of pupil contraction. ($r = -0.322, p < 0.001$; $r = -0.234$, $p = 0.01$; $r = -0.249$, $p = 0.006$ and $r = 0.265$, $p = 0.003$, respectively) (Fig. 1).

Discussion

In our study, we found that patients with NPDR exhibited significantly hindered static pupil responses in comparison with normal values with respect to scotopic PD, mesopic PD, and low photopic PD. In addition, considering dynamic pupil responses, the resting PD, velocity of pupil contraction, and velocity of pupil dilatation were found to be significantly reduced, whereas the duration of pupil contraction was significantly increased when compared with typical findings. Overall, in these patients, while scotopic PD and low photopic PD were significantly lessened relative to those of patients with DM without DR, no significant difference was observed between these two groups in terms of dynamic pupil responses.

In patients with DM, complications, such as DR and diabetic neuropathy, may develop due to microvascular complications, hypercoagulability, and increased vascular endothelial growth factor that may become clinically visible after a certain amount of time. Therefore, it is important to detect DAN, which has ocular autonomic effects and impacts on the heart and gastrointestinal system in patients with DM. It has been reported that autonomic nervous system dysfunction, which is associated with increased mortality, can be detected before the appearance of cardiovascular autonomic function abnormalities by identifying deteriorations in pupil function [6, 9, 17–20].

Different phases of pupil reactions are innervated by the SNS and PNS, which are parts of the autonomic nervous system. Therefore, evaluation of the pupillary response to light provides information about neuronal pathways indirectly controlling pupillary reactions. While pupil contraction mainly provides PNS, SNS has a minimal effect. Therefore, the PD in response to light and pupillary function parameters reflects parasympathetic functioning. Meanwhile, the sympathetic system controls the PD at rest. However, both nervous systems are effective in redilation. In the dysfunction of the sympathetic system, there is a delay in miosis and dilatation in the dark, whereas during the dysfunction of the parasympathetic system, mydriasis and delayed shrinking in response to light are apparent. As such, the pupillary response to light can be used to screen for autonomic dysfunction in diabetic patients where autonomic neuropathy can be observed [21–23].

There are many studies on the use of pupillometry in patients with DM in terms of DAN detection. Some of these studies cautioned that this method did not provide accurate results, whereas others suggested that this method was useful in screening high-risk patients

Table 3 Dynamic pupillometry measurements of the groups

Characteristics	Group 1 (with DM with DR)	Group 2 (with DM without DR)	Group 3 (control)	Analysis of variance among groups**		Pairwise comparisons (post hoc analysis ***) *p*-value
				F	*p*-value	
Resting diameter (mm)	3.89 ± 0.63	4.11 ± 0.46	4.20 ± 0.49	3.65	0.029*	GR 1 − GR 2 = 0.15 GR 1 − GRB 3 = 0.02* GR 2 − GR 3 = 0.73
Amplitude of pupil contraction (mm)	1.68 ± 0.40	1.79 ± 0.28	1.83 ± 0.21	2.32	0.102	
Latency of pupil contraction (ms)	167.70 ± 20.66	166.57 ± 19.53	167.92 ± 17.48	0.56	0.945	
Duration of pupil contraction (ms)	459.50 ± 26.67	445.17 ± 46.17	433.32 ± 57.83	3.33	0.039*	GR 1 − GR 2 = 0.33 GR 1 − GR 3 = 0.03* GR 2 − GR 3 = 0.47
Velocity of pupil contraction (mm/s)	5.98 ± 2.08	6.65 ± 1.35	6.97 ± 0.71	4.60	0.01*	GR 1 − GR 2 = 0.11 GR 1 − GRB 3 = 0.01* GR 2 − GR 3 = 0.61
Latency of pupil dilatation (ms)	600.55 ± 112.54	604.40 ± 81.93	596.75 ± 64.49	0.78	0.925	
Duration of pupil dilatation (ms)	1736.95 ± 106.68	1730.35 ± 107.36	1702.82 ± 140.62	0.92	0.401	
Velocity of pupil dilatation (mm/s)	2.74 ± 0.63	2.96 ± 0.41	3.06 ± 0.27	4.86	0.008*	GR 1 − GR 2 = 0.09 GR 1 − GR 3 = 0.008* GR 2 − GR 3 = 0.61

