

Original Research Article

TITLE NAME: Correlation between corneal sensitivity and peripheral neuropathy in type 2 diabetics attending the endocrinology clinic of University of Port Harcourt Teaching Hospital (UPTH).

ABSTRACT

AIM: To correlate the occurrence of corneal sensory loss with peripheral neuropathy in Type 2 diabetics.

STUDY DESIGN: A hospital based case control study

PLACE AND DURATION: A study conducted on type 2 diabetics attending the endocrinology clinic of University of Port Harcourt Teaching Hospital (UPTH), Rivers State, Nigeria between October 28th 2013 and February 28th 2014.

METHODOLOGY: Participants were selected using consecutive allocation of type 2 diabetics as they presented to the Endocrinology Clinic of University of Port Harcourt Teaching Hospital. Diabetic-free controls were recruited simultaneously. Data of each participant was documented on standard proforma and subsequently had ocular examinations. Central corneal sensitivity was assessed using a Cochet-Bonnet Aesthesiometer, peripheral neuropathy was assessed using the Biothesiometer

RESULTS: A total of 120 diabetics and 120 age and sex-matched controls constituted the study population. Their mean age was 55.6 ± 10.5 years with an age range of 30 to 82 years (diabetics: 56.6 ± 10.9 years and healthy control subjects: 54.5 ± 10.1 years). Corneal sensitivity in the right

eye of diabetics was: 52.4 ± 6.7 mm and 55.5 ± 4.9 mm in controls while that in the left eye was 51.1 ± 9.0 mm in diabetics and 54.0 ± 5.2 mm in control. The mean value pressure applied to the central cornea in diabetics was 0.54 ± 0.16 gm/mm² and 0.47 ± 0.09 gm/mm² in controls. The average vibration perception threshold in diabetics was 21.3 ± 7.4 and 16.6 ± 3.8 in control. Corneal sensitivity in diabetics with symptoms of neuropathy was 51.8 ± 6.7 and 56.3 ± 5.8 in diabetics without symptoms (p-value 0.014). The corneal sensitivity in diabetics with peripheral neuropathy-biothesiometer readings > 25 mV- was 46.5 ± 7.2 and 54.2 ± 5.4 in diabetics without peripheral neuropathy-biothesiometer readings of < 25 mV (p-value < 0.001).

CONCLUSION: Corneal sensitivity was significantly lower in diabetics with peripheral neuropathy when compared to diabetics without peripheral neuropathy.

KEY WORDS: Corneal Sensitivity, Type 2 diabetics, Peripheral Neuropathy

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, action, or both.(1) The United States of America Diabetes Data Group and World Health Organization (WHO) have issued a diagnostic criterion for DM which includes symptoms of DM plus random blood sugar greater than 11.1mmol/l (200mg/dl) or fasting plasma glucose greater than 7.0mmol/l(126g/dl).(2) Such symptoms include frequent urinating, excessive hunger, weight loss, increased thirst, and blurred vision.

The prevalence of this global problem is increasing dramatically (3,4) currently ranked as the sixth leading cause of death worldwide. In Africa, it is considered the commonest endocrine disorder. At the University of Port Harcourt Teaching Hospital (UPTH), diabetes accounted for

approximately 14% of all new cases seen in the Medical Clinics in 1994, and over 18% of all the Medical out-patient consultations in the same year.(5) A ten year retrospective study between 1995 and 2004 identified DM and its complications in 10.4% of admissions in the same hospital.(6) In 2012, Iyagba estimated 350 new patients with type 2 diabetes were seen in the Endocrinology Clinic of University of Port Harcourt Teaching Hospital.(7)

Diabetic complications may be classified broadly as acute or chronic. Acute complications include diabetic ketoacidosis, hyperosmolar hyperglycaemic states, lactic acidosis, and hypoglycaemia while chronic complications may be vascular, neurologic or both. Neurologic complications include diabetic peripheral neuropathy (DPN) which is one of the commonest long term complications affecting nearly 50% of all diabetics and is the major reason for hospital admission in this population.(8,9)

BASIS OF NEURONAL LOSS

Several theories have been proposed to explain the pathogenesis of DPN including the Polyol pathway (10), accumulation of advanced glycosylation end-products (11), low levels of growth factors(12), free radical-Oxidative Stress(13) and immunologic factors(14).

Corneal diseases can not only develop in diabetic patients but are also difficult to manage. In addition, corneal damage can cause disturbances in the management of proliferative diabetic retinopathy before and after surgeries such as vitrectomy (15) and can ultimately affect the outcome of cataract surgeries in diabetics.

