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Original Article

Ophthalmology Section

# Correlation of Pupil Cycle Time and Postural Hypotension as a Marker for Diabetic Neuropathy

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## ABSTRACT

**Introduction:** Diabetic Neuropathy (DN) can involve autonomic nervous system like cardiovascular system and pupillary reflex. Cardiovascular DN can be measured by estimating the change in Blood Pressure (BP) based on position. Ocular DN can be evaluated by using Pupil Cycle Time (PCT), which is an early diagnostic tool to estimate ocular DN. It is a simple way to measure autonomic reflex activity and is a specific test to study parasympathetic function.

**Aim:** To assess the correlation of effects of postural hypotension and PCT on persistent diabetes.

**Materials and Methods:** The prospective cross-sectional study was conducted in Ophthalmology Out Patient Department (OPD) at KS Hegde Medical Academy, Mangalore, Karnataka, India, from January 1st 2019 to December 31st 2019. The study included 60 male patients between the age group of 40-60 years which were divided into two groups of 30 diabetics (Random Blood Sugar (RBS) >200 mg/dL, Fasting Blood Sugar (FBS) >126 mg/dL and Glycated Haemoglobin (HbA1c) >6.5%) and 30 non diabetics. The blood pressure of all the patients were recorded using a sphygmomanometer in sitting and standing positions. PCT was measured in both eyes using Haggstreit-type of slit lamp after the subject was seated in a dimly lit room after dark adaptation for 15 minutes.

**Results:** The mean age of patients in the diabetic group was 54±3.2 years and the non diabetic group was 52±2.7 years. The mean HbA1c of diabetics was 6.9±0.8%. The mean BP among diabetics in standing position was 133.86±29.34 mmHg systolic and 87.4±16.72 mmHg diastolic whereas in sitting position, it was 141.66±28.17 mmHg systolic and 85.26±13.39 mmHg diastolic. The mean BP among non diabetics in standing position was 129.46±24.84 mmHg systolic and 83.46±13.52 mmHg diastolic whereas in sitting position, it was 132.06±26.48 mmHg systolic and 81.26±11.45 mmHg diastolic. The mean PCT-I and PCT-II in diabetics was 1000.52±187.73 and 1006.09±199.45, respectively. The systolic and diastolic BP, both during sitting and standing postures, in diabetic patients were high. The mean PCT-I and PCT-II in non diabetics was 853.23±181.54 and 880.17±192.72, respectively. The PCT-I and PCT-II were found to be significantly high in diabetic patients as compared to controls. The PCT-I and PCT-II negatively correlated with both diastolic and systolic blood pressure in sitting and standing postures.

**Conclusion:** Prolongation of PCT in diabetics correlates significantly with evidence of autonomic neuropathy obtained from testing of postural BP variations. Patients whose cardiovascular reflexes are very abnormal tend to have pupils which cycle slowly.


**Keywords:** Autonomic neuropathy, Haggstreit-type of slit lamp, Postural blood pressure

## INTRODUCTION

Autonomic innervations are possessed by almost every organ system in the body. Various quantitative investigation procedures have been developed for evaluation of autonomic activity which includes cardiovascular, sudomotor, gastrointestinal, renal, sexual and respiratory functions. DN is known to affect the cardiovascular, gastrointestinal and genitourinary systems [1]. BP variations are also a common manifestation of autonomic neuropathy secondary to diabetes. Patients usually present with generalised weakness, decreased vision, fatigue and episodes of loss of awareness. These have been known to occur as a result of change in heart rate, pumping ability of the heart and resistance to splanchnic vessels. The major factor responsible for a decrease in BP is a decrease in catecholamine production while standing and failure of lower limb vessels to increase resistance when required [1].

The PCT is a simple and sensitive test to measure dysfunction of autonomic nervous system. PCT is the time that pupil takes to constrict and dilate once, when stimulated with a slit beam of light [2]. Stimulation of parasympathetic nerves excites the sphincter pupillae which leads to miosis. On the other hand, stimulation of sympathetic nerves excites the dilator muscle and leads to mydriasis. Autonomic function of the iris can be assessed by the measurement of PCT [3].

