Original Research Article

Pupil abnormalities in Type 2 Diabetes Mellitus: As an indicator of Diabetic Autonomic Neuropathy

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Abstract

Background: Diabetic autonomic neuropathy is a recognized complication of type2 diabetes mellitus. It affects cardiovascular, gastrointestinal, genitourinary, sudomotor as well as ocular systems. Small pupil size and impaired pupillary response to darkness or light constitutes ocular autonomic dysfunction. **Purpose:** To study the relation between pupil abnormalities and the underlying Diabetic Autonomic Neuropathy (DAN) in type 2 diabetes mellitus patientsMaterial **and methods:** In this prospective, observational, cross-sectional study a total of 62 type 2 diabetic patients (33 females and 29 males) and 60 healthy age and sex matched controls (32 females and 28 females) were selected. The diabetic patients were further divided into two groups based on presence or absence of DAN. Horizontal Pupil Diameter (HPD) was measured in dark and in light (before and 60 minutes after instillation of 1% Tropicamide drops) using a pupil ruler and Pupil Cycle Time (PCT) was measured using slit lamp. **Results:** HPD in dark (5.367±1.16mm) as well as in light before (4.209± 0.39mm) and after(7.524±0.46mm) dilatation with 1% Tropicamide was significantly smaller($p<0.01$) in diabetic group than control(6.153±1.24mm,4.503±0.24mm and 8.017±0.38mm respectively). PCT was significantly prolonged($p<0.01$) in the diabetic group(965.77±152.73ms) than control (898.3±342.4ms). The reduction in HPD and prolongation of PCT was more evident in the diabetics with DAN($p<0.01$)with mean values of dark adapted HPD, light adapted HPD before and after dilatation, and PCT being 4.647±43mm,3.931±72mm, 7.111±38mm and 1025.05±164.12 respectively. **Conclusion:** The significant smaller HPD and prolonged PCT in patients without DAN compared with that of healthy subjects and further shortening of HPD and prolongation of PCT in patients with DAN could be a sign for early involvement of the pupil function before manifestation of systemic autonomic diabetic neuropathy.

Key words: Autonomic neuropathy, Diabetes mellitus, Horizontal pupil diameter, Pupil cycle time.

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Introduction

Diabetes mellitus is a metabolic disorder which affects many body systems. Type 2 diabetes mellitus also called non-insulin dependent diabetes mellitus constitutes about 80% of cases and is associated with many acute as well as long term complications. One of the recognized complications of type2 diabetes mellitus is diabetic autonomic neuropathy (DAN)[1]. It is associated with longer duration of disease. In it cardiovascular, gastrointestinal, genitourinary, sudomotor and ocular systems are affected, thus leading to considerable morbidity and mortality[2]. Symptoms may range from tachycardia, painless myocardial infarction, orthostatic hypotension, gastroparesis, diarrhea, constipation, erectile dysfunction, neurogenic bladder, hypoglycemia, to sweating disturbance. Inspite of its significant negative impact on survival and quality of life, it's among the least recognized and understood complications of diabetes mellitus[2]. As per Diabetes Control and Complications Trial and other studies, intense glycemic control can prevent DAN, and early-stage DAN can be reversed with intense glycemic control[3-5]. Therefore, identification of these high-risk subjects is crucial to improve the long-term outcomes of people suffering with diabetes. As the expression pattern of DAN is highly variable, it is difficult to detect this disease on routine physical examination.

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Cardiovascular autonomic neuropathy (CAN) is among one of the manifestations of DAN which causes abnormalities in vascular dynamics and heart rate control[6]. It may result into postural hypotension, resting tachycardia, exercise intolerance, and an increased incidence of silent myocardial infarction.