Only few studies have focused on the importance of corneal diseases and corneal sensitivity in diabetic patients in Nigeria hence the importance of this study. Peripheral neuropathy is a key arm of neurology with diabetes mellitus being the commonest cause. The diagnosis of peripheral

66 neuropathy is often subjective compounded by the absence of relevant instruments in developing
67 countries such as Nigeria, thus, this study will provide a quick and effective means of identifying
68 diabetics at risk of peripheral neuropathy sparing them a life time of pain.

69 **MATERIALS AND METHODS**

70 Hospital-based case control study of type 2 diabetics attending the Endocrinology Clinic of
71 University of Port Harcourt Teaching Hospital and a similar number of age and sex matched
72 diabetic free control.

73 **INCLUSION CRITERIA FOR PATIENTS**

74 Patients with Type 2 DM attending the Endocrinology Clinic who give written informed consent
75 or thumb printed consent.

76 **INCLUSION CRITERIA FOR CONTROL**

77 Diabetes free, apparently healthy age and sex-matched controls that gave written informed
78 consent or thumb print.

79

80 **EXCLUSION CRITERIA FOR PATIENTS AND CONTROL**

- 81 1. Patients who did not give informed consent
- 82 2. Corneal scarring, thinning, abrasions or vascularisation from other causes
- 83 3. History of ocular surgery or trauma
- 84 4. History of chronic ocular disease or recurrent infection example: herpetic keratitis
- 85 5. Use of anti-glaucoma eye drops

6. Contact lens wear

7. Patients who have had any laser treatment (Refractive, Retinal photocoagulation, Yttrium Aluminium Garnet etc)

8. Diabetics with HIV infection

9. Severe (critical) medical illness that will interfere with the ability to carry out the study

10. Patients on neurotoxic medications such as Isoniazid

11. Patients with Type 1 DM and gestational DM.

ETHICAL CONSIDERATION

Approval to carry out this study was sought and obtained from the following: Ethics Committee of University of Port Harcourt Teaching Hospital, Head, Department of Ophthalmology (UPTH), Head, Department of Internal Medicine (UPTH) and consultant in charge of Endocrinology unit.

SAMPLING TECHNIQUE

The study involved consecutive recruitment of diabetics as they presented to the Endocrinology Clinic. There was no bias in subject selection.

The interviewer administered questionnaire was administered to obtain background information (including biodata, past ocular history and symptoms of neuropathy such as numbness, pain or burning sensation, pricking sensation and unsteady gait) on each eligible participant.

Corneal sensitivity was measured using the Luneau Cochet-Bonnet Corneal Aesthesiometer (LuneauOphthalmologie, France. Western Ophthalmics; WO-7760, Lynnwood, Washington) while peripheral neuropathy was assessed by measuring the vibration perception threshold with the Biothesiometer (Bio-Medical Instruments, Co, Newbury, OH, U.S.A).

107 **CORNEAL SENSATION**

108 The observer sat in front of the seated patient, who was asked to look at a point behind and
 109 above the observer. Free length of nylon thread was kept at 60mm, and then aesthesiometer
 110 advanced slowly towards the central cornea (~10mm above the 6 O'clock position) of the
 111 patient's eye which was to be tested. The thread was kept at right angle to the anterior corneal
 112 surface and moved delicately against the cornea with just enough force that the thread becomes
 113 just visibly curved. At that point, the patient was asked to say whether he/she feels the touch
 114 sensation or not. If the patient did not feel it, the thread was reduced by 5mm every time and the
 115 procedure repeated. The length of remaining thread was read-off the Standard Conversion Chart
 116 of Cochet and Bonnet and converted in pressure per cross sectional area of the nylon thread.

117 **VIBRATION PERCEPTION THRESHOLD:**

118 Vibration Perception Threshold was tested using the hand held biothesiometer at the dorsum of
 119 the hallux on the on the lateral malleolus. The voltage of the vibrator was increased until the
 120 patient could feel a vibration on three separate occasions at 2 minute intervals. The mean of these
 121 values was used to determine the vibration perception threshold. There was blinding (done by the
 122 assistant) of the patients to avoid bias. The vibration perception is abnormal when the mean
 123 voltage of three readings exceeds 25 milliVolts.