Diabetic autonomic neuropathy occurs in approximately 50% of individuals with long standing type 2 diabetes mellitus [4]. The development of autonomic neuropathy correlates with the duration of diabetes and glycaemic control; both myelinated and unmyelinated nerve fibres are lost. This is due to increased metabolic products produced by phosphorylation and subsequent glycolysis of increased intracellular glucose. Metabolites like sorbitol are produced which alters redox potential, generates reactive oxygen species and likely leads to other types of cellular dysfunction. Axonal degeneration of metabolic origin tends to evolve over several weeks to a year or more and demyelinating neuropathies develop in diabetic patients [4]. Degenerating autonomic nerve endings in the iris have been observed. The diabetic iris actually shows an increased response to both cholinomimetic and sympathomimetic drugs which indicates denervation hypersensitivity [5].

The PCT is a novel method to investigate the effects of persistent diabetes and to correlate its effect on postural hypotension. The aim of this study was to assess the correlation of effects of postural hypotension and PCT on persistent diabetes.

## MATERIALS AND METHODS

This prospective cross-sectional study was conducted in Ophthalmology OPD at KS Hegde Medical Academy, Mangalore, Karnataka, India, from January 1st 2019 to December 31st 2019. The study was conducted after obtaining an approval from the Institutional Ethics Committee (IEC) on November 22nd 2018 (INST. EC/EC/064/2018-19).

Sixty patients between the age group of 40-60 years which were divided into two groups of 30 diabetics and 30 non diabetics. The non diabetics included patients who presented to the eye OPD with ocular complaints. A written consent was obtained from all patients who participated in the study.

The diabetic patients were admitted for systemic control of blood sugars and were referred to the OPD for diabetic retinopathy evaluation.

**Inclusion criteria:** Group-1 included type-2 diabetic patients diagnosed as per World Health Organisation (WHO) criteria, (RBS >200 mg/dL, FBS >126 mg/dL and HbA1c >6.5%) [1] (WHO 1980 Technical report series 646) without any history of ketoacidosis, more than 10 years of diabetes and co-existence of neuropathy diagnosed clinically. Group-2 included normal subjects.

**Exclusion criteria:** Severe non proliferative and proliferative diabetic retinopathy, ocular disease and disorders known to affect autonomic function as well as peripheral nervous system like Systemic Lupus Erythematosus (SLE), Rheumatoid arthritis, Myasthenia gravis patients taking drugs like dopamine, adrenaline or dobutamine which could affect autonomic function were excluded from the study.

**Sample size calculation:** On the basis of the study conducted by Young JB and Landsberg L assuming 95% confidence level, 80% power, mean blood glucose levels (FBS) of 131±3.8 mg/dL in the diabetic group and 113±2.7 mg/dL in the non diabetic group, estimated effect size is 0.8, an estimated sample size of 30 in each group was calculated. Sample size was estimated using G*Power 3.1.9.4 I [3].

### Study Procedure

The blood pressure (systolic and diastolic) of the patients was measured using sphygmomanometer and a stethoscope. The patients were asked to stand for five minutes and the blood pressure was recorded and documented. Next, they were asked to sit for five minutes and the blood pressure was recorded and documented. The mean systolic and diastolic pressure of the patients in standing and sitting positions were calculated. Neuropathy with burning, tingling sensation and painful or numb feet was diagnosed clinically with 10 g Semmes-Weinston monofilament test and vibration test using a 128 MHz tuning fork. PCT was measured in both eyes using Haggstreit-type of slit lamp. The subject was seated in a dimly lit room after dark adaptation for 15 minutes. Then asked to gaze at a fixed point to get accurate measurement. A horizontal beam of light of width of 1 mm wide slit beam of moderate intensity was focused through the slit lamp, accurately on the inferior margin of the pupil. The beam of light was slowly elevated until it overlaped the pupil. The pupil-initiated cycle of constriction was when light entered through the pupil and dilatation was when light escaped. The stopwatch was incorporated to an oscillator of 1 KHz, which gave an accuracy of 1 millisecond. It was connected to a counter on which the number of cycles to be counted could be selected. The counter started the stopwatch at the beginning and end of the preselected number of cycles, which reduced human error to minimum. The stopwatch was calibrated on an oscilloscope. Count was performed in both right and left eyes. For the purpose of analysis, the longer cycle of the two estimated from each subject was considered. The oscillatory cycles were timed for 60 cycles (two 30 cycles). The time taken for single cycle from the first 30 cycles was recorded as PCT-I and from the next 30 cycles was taken as PCT-II.