Small pupil size and impaired pupillary response to darkness or light constitutes ocular autonomic nervous dysfunction in adults with type 2 diabetes[7-9]. Significant associations between small pupil size and a wide range of diabetic complications like cardiovascular autonomic dysfunction, peripheral sensory loss, retinopathy, nephropathy, unduly prolonged and severe hyperglycemia have been found[10]. The conventional diagnostic tools used for assessing DAN include a series of tests which requires trained technicians and are time-consuming as well as complicated which limits its use in common clinical practice[11]. Thus, there is a need for simple devices and methods for evaluation of autonomic functions in the everyday clinical practice.The Autonomic Nervous System (ANS) has direct control on Pupil Light Reflex. Size of the pupil is controlled by circular (sphincter) and radial (dilator) muscles of the iris. The parasympathetic nervous system (PNS) innervates the circular muscle while the sympathetic nervous system (SNS) innervates the radial muscle. Thus, the evaluation of pupil light reflex allows the evaluation of both the PNS and SNS dysfunctions. Dysfunction of the PNS causes relative mydriasis in photopic conditions and diminished constriction to light, whereas dysfunction of the SNS causes relative miosis of the pupil in scotopic conditions and increased re-dilatation lag. Therefore, studying pupil abnormalities can help in detection of ANS abnormality and thus in diagnosis of DAN. Horizontal Pupil Diameter (HPD) measurement & Pupil Cycle Time (PCT) estimation can be used to diagnose pupil abnormalities. Also, these have been

studied in various disease conditions affecting the Autonomic Nervous System (ANS), especially diabetes. These techniques are simple, non-invasive and inexpensive.The aim of this study was to find the correlation between pupil abnormalities in diabetic patients with their underlying Diabetic Autonomic Neuropathy.

Methods

This was a prospective, observational, cross-sectional study conducted in a tertiary care teaching institute of Eastern India. The study was conducted between November 2018 to March 2020 after taking approval from the Departmental Research Committee. Patients with type 2 diabetes mellitus of either sex and more than 40 years of age, attending Ophthalmology OPD were included in the study. Subjects who had cataract greater than NO2 or NC2 by LOCS III classification, pseudoexfoliation syndrome, corneal opacity or dystrophy, uveitis, rubeosis iridis or irregular or asymmetric pupil, glaucoma, vitreous hemorrhage, previous ocular trauma or ocular surgery, optic nerve disease, pseudophakia or aphakia, systemic diseases that could affect pupil, history of medication that could affect autonomic function were excluded from the study.Non diabetic patients were taken as controls from Ophthalmology OPD. Informed consent was taken from all participants, and the tenets of the Declaration of Helsinki was followed.After taking a brief initial history regarding diabetes including duration and HbA1c level, a basic ophthalmological examination was done. The ophthalmological examination consisted of visual acuity, slit lamp examination of anterior segment of eye, applanation tonometry and indirect ophthalmoscopy. By convention, all the measurements were taken from right eye only.The patients were further divided into two groups based on the presence or absence of DAN which was found by performing Cardiovascular autonomic function (CAF) tests to evaluate Cardiovascular Autonomic Neuropathy (CAN). Currently there are no generally accepted definitions or diagnostic methods for identifying CAN. In general, certain abnormal results of various cardiovascular autonomic function tests are being used as diagnostic criteria for cardiovascular autonomic neuropathy[12].

We performed four types of cardiovascular autonomic function tests; more than two abnormal results were considered diagnostic for cardiovascular autonomic neuropathy. The tests included:

1. **HR response to standing:** The R-R interval (time between two consecutive R waves in the electrocardiogram) was measured at beat 15 and beat 30 upon standing after 3 minutes of lying supine. A 30:15 ratio of less than 1.03 was taken as abnormal.
2. **Systolic BP response to standing:** Systolic BP was first measured in supine position and again 2 minutes after standing. A fall of more than 30 mmHg was taken as abnormal.
3. **Beat-to-beat HR variation:** The patients were laid supine and breathed at a rate of six breaths per minute. A difference in HR of less than ten beats per minute was taken as abnormal.
4. **HR response to Valsalva maneuver:** Valsalva ratio (VR) defined as the longest R-R interval following the Valsalva maneuver and the shortest R-R interval during the maneuver. A VR value greater than 1.17 was taken as abnormal.

These diagnostic tests of cardiovascular reflexes allow extensive evaluation of diabetic cardiovascular autonomic neuropathy and are simple, sensitive and reproducible[2].

Measurement of pupil cycle time

PCT was measured using the method described by Miller et al[13]. The subjects were made to sit at a slit lamp in a dimly illuminated room and were asked to look into a far distance. A narrow horizontally aligned beam of light with moderate intensity, measuring 9 mm in length and 0.5 mm in width was focused on the inferior pupillary margin, to initiate pupil cycle constriction and dilation. The time taken by 100 such cycles in seconds in two runs of 30 and one of 40 cycles was measured using a hand-held electronic stopwatch measuring $1/100^{th}$ of a second. Then by simple division mean PCT was calculated. All the measurements were taken by a single examiner.