124 **BLOOD GLUCOSE ESTIMATION**

125 Blood sugar estimation was carried out on both diabetics and control by assessing:

126 Fasting blood sugar: Normal $\leq 6.9\text{mmol/l}$

127 Glycosylated haemoglobin:

128 4-6.5%: Normal for patients without diabetes mellitus (average blood glucose: 3-8mmol/l)

129 6.5-7.5%: Target range for those with diabetes mellitus (average blood glucose: 8-10mmol/l)

130 8-9.5%: High (average blood glucose: 11-14mmol/l)

131 >9.5%: Very high (average blood glucose: ≥ 15 mmol/l)

132 Data obtained were analyzed using commercially available statistical data management software-

133 Statistical Package for Social Sciences Package version 17 (SPSS-17).

134 RESULTS

135 One hundred and twenty (n= 120) type 2 diabetic patients were compared with 120 healthy
136 diabetes-free control.

137 AGE AND SEX DISTRIBUTION OF SUBJECTS

138 The mean age of the included subjects was 55.6 ± 10.5 years with an age range of 30 to 82 years
139 and this did not significantly differ between the groups; diabetics- 56.6 ± 10.9 years and healthy
140 control- 54.5 ± 10.1 years (t- test 1.601, p-value 0.111).

141 There were more female subjects than the male counterparts with a male to female ratio for the
142 diabetic group 1: 1.6 and healthy control 1: 1.1.

143 **Table 1: Age group and gender distribution of study groups**

Variables	Diabetics N =120	Controls N=120	X^2	p-value
Age groups (years)				
<40	6 (5.0)	5 (4.2)	0.091	0.917
40- 49	29 (24.2)	35 (29.2)	0.563	0.453
50-59	38 (31.7)	44 (36.7)	0.431	0.508

60-69	31 (25.8)	27(22.5)	0.276	0.599
>70	16 (13.3)	9 (7.5)	1.960	0.116
Gender				
Male	46 (38.3)	57 (47.5)	1.171	0.278
Female	74 (61.7)	63 (52.5)	0.883	0.347

144 Non parametric chi-square tests

145 **FEATURES OF PERIPHERAL NEUROPATHY AMONG DIABETIC SUBJECTS**

146 Of diabetic subjects, 61.7% (n= 74) had numbness of the limbs and this was statistically
 147 significant ($X^2=6.533$, df= 1, p-value 0.011). Other features of neuropathy are shown in Table 2.
 148 More than three-quarters of the diabetic subjects had neuropathy symptoms (87.5%; n= 105) and
 149 this proportion was statistically significant ($X^2= 66.12$, df= 1, p-value <0.001). However, less
 150 than one-thirds of diabetics had biothesiometer readings of >25mV(24.2%; 29).

151 **Table 2: Features of Peripheral Neuropathy among Diabetic Subjects**

Variables	No of diabetic subjects N =120	Percentage 100.0	X^2	p-value
SYMPTOMS:				
Numbness of the limbs				
Yes	74	61.7	6.53	0.011
No	46	38.3		
Pricking sensation of the limbs				
Yes	33	27.5	24.30	0.001
No	87	72.5		
Pain/burning sensation of the limbs				
Yes	34	28.3	23.16	0.001
No	86	71.7		
Unsteady gait				
Yes	16	13.3	64.53	< 0.001
No	104	86.7		

SIGNS:

Peripheral Neuropathy (biothesiometer reading >25Mv)

Yes	29	24.2	32.03	< 0.001
No	91	75.8		

152 Non parametric chi-square tests

153 **LEVEL OF CORNEAL SENSITIVITY IN STUDY SUBJECTS**

154 The mean level of corneal sensitivity in diabetics was 52.4 ± 6.7 which was lower than that in
 155 controls 55.5 ± 4.9 . This was statistically significant (p-value <0.05 respectively) as shown in
 156 Table 3. The mean value pressure applied was higher in diabetics compared with health control
 157 in both eyes and this was statistically significant (p-value <0.001). In the diabetic group, the mean
 158 corneal sensitivity in the right eye was 52.4 ± 6.7 compared to 51.1 ± 9.0 in the left eye. There
 159 was no statistically significant difference between both eyes.