## STATISTICAL ANALYSIS

Statistical analysis of the data was done using the software Statistical Package for the Social Sciences (SPSS) version 20.0 at 95% confidence level. Categorical variables were presented as percentage. Continuous variables were presented as Mean±Standard Deviation (SD). The comparison of BP and PCT in the diabetic and non diabetic group was done using the paired t-test. Correlation between PCT and blood pressure in sitting and standing positions was done using Karl Pearson's Coefficient of correlation. A p-value of <0.05 was considered statistically significant.

## RESULTS

The mean age of patients in the diabetic group was 54±3.2 years and the non diabetic group was 52±2.7 years (p=0.127). In the diabetic group, 20 (65%) were males and 10 (35%) were females whereas in the non diabetic group, 17 (57%) were males and 13 (43%) were females. The mean HbA1c of diabetics was 6.9±0.8%.

The study showed significant difference between the systolic blood pressure, diastolic blood pressure both during sitting posture and standing posture in control and diabetic patients [Table/Fig-1]. In the same way, the PCT-I and PCT-II was significantly high (p=0.003 and p=0.0005, respectively) in diabetic patients as compared with the means of controls [Table/Fig-1].

| Variables | Control | Diabetic patients | 95% CI | p-value |
|---|---|---|---|---|
| SBP in mmHg (standing) | 129.46±24.84 | 133.86±29.34 | -18.44 to 9.65 | 0.004 |
| DBP in mmHg (standing) | 83.46±13.52 | 87.4±16.72 | -5.79 to -9.92 | 0.008 |
| SBP in mmHg (sitting) | 132.06±26.48 | 141.66±28.17 | -23.73 to -4.53 | 0.004 |
| DBP in mmHg (sitting) | 81.26±11.45 | 85.26±13.39 | -10.44 to -2.44 | 0.003 |
| Pupil cycle time-I (msec) | 853.23±181.54 | 1000.52±187.73 | -242.73 to -51.84 | 0.003 |
| Pupil cycle time-II (msec) | 880.17±192.72 | 1006.09±199.45 | -287.28 to -84.55 | 0.0005 |

**[Table/Fig-1]:** Clinical and biochemical parameters in controls and diabetic patients with varying severity of Diabetic Neuropathy (DN) (values are mean±SD, n=30 each). **By students t-test. The p-value <0.01 when compared, PCT-I and PCT-II between control and diabetic patients

PCT-I and PCT-II negatively correlated with both diastolic and systolic blood pressure in sitting and standing postures [Table/Fig-2,3], but these correlations were not found to be statistically significant.

| Parameters | Pupil cycle time-I | |
|---|---|---|
| | R-value | p-value |
| SBP in mmHg (standing) | -0.346 | 0.061 |
| DBP in mmHg (standing) | -0.191 | 0.312 |
| SBP in mmHg (sitting) | -0.196 | 0.298 |
| DBP in mmHg (sitting) | -0.171 | 0.365 |

**[Table/Fig-2]:** Correlated PCT-I with blood pressure in both sitting and standing postures.

| Parameters | Pupil cycle time-II | |
|---|---|---|
| | R-value | p-value |
| SBP in mmHg (standing) | -0.100 | 0.598 |
| DBP in mmHg (standing) | -0.088 | 0.645 |
| SBP in mmHg (sitting) | -0.145 | 0.444 |
| DBP in mmHg (sitting) | -0.166 | 0.380 |

