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Research Article

A Cross-Sectional Study to Determine the Pupillary Responses by Pupillometer Serius Tomogram in Type 2 Diabetes Mellitus and Normal Population

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ABSTRACT

Purpose: To assess the relationship between biochemical parameters of diabetes mellitus with pupil responses.

Methods: An observational case control study on 35 participants of diabetes mellitus type 2 and an age matched healthy population formed the 'control group'. All the participants underwent a standard ophthalmologic examination. Pupillometry was performed using the automated quantitative pupillometry system. Weight, waist circumference and body mass index was documented for all diabetic patients. Diabetic patients were additionally assessed for HbA1c levels, lipid profile.

Results: There was a negative correlation of HbA1c and duration of diabetes mellitus with the static pupillary measurements. There was a significant negative and weak correlation of dynamic resting diameter right eye with the duration of diabetes mellitus, followed by medium correlation with dynamic resting diameter left eye and weak correlation with dynamic amplitude left eye.

Conclusion: Pupillometry can be used to screen the diabetic autonomic neuropathy in diabetic patients.

Keywords: Diabetes mellitus; Automated pupillometry; Scotopic pupil; Mesopic pupil

INTRODUCTION

Diabetes Mellitus (DM), one of the most widespread metabolic diseases marked by hyperglycemia, decreased insulin production and insulin resistance, is becoming more and more prevalent [1]. A significant microvascular consequence of diabetes is Diabetic Retinopathy (DR), the largest cause of blindness and visual impairment in the globe [2,3]. Early detection of DR and quick, effective treatment are essential for preventing serious visual loss [4].

Diabetic Autonomic Neuropathy (DAN) is one of the recognized and subclinical effects of Diabetes Mellitus (DM) [5]. The quality of life and overall survival of DM patients are significantly impacted. Thus, by identifying and treating DM patients early, we can enhance their quality of life.

Pupilary reflexes are regulated by the autonomic nervous system's parasympathetic and sympathetic divisions [6,7]. Therefore, pupillary responses to an external light stimulus may offer us a method to indirectly assess the health of the brain networks that control pupil size. Even while diminished pupillary size and attenuated light responses are now recognized as signs of the autonomic nervous system impairment that occurs in DM, pupillometry is a useful non-invasive method for detecting autonomic dysfunction [8-10].

Recent developments in automated pupillometry technology have made it possible to objectively, quantitatively, non-invasively and repeatedly measure static and dynamic pupillary responses [11,12].

Patients with DM have been found to have smaller resting pupil diameters and reflex amplitudes than people without this illness, even before the disease becomes clinically evident. DM has been

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shown to have an effect on static pupil size. Although DM has been proven to have an impact on static pupil diameter, little research has been done on dynamic pupil responses (delay, duration of contraction and dilatation, speed of dilatation) [13,14].

Additionally, the relationship between biochemical parameters of diabetes mellitus with pupil responses has not been determined previously. From this perspective, we aimed to assess the relationship between biochemical parameters of diabetes mellitus with pupil responses and to determine a change in pupillary responses with severity of diabetic retinopathy.

MATERIALS AND METHODS

An observational case control hospital based study was conducted at this tertiary care centre in northern India between January 2022 and August 2022 after obtaining institutional ethical clearance from Command Hospital, Lucknow (Cert No. 020/2023) and written informed consent from the study population. The study was performed in accordance with the tenets of the Declaration of Helsinki. The patients diagnosed with diabetes mellitus type II visiting the ophthalmology department of this tertiary care hospital from January 2022 to August 2022 meeting the inclusion criteria lay down for the study group were included and labelled as 'study group'. An age matched healthy population formed the 'control group'.

Fundus photography, fundus fluorescein angiography and optical coherence tomography were used to examine the presence and phases of the DR in the DM patients. The various stages of DR were described using the early treatment diabetic retinopathy study criteria [15]. All of the control individuals underwent a standard ophthalmic checkup at the ophthalmology clinic and were all in good health, free of any ocular or systemic disorders. Blood samples from the DM patients were obtained to assess the lipid profile and HbA1c levels.