Measurement of Horizontal Pupil Diameter

Subjects were requested to sit for 15 minutes in a dark room, to allow for dark adaptation. Then the dark adapted or scotopic HPD was measured using a pupil ruler after asking the patient to focus at a distant target. To measure the mesopic HPD the subjects were made to sit in a moderately illuminated room for 15 minutes and similar to scotopic HPD, mesopic HPD was measured. Now, 1% Tropicamide was instilled three times at an interval of 15 minutes and after 60 minutes HPD was measured again using a pupil ruler.

Statistical Analysis

A table of descriptive statistic was prepared where each variable was expressed as its mean ± SD. To analyze the difference in Horizontal pupil diameter (HPD) and Pupil cycle time (PCT) across the three groups i.e. control, diabetics without DAN and diabetics with DAN One-Way ANOVA test was used. The qualitative information contained 3 unique categories, which was expressed as two separate dummy variables D1 and D2. D1 would take a value of 1 for diabetics without DAN and D2 would take a value of 1 for the diabetics with DAN. Four separate regression models were run, each containing D1 and D2 as regressors. The regress in these models were PCT (in ms), dark adapted HPD (in mm), HPD in light before and after dilatation with 1%Tropicamide (in mm) respectively. The regression analysis was carried out using statistical package for Social Sciences-SPSS (version 21.0). The coefficients obtained from these regression models were tested for statistical significance at 5% level of significance.

Results

A total of 62 type 2 Diabetes Mellitus patients (33females & 29 males) and 60 non-diabetic patients as controls (32 females & 28 males) were included in the study. After doing cardiovascular autonomic function testing 19 diabetic patients were found to have DAN (10 females & 9 males).The mean ages of the controls, diabetics without DAN and Diabetics with DAN were 48±4.63years, 49.69±7.97 years and 54.52±2.82 years respectively. The mean dark adapted HPD in control group was 6.153±1.24 mm while the mean dark adapted HPD of diabetics without DAN was 0.786 mm less than the control group. This difference was significant at less than one percent level of significance ($p<0.01$). The mean dark adapted HPD of diabetics with DAN was 1.506 mm less than the control group. This difference was also significant at less than one percent level of significance ($p<0.01$).The mean HPD in light before dilation with 1% Tropicamide in control group was 4.503±0.24 mm, while the mean HPD for diabetics without DAN and with DAN were 0.294 mm and 0.572mm less than the controls. Both the differences were clinically significant at less than one percent level of significance ($p<0.01$).

The mean HPD after dilation with 1% Tropicamide in control group was 8.017±0.38 mm while it was 0.493 mm and 0.906 mm less than the controls for diabetics without and with DAN respectively. These differences were also significant at less than one percent level of significance ($p<0.01$).The mean PCT for Control group was 898.3±342.4 ms while mean PCT of diabetics without DAN was 67.47 ms more than the controls. This difference was significant at less than 1% Level of Significance ($p<0.01$).The mean PCT of diabetics without DAN was 126.75 ms more than the mean PCT of the control group. This difference was also significant at less than 1% Level of Significance ($p<0.01$).

Table 1: Clinical characteristics and results of pupillary abnormality tests in study subjects

	Mean age (in years)	Mean duration of Diabetes (in years)	Mean HbA1c	Dark adapted HPD† (in mm)	HPD† in light before dilatation (in mm)	HPD† in light after dilatation (in mm)	PCT‡ (in m)
Controls	48±4.63	-	-	6.153±1.24	4.503±0.24	8.017±0.38	898.3±342.4
Diabetics without DAN*	49.69±7.97	9.35±2.79	8.76±4.93	5.367±1.16	4.209±0.39	7.524±0.46	965.77±152.73
Diabetics with DAN*	54.52±2.82	13.78±4.38	9.36±4.68	4.647±43	3.931±72	7.111±38	1025.05±164.12