*$p < 0.05$, **analysis of variance, ***Tukey's test

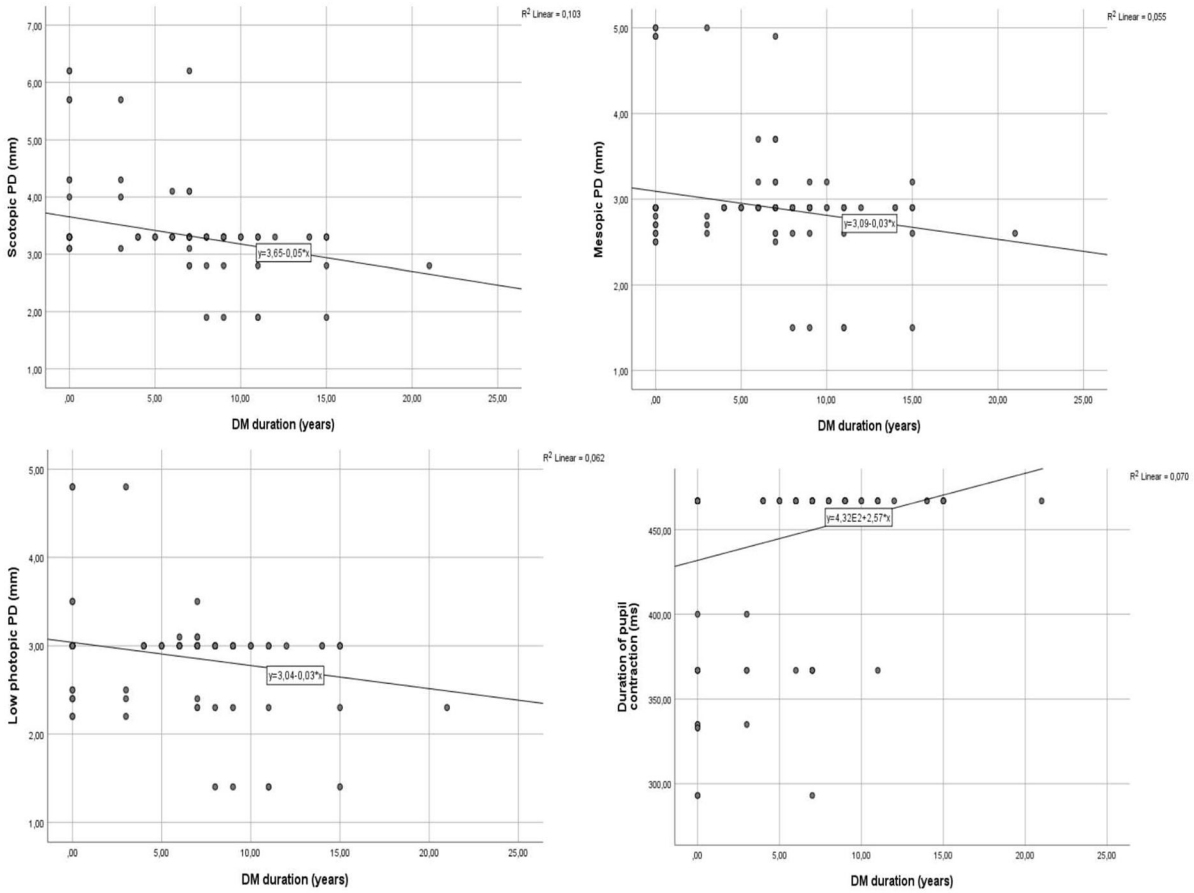

Fig. 1 Correlation between duration of DM and scopic PD, mesopic PD, low photopic PD and duration of pupil contraction

with DM and could be adopted as an important screening tool. In one investigation, both patients with and without cardiac autonomic neuropathy exhibited smaller pupil diameters and reduced amplitude reflexes, and the authors suggested that pupillary involvement may occur before general autonomic system involvement. Elsewhere, authors of a different study postulated that pupillary involvement may occur before the occurrence of eye symptoms [24–28]. We also found that static and dynamic pupil responses were affected in patients with DM who had not yet developed DR. Therefore, automatic pupillometry can be a valuable screening tool for the early detection of DAN in all patients with DM.

A meta-analysis revealed that the amplitude of pupil contraction and velocity of pupil contraction parameters can be used to evaluate parasympathetic dysfunction. Similarly, in another study, it was reported that pupil reactions in patients with NPDR may show PNS dysfunction, whereas elsewhere, pupil reactions were impaired in most patients with PDR [29, 30]. DAN has been reported by some research to be caused by structural changes due to the loss of dilator pupillae and constrictive pupillae muscles, nerve endings, and nerve fibers. Also, during a confocal microscopic examination, sub-basal nerve fiber changes were reported in the cornea in parallel with diabetic neuropathy [31, 32].

In studies with results similar to those in our study, it was found that the low photopic PD, velocity of pupil contraction, and velocity of pupil dilatation were reduced in patients with NPDR relative to the control group. In addition, we also found that the resting diameter, scotopic PD, and mesopic PD were lower, and the duration of pupil contraction was longer in

patients with NPDR than in the healthy (control) group.

Our study has some limitations. The first is its relatively small number of participants. Second, the generalizability of our findings may be limited due to the single-center and cross-sectional nature of this study. Another limitation is that proliferative DR patients were not included in this study. However, it was important to confirm the automatic pupillometer used in our study as an easily applicable tool by which to detect DAN.

In conclusion, we found that pupillary involvement was present in both patients with DM with and without NPDR. Therefore, automatic pupillometry can be considered as an easily applicable, noninvasive screening option for the early diagnosis of DAN to reduce mortality and morbidity rates attributed to this disease.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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