The duration of the condition and the treatments used were all included in the thorough ophthalmic and systemic histories. Each diabetes patient's weight, waist size and body mass index were recorded.

Patients who had used anticholinergic medications for urinary symptoms or anti-prostate medications like alfuzosin, prazosin or tamsulosin, as well as those with iris or pupil anomalies like coloboma, synechia, rubeosis iridis, sphincter tear and anisocoria, as well as those with pseudo exfoliation syndrome, glaucoma, a history of head or orbit. Additionally, subjects who were uncooperative during pupillometry measurements were not included.

Additionally, subjects who did not cooperate well enough for pupillometry measurements were disqualified. All of the subjects completed a typical ophthalmologic examination, which included a measurement of intraocular pressure using a Goldmann Applanation tonometer, a best corrected visual acuity test using the Snellen chart, Slit lamp biomicroscopy was used to examine the anterior segment, as well as a dilated fundus examination with a 90 D lens, direct ophthalmoscopy and indirect ophthalmoscopy with a 20 D lens [16].

The automated quantitative pupillometry system (Sirius tomograph) was used for the pupillometry procedure. No contact ocular examination and pupil dilation were done prior to the pupillometry examination. Participants were asked to fixate on a target in the center of the test field during the pupil recording in order to manage fixation stability. To assure the accuracy of measurements and the proprietary analysis, participant's pupil outlines were highlighted on the image. In order to do automatic static and dynamic pupillometry, the device's software was used.

Under different regulated lighting conditions, the pupil diameter and its offset from the corneal vertex are automatically measured. With the pupillograph as the only source of light in the examination room, the user had a choice of three lighting conditions:

- Scotopic, the only visible light source being the LED source (0.4 lux).
- Mesopic, the disk was illuminated in such a manner as to bring ambient light intensity to about 4 lux.
- Photopic, the disk was illuminated in such a manner as to bring ambient light intensity to about 40 lux.
- Dynamic, the capture began with the disk rings fully illuminated (500 lux ca.); it is switched off at the moment capture begins to ensure monitoring pupil dilation in conditions from photopic to scotopic conditions and analyze pupil size and pupil offset instant by instant.

Three consecutive measurements were taken for each participant and their average values were calculated for data analysis.

Statistical analysis

The data was analysed using SPSS version 24.0. Descriptive summary using percentages, mean and standard deviation have been used to present the study results. Probability (p) was calculated to test statistical significance at the 5% level of significance. Categorical variables were analysed using *Chi square* test. Continuous variables were calculated using independent t test.

Sample size: For sample size estimation, study conducted by Kiziltoprak H, et al. was used and the sample size formula used is: $X=(Z_{1-a/2}+Z_{1-\beta}) \times 2\sigma^2/d^2$, $Z_{1-a/2}$ critical value of the normal distribution at a/2 (for a confidence level of 95%, a=0.05 and the critical value is 1.96). $Z_{1-\beta}$-critical value of the normal distribution at β (for power of 80%, β=0.2 and the critical value is 0.84) σ^2-Pooled variants calculated using the standard deviation values of mean scotopic PD (mm) of patients with diabetes mellitus and without diabetes mellitus taken from previous studies (value is 0.397). d-hypothesized difference (value is 0.5). To detect a hypothesized difference of 0.5 units in the outcome measure, between diabetics and non-diabetics at 80% power and 95% confidence interval, the required minimum sample size is 25. Taking 10% drop outs, the minimum sample size will be 28 patients in each group. Hence total 35 study participants were enrolled in both the groups.

RESULTS

Total 35 participants were included in each group. The mean age of the study participants in the diabetic and non-diabetic group was similar *i.e.*, 60.57 ± 9.19 and 60.57 ± 9.19 years respectively. There was no difference in the distribution of males and females in both the groups. Hence both the groups were age and sex matched. Similarly, there was no statistically significant difference in the two groups for BMI, waist circumference, BVCA right and left (Table 1).