*Diabetic autonomic neuropathy †Horizontal pupil diameter ‡Pupil cycle time

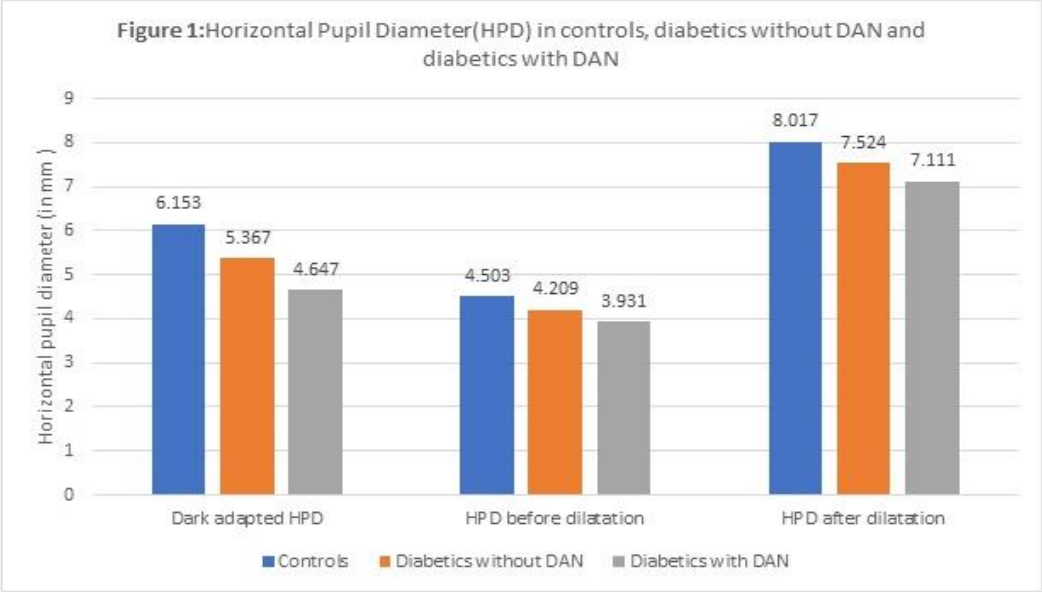

Fig 1: Comparison of horizontal pupil diameter (HPD) in controls, Diabetics without DAN and in Diabetics with DAN

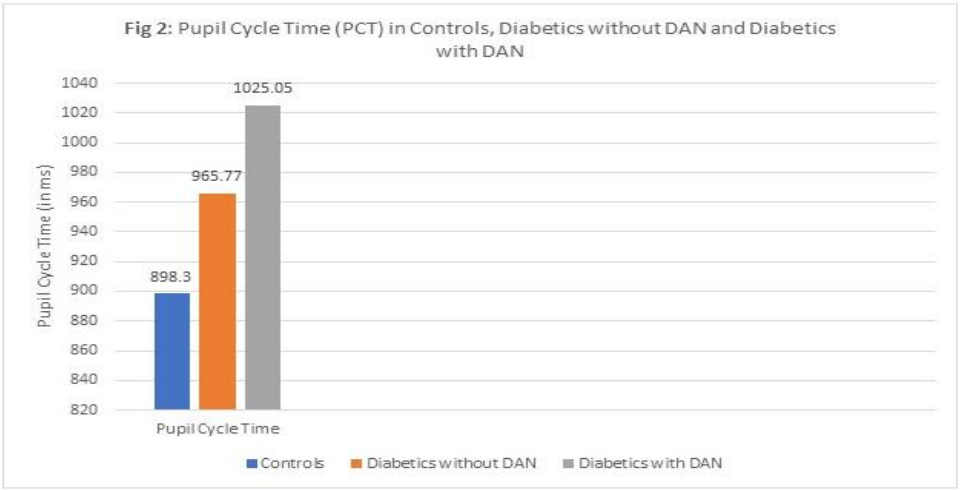

Fig 2: Comparison of pupil cycle time (PCT) in controls, Diabetics without DAN and in Diabetics with DAN

Discussion

During the early period of type 2 diabetes mellitus the clinical features of diabetic autonomic neuropathy are usually not present. However, within 1 year of diagnosis subclinical autonomic dysfunction may be seen[14]. Early detection of DAN is crucial as it is often asymptomatic in its early stages but neglecting it may give rise to symptoms like constipation, diarrhea, erectile dysfunction, silent myocardial infarction, and even sudden death[15-18].