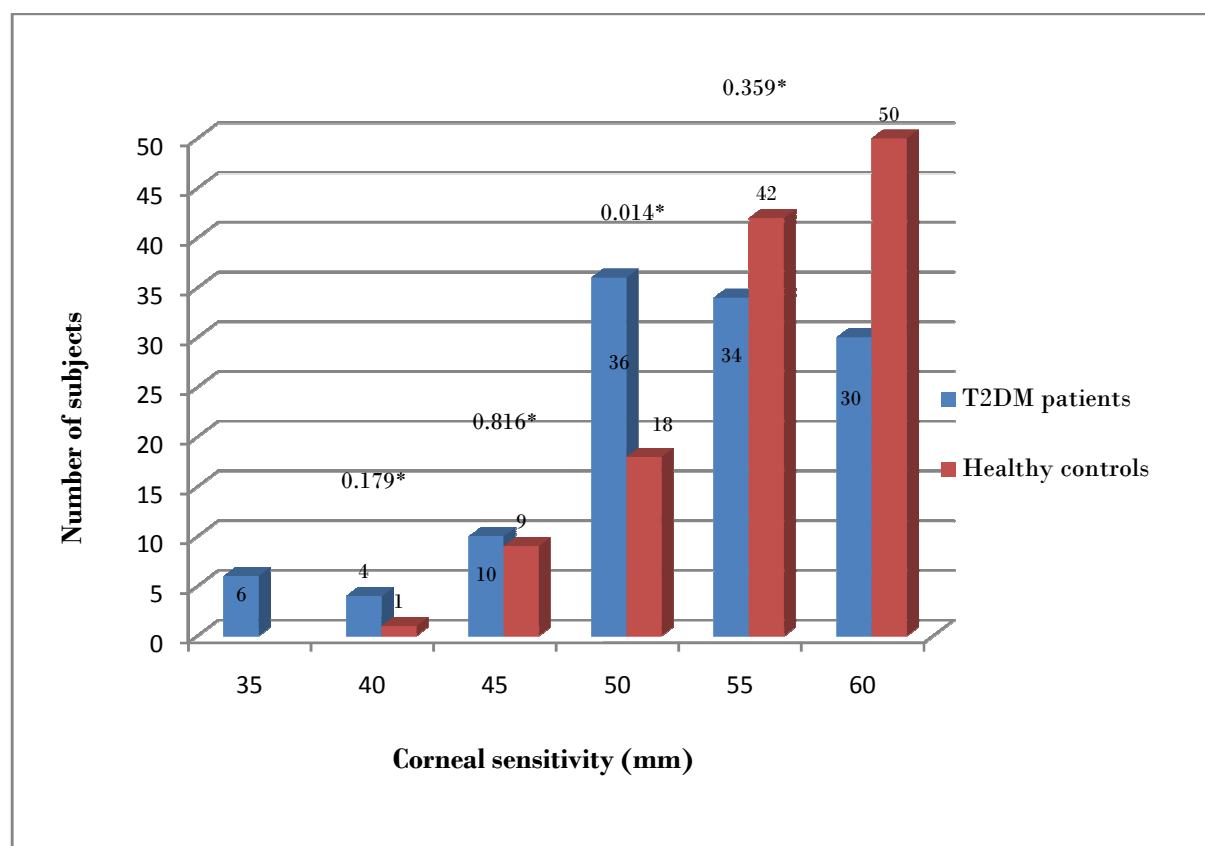
160 **Table 3: Level of Corneal Sensitivity in Study Subjects**

Variables	Mean $\pm$ S.D	range	Mean diff $\pm$ S.D	Conf interval	t- test p-value	
Corneal sensitivity threshold (mm)						
RIGHT EYE						
Diabetics	52.4 ± 6.7	30 to 60				
Control	55.5 ± 4.9	40 to 60	- 3.1 $\pm$ 0.8	- 4.6 to -1.6	-4.082	<0.001
LEFT EYE						
Diabetics	51.1 ± 9.0	0 to 60				
Control	54.0 ± 5.2	40 to 60	- 2.9 $\pm$ 0.1	- 4.8 to -1.0	- 3.019	0.003
Mean value pressure (gm/mm²)						
RIGHT EYE						
Diabetics	0.54 ± 0.16	0.4 to 1.4				
Control	0.47 ± 0.09	0.0 to 0.7	0.07 $\pm$ 0.02	0.03 to 0.10	4.267	<0.001
LEFT EYE						
Diabetics	0.60 ± 1.4	0.4 to 15.4				
Control	0.47 ± 0.1	0.0 to 0.7	0.13 $\pm$ 0.03	0.06 to 0.19	3.855	<0.001

161 Independent t-tests.

162 **FREQUENCY OF STUDY SUBJECTS AT DIFFERENT LEVELS OF CORNEAL**
 163 **SENSITIVITY**

164 Seventy (58.3%) of control had corneal sensitivity of less than 60mm which was less than
 165 control (n= 90;75%). Six subjects (0.8%) had corneal sensitivity level of 35mm and were all
 166 diabetics ($X^2= 6.00$ df=1, p-value 0.0143).