Table 1: Baseline characteristics of the study participants.

Variables		Group DM	Group non-DM	p-value
Age		60.57 ± 9.19	60.57 ± 9.19	1.000*
Gender	Male	19 (54.3%)	19 (54.3%)	1.000#
	Female	16 (45.7%)	16 (45.7%)	
BMI		25.77 ± 4.35	25.79 ± 4.31	0.985*
Waist circumference		92.80 ± 6.85	92.80 ± 6.85	1.000*
BCVA (LOG MAR) RT		0.506 ± 0.325	0.506 ± 0.325	1.000*
BCVA (LOG MAR) LT		0.406 ± 0.270	0.406 ± 0.270	1.000*
Duration of diabetes mellitus		8.74 ± 3.23	-	-
HbA1c		7.43 ± 0.63	-	-

Note: *Independent t test, #*Chi square* test

The mean photopic pupillary diameter were 3.90 ± 0.42 and 3.82 ± 0.66 mm in right and left eye among diabetics and 4.39 ± 0.44 and 4.26 ± 0.64 mm in control group, there was a statistical difference observed on comparing photopic diameter of each eye in both groups (p value-0.0001 and 0.001 in right and left eye respectively). There was no statistically significant difference of mean scotopic and mean mesopic pupillary diameter between the two groups. Similarly, no difference was observed for mesopic and photopic pupillary diameter between the diabetics and non-diabetics. (Figure 1).

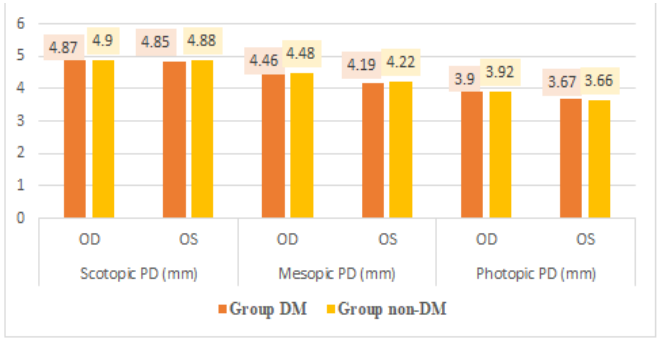

Figure 1: Static pupillmetry measurements in both the groups.

The difference in mean dynamic resting diameter, mean dynamic latency, mean dynamic duration in both eyes was not statistically significant across both groups. The mean dynamic amplitude among diabetics in right and left eye was 0.40 ± 0.122 and 0.39 ± 0.092 mm; and in control group was 0.59 ± 0.114 and 0.62 ± 0.093 mm. This difference across both the groups was statistically significant (p value-0.0001 in both eyes). The mean dynamic velocity among diabetics was 0.18 ± 0.071 and 0.31 ± 0.668; and in control group was 0.22 ± 0.072 and 0.63 ± 0.670 in right and left eye respectively. This difference was also statistically significant (p value-0.022 and 0.049 in right and left eye respectively) (Figure 2).

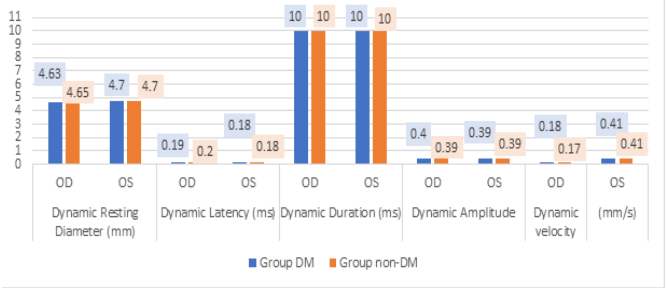

Figure 2: Dynamic pupillmetry measurements in both the groups.