**[Table/Fig-3]:** Correlated PCT-II with blood pressure in both sitting and standing postures.

## DISCUSSION

The aim of this study was to compare the PCT of patients with type II diabetes and healthy control subjects and to analyse the effect of variables like age, sex, HbA1c levels and BP on PCT. Mean PCT was prolonged in diabetics when compared with control subjects. There was prolongation of PCT with increasing age, but the correlation of PCT with age could only be demonstrated in the control group, as diabetes, by itself, can prolong the PCT. A study conducted by Miller SD and Thompson HS found that beyond the age of 50 years,

there was a lengthening of PCT [6], whereas Dustman RE and Beck EC found the same in a group of older subjects, with a mean age of 67 years [7].

In the present study, there was a tendency towards a lengthening of the PCT in control group with advancing age. This was comparable with the study conducted by Manor RS et al., which also showed the tendency for PCT to increase with age whereas the above findings were negated by Sood AK et al., who did not find any significant correlation between age and PCT [8,9].

In this study, mean PCT of diabetic patients was 1003 ms, whereas mean PCT of controls was 870 ms with SD of 183.14 ms and 194.36 ms, respectively. This increase in mean PCT, in diabetic group could also be due to increased distribution of elderly patients in the diabetic group, which was also observed in the study conducted by Manor RS et al., [8]. The prolonged PCT in diabetics as compared to healthy normal subjects points towards a possibility of pupillary autonomic neuropathy as the probable explanation for this result. Similar finding was cited by many other studies like Smith SE et al., [10].

Martyn CN and Ewing D; Kim GC et al., concluded that PCT is prolonged in diabetics and correlates well with evidence of autonomic neuropathy [11,12]. PCT may be prolonged due to the inability of the iris smooth muscle to contract, which can happen due to structural abnormalities in iris muscle in diabetes. Ultrastructural studies have demonstrated abnormalities in the muscles of the diabetic iris, though these may be a consequence to damage to the innervating fibres. It is more likely that the prolongation of PCT is caused by an abnormality in the innervation of the iris than an abnormality in the smooth muscle. In this cross-sectional study, the PCT was significantly correlated with the duration of diabetes but not with postural changes in the BP whereas the study by Martyn CN and Ewing D showed prolongation of PCT in diabetics correlated well with the evidence of autonomic neuropathy obtained by testing BP [11]. Patients whose BP was very abnormal tend to have pupils which cycle slowly. However, abnormal BP does not necessarily reflect autonomic dysfunction in other systems. The imperfect correlation of PCT with BP suggests that autonomic dysfunction in different organ systems does not tend to occur spontaneously. Various techniques have been used for recording and measuring pupillary reactions using infrared video camera and using computer software to analyse these images. These studies have shown association between abnormalities in pupil with autonomic and peripheral nerve dysfunction [13].

This study suggested that measurement of PCT is particularly sensitive to dysfunction in the parasympathetic efferent limb of the pupil reflex arc and this measurement will also be a useful addition to the existing tests of autonomic dysfunction.

### Limitation(s)

The PCT is observer dependent and may be artificially prolonged by undetected cycles and can be interrupted by frequent blinking. Also, changes in intensity of stimulus and fixation pattern can lead to changes in strength and duration of pupillary contraction, which can also alter PCT. Another limitation was that the PCT values may not be reliable if the patient has an afferent or efferent pupillary defect, which was not assessed during the study.

## CONCLUSION(S)

This study shows that iris is one of the structures which have innervation by autonomic nervous system and also how assessment of PCT can help to quantify the functioning of the pupil. It is a reliable and sensitive method which was a non invasive and easily performable. The study also suggests that measurement of PCT is useful to assess abnormalities in the parasympathetic system of light reflex in diabetics.

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