167
 168 Key * represents the p-values using non parametric chi-square test

169 **Figure 1: Frequency of study subjects at different levels of corneal sensitivity.**

CORNEAL SENSITIVITY AND PERIPHERAL NEUROPATHY IN DIABETICS

Table 4 demonstrates a reduction in corneal sensitivity in diabetics with symptoms of neuropathy- 51.8 ± 6.7 -compared to those without symptoms- 56.3 ± 5.8 (p-value 0.014). In a similar way, the corneal sensitivity in diabetics with peripheral neuropathy was 46.5 ± 7.2 and this was low compared to 54.2 ± 5.4 in diabetics without peripheral neuropathy (p-value <0.001).

Table 4: Corneal Sensitivity and Peripheral Neuropathy in diabetics

Variable	n	Corneal sensitivity (mm)	MVP (gm/mm ²)
Symptoms of Peripheral Neuropathy			
Present	105	51.8 ± 6.7	0.55 ± 0.16
Absent	15	56.3 ± 5.8	0.47 ± 0.11
<i>Mean diff</i>		-4.5 ± 0.2	0.09 ± 0.04
<i>p- value</i>		0.014	0.044
Peripheral Neuropathy			
Present	29	46.5 ± 7.2	0.70 ± 0.22
Absent	96	54.2 ± 5.4	0.50 ± 0.11
<i>Mean diff</i>		-7.7 ± 0.1	0.09 ± 0.04
<i>p- value</i>		<0.001	< 0.001

Two tailed *Independent t-tests* of analyses

MVP=mean value pressure (gm/mm²), AVPT = average vibration pressure threshold

RELATIONSHIP BETWEEN CORNEAL SENSITIVITY AND VIBRATION PRESSURE THRESHOLD (PERIPHERAL NEUROPATHY) IN DIABETICS

A bivariate linear regression in Figure 2 demonstrates a statistically significant strong negative correlation between corneal sensitivity and vibration pressure threshold (peripheral neuropathy) ($r = -0.510$, $p\text{-value} < 0.001$). Corneal sensitivity reduces significantly with increase in the vibration pressure threshold and for every 10mV rise in vibration pressure threshold corneal sensitivity reduced by $-0.5 \pm 0.1\text{mm}$ (C.I. -0.6 to -0.3mm).