There was a negative correlation of HbA1c and duration of diabetes mellitus with the static pupillary measurements, but it was not significant except for scotopic pupillary response in left eye, mesopic pupillary response in right eye and mesopic pupillary response in left eye with duration of diabetes (p<0.05) (Table 2).

Table 2: Correlation of Hba1c and duration of diabetes mellitus with static pupillary diameters.

Static pupillary measurements		HbA1C	Duration of DM
Scotopic OD	Correlation coefficient	-0.142	-0.304
	P value	0.417	0.075
Scotopic OS	Correlation coefficient	-0.043	-0.462
	P value	0.804	0.005
Mesopic OD	Correlation coefficient	-0.09	-0.359
	P value	0.609	0.034
Mesopic OS	Correlation coefficient	-0.101	-0.446
	P value	0.562	0.007
Photopic OD	Correlation coefficient	-0.124	-0.245
	P value	0.478	0.156
Photopic OS	Correlation coefficient	-0.047	-0.308
	P value	0.787	0.071

There was a negative correlation of HbA1c with dynamic resting diameter in both eyes, dynamic latency in left eye, dynamic amplitude in left eye and dynamic velocity in both eyes and it was not statistically significant. There was a significant negative and weak correlation of dynamic resting diameter right eye with the duration of diabetes mellitus, followed by medium correlation with dynamic resting diameter left eye and weak correlation with dynamic amplitude left eye (Table 3).

Table 3: Correlation of Hba1c and duration of diabetes mellitus with dynamic pupillary diameters.

Dynamic pupillary diameters		HbA1C	Duration of DM
Dynamic resting diameter OD	Correlation coefficient	-0.175	-0.341
	P value	0.314	0.045
Dynamic resting diameter OS	Correlation coefficient	-0.088	-0.446
	P value	0.613	0.007
Dynamic latency of OD	Correlation coefficient	0.15	-0.034
	P value	0.39	0.848
Dynamic latency of OS	Correlation coefficient	-0.065	-0.194
	P value	0.712	0.264
Dynamic amplitude OD	Correlation coefficient	0.028	-0.14
	P value	0.872	0.424
Dynamic amplitude OS	Correlation coefficient	-0.276	-0.39
	P value	0.109	0.02

Dynamic velocity OD	Correlation coefficient	-0.01	-0.096
	P value	0.953	0.584
Dynamic velocity OS	Correlation coefficient	-0.217	-0.02
	P value	0.21	0.908

There was a statistically significant difference in the mean values of pupillary measurements for static scotopic both eyes, static mesopic both eyes, static photopic right eye, dynamic resting diameter both eyes and dynamic latency left eye with the medication taken by the 35 diabetics in the study group (Figure 3).

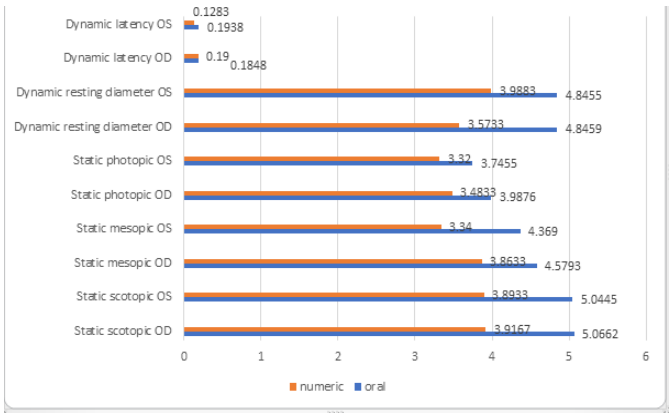

Figure 3: Association of pupillary measurements with the medication among diabatics.

DISCUSSION

The most severe ocular consequence of diabetes mellitus and the main factor in newly diagnosed instances of adult blindness is Diabetic Retinopathy (DR) [17]. Based on the degree of clinically obvious vascular anomalies, current criteria advise classifying stages of DR [18]. Nevertheless, there is growing evidence that these individuals also have anomalies in the retinal vasculature in addition to neuronal dysfunction, even at the earliest stages of the disease [19]. For instance, it has long been known that diabetics have unusually tiny steady-state pupils, which is due to aberrant sympathetic nervous system innervation.