Miosis is the most common pupillary sign in diabetes[10]. In patients with a longer duration of diabetes smaller pupils has been demonstrated in a number of previous studies[19-22]. In our study also we found smaller pupil in the diabetic group as compared to healthy controls, also the HPD became further small with duration and presence of DAN in the diabetics. Smith and Dewhirst found that as the resting pupillary diameter in the dark-adapted state was mainly under sympathetic control, the smaller pupils in subjects with diabetes was a sign of sympathetic dysfunction[23]. In our study also we ascertained a smaller dark adapted HPD in diabetics thus pointing towards sympathetic dysfunction.

In diabetic patients commonly a small pupil with intact light reflexes is found, while a large pupil with poor light reflexes is found less, suggesting that the sympathetic iris innervation is more susceptible to damage than the parasympathetic innervations[13]. Tropicamide 1% is an anticholinergic drug which produces less mydriasis in diabetic pupils than in nondiabetic pupils, which is probably because it works by paralyzing the parasympathetic constrictor drive, thus allowing the sympathetic input to the dilator to dominate. The loss of sympathetic tone in patients with diabetic neuropathy thus explains its lesser efficacy.Several studies have suggested that in diabetes sympathetic autonomic dysfunction occurs before parasympathetic dysfunction[19,23,24]. Our study confirmed this hypothesis. All the patients with diabetes had smaller pupillary diameter in dark and a decreased sensitivity to Tropicamide 1% which further deteriorated in DAN group.Pupillary cycle time has been widely used for examination of ocular DAN since its introduction by Miller et al[13]. As it has been known to precede cardiovascular DAN, it can be used as an early diagnostic tool for ocular DAN[19]. Its afferent signals consist of retina, optic nerve, and optic tract whereas oculomotor nerve, ciliary ganglion, and iris sphincter muscle constitutes the efferent signals, any injury to this pupillary reflex arc can cause prolongation of PCT. According to Alio et al,[25] in diabetes patients with more than 10 years duration sympathetic denervation may occur more dominantly than parasympathetic denervation. Tadayuki et al reported histologic differences in iris muscle cells between diabetes patients and normal controls[26]. The characteristics of diabetic iris muscle cells included many pigment granules, concentric lamellar appearance, and many lipid droplets. The findings were more frequent with longer duration of diabetes, poor glycemic controls and in dilator muscles than in sphincter muscles.As in this study, many previous studies have also demonstrated that patients with longer durationof type 2 diabetes but no other manifestations of DAN also have smaller pupil size than controls[19-22].A study by Smith SE et al suggested the occurrence of ocular autonomic nervous system dysfunction before cardiovascular autonomic dysfunction[19]. Also, Pena et al emphasized that the pupillary symptoms were the earliest evidence of autonomic nerve dysfunction[27]. The result of our study favors this as pupil abnormalities were significant even in the group without autonomic dysfunction.

Datta et al reported significant PNS dysfunction in subjects with diabetes as compared to healthy subjects[28]. In contrast to it we didn't find any significant relation between diabetic eyes and PNS dysfunction.

There are conflicting reports regarding whether or not pupillary autonomic dysfunction is seen earlier than cardiac autonomic dysfunction[29-31]. An early autonomic dysfunction with progression in duration of Diabetes was observed in the study as the pupillary parameters were deranged even before the onset of DAN. Measurement of HPD in dark as well as in light (before and after instillation of 1% Tropicamide) along with PCT can be valuable tool for the early detection of autonomic dysfunction and can be utilized in DAN screening .These simple and inexpensive techniques can potentially improve the outcome of patients with diabetic autonomic neuropathy by detecting it at sub-clinical stages.

Limitations

Manual methods of measurement of HPD and PCT, lesser number of cases along with inherent bias associated with hospital- based studies is a limitation of our study.

Although ANS dysfunction is crucial for abnormal PLR, structural changes of the iris in diabetes may act as contributory mechanism.

Conclusion

Our results clearly show that sympathetic denervation does exist in the pupil of diabetic patients and that it can be assessed by measuring HPD and PCT. The significant smaller HPD and prolonged PCT in patients without DAN compared with that of healthy subjects and further shortening of HPD and prolongation of PCT in patients with DAN could be a sign for early involvement of the pupil function before manifestation of systemic autonomic diabetic neuropathy.

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