The use of pupillometry as a tool for evaluating retinal function in patients with acquired and hereditary retinal illness has experienced a significant resurgence in interest as a result of relatively recent breakthroughs in the understanding of the neural mechanisms that govern the pupil response. Some studies have shown the relevance of using pupillometry as an inexpensive autonomic screening tool in diabetics.

This study found statistically significant difference in photopic static pupillometry and dynamic amplitude and dynamic velocity among diabetics and non diabetics. Similar results were observed in a study by Kiziltoprak H, et al. They also observed that DM patients with proliferative DR and non-proliferative DR had statistically substantially lower amplitude of pupil contraction, velocity of pupil contraction and velocity of pupil dilatation values than did controls. Previous researches have also shown some impaired static or dynamic pupillometric variables in diabetics, even in absence of DR.

Similarly, Ortube MC, et al. showed statistically significant variations in constriction velocity and amplitude when they compared mild to severe non-proliferative DR patients with a control group. These numbers showed a strong correlation with DR severity but not with DM duration. When compared to non-diabetic controls, Muppidi S, et al. discovered that those with moderate to severe autonomic dysfunction had considerably lower reflex constriction amplitudes.

The difficulty with night vision that some diabetic patients report can be mechanically attributed to a lack of sympathetic innervation to the iris' dilator muscles, whereas a reduction in the reflex response to light is due to a defect in the parasympathetic control of the sphincter muscles. Pupil involvement may be a precursor to diabetic autonomic neuropathy, as evidenced by the finding that diabetic patients with moderate autonomic dysfunction have substantially smaller pupil diameters than healthy controls.

There was a significant negative and weak correlation of dynamic resting diameter right eye with the duration of diabetes mellitus, followed by medium correlation with dynamic resting diameter left eye and weak correlation with dynamic amplitude left eye. There was a negative correlation of HbA1c and duration of diabetes mellitus with the static pupillary measurements, but it was not significant except for scotopic pupillary response in left eye, mesopic pupillary response in right eye and mesopic pupillary response in left eye with duration of diabetes.

It has been previously investigated if HbA1c levels and the length of DM are related to diabetic autonomic neuropathy. According to a research, the length of the diabetes and the HbA1c levels were modestly and inversely connected with the values for the resting diameter, scotopic pupil diameter, high photopic pupil diameter and velocity of pupil contraction (p 0.05 for each). Additionally, the HbA1c readings were substantially connected with low photopic pupil diameter (p=0.006, r=0.370) and the length of the DM was significantly correlated with the amplitude of pupil contraction (p 0.001, r=0.404). Another study by Bista Karki S, et al., was in concordance with the findings of this previous study.

Slight difference in the correlation from previous studies could be the difference in mean HbA1c levels, duration of DM and indices compared between types of DR in those who were diabetics with control groups, which were not done in our study.

However, correlations of both eyes have been compared simultaneously with duration and HbA1c levels in our study.

This study also studied the effect of medication on indices of pupillometry in the diabetic groups which has not been done by other studies. There was a statistically significant difference in the mean values of pupillary measurements for static scotopic and mesopic both eyes, static photopic right eye, dynamic resting diameter both eyes and dynamic latency left eye with the medication taken by the 35 diabetics in the study group.

The limitation of our study is that we have not assessed the grading of diabetic retinopathy in those who were diabetics, so correlation of those stages and its effect on autonomic neuropathy could not be assessed. The small sample size and it involving a tertiary care centre could not assure the generalisability of results. Larger follow-up studies and randomised studies need to be carried out.

CONCLUSION

The continuous advancements in technology and research methodologies offer exciting possibilities for leveraging pupillary responses as non-invasive tools for diabetic management and risk assessment in future. Further studies are warranted to validate the findings and explore the complete potential of pupillary responses in enhancing diabetic care.

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