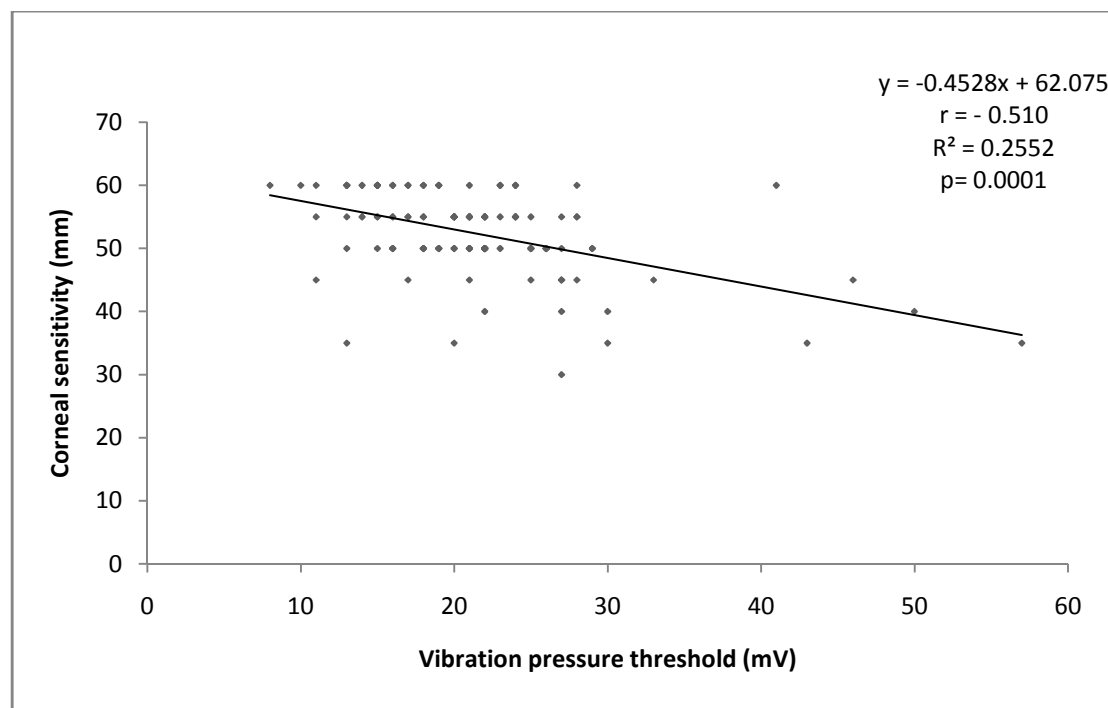


Figure 2: Relationship between corneal sensitivity and vibration perception threshold (peripheral neuropathy) in diabetics

DISCUSSION

The focus in relation to consequences of nerve damage in diabetes mellitus has been the loss of sensation in the feet predisposing to the development of foot ulceration and lower extremity amputation; however, studies have repeatedly shown corneal sensitivity is reduced in diabetics

leading to keratopathy(14) and a susceptibility to corneal erosions/abrasions ranging from superficial erosions to extensive, full thickness, confluent epithelial lesions which have been reported to occur in 47% to 64% of diabetic patients.(16) In Nigeria, there is paucity of data on corneal changes in patients with DM but Adeoti *et al* (17) in a prospective study on 181 diabetic patients identified superficial punctate keratopathy in 5.53% (n=10) of patients, while 0.55% (n=1) had corneal ulcer and abscess. On the other hand, in identifying causes of low vision among 100 new patients examined in the Diabetic Eye Clinic of Nnamdi Azikiwe Teaching Hospital Nnewi, Nigeria, Nwosu(18) reported corneal opacity (leukoma) as one of the causes of blindness in the 18 patients who were bilaterally blind and 26 patients who had unilateral blindness

REDUCED CORNEAL SENSITIVITY IN DIABETICS

The loss of corneal sensation in diabetics has been documented in various studies since first credited to the presence of concomitant glaucoma in a diabetic patient.(19) Similar to this study, Schultz *et al*(20) found a reduction in corneal sensitivity in 18% of a group of randomly selected diabetic patients. This was corroborated by Dogru *et al* (21) who further reported that corneal sensitivity was significantly lower in diabetics with poor metabolic control and peripheral neuropathy.

CORNEAL SENSITIVITY AND PERIPHERAL NEUROPATHY

Nielsen (22) provided preliminary evidence of an association between reduced corneal sensitivity and diabetic peripheral neuropathy in 1978. Similar to this study, he investigated 36 diabetics and 45 controls and assessed their corneal sensitivity using the Cochet-Bonnet's

aesthesiometer and vibratory perception of the left index finger and great toe using the biothesiometer; a higher percentage, 83% of the diabetics had a corneal sensitivity below 60 mm against 38% of the controls; this is similar to findings in this study in which 75% of diabetics against 58.3% of control had a corneal sensitivity below 60mm. Likewise a significantly reduced vibratory perception was noted among the diabetics. The reductions of corneal sensitivity and vibratory perception were correlated in the diabetics as in this study. He got similar findings one year later when he increased his sample size to 100 diabetics and 100 controls and in addition assessed their Achilles tendon reflex.

Nuho *et al* (23) reported corneal sensitivity was reduced in two groups of diabetics (one with peripheral neuropathy and the other without neuropathy). In the peripheral neuropathy group, all of its subjects (100%) had low corneal sensitivity while 75% of patients without peripheral neuropathy had reduced corneal sensitivity. Similarly, Tavakoli *et al*(14) demonstrated that the reduction of corneal sensitivity in diabetics progresses with severity of neuropathy suggesting that corneal nerve fiber damage accompanies somatic nerve fiber damage. Pritchard *et al* (24) also investigated the association between corneal sensitivity and established measures of diabetic peripheral neuropathy in 93 diabetics with peripheral neuropathy, 146 diabetics without neuropathy, and 61 controls using the non-contact corneal aesthesiometer, neuropathy disability score, diabetic neuropathy scoring system, neuropad, electrophysiological parameters, and quantitative scoring systems. They concluded that the reduction in corneal sensitivity, although not strongly related, is associated with other functional measures of DPN and might provide a useful adjunct in identifying function loss of small nerve fiber integrity.

This study has emphasized the need to pay attention to cornea sensitivity of diabetic patients particularly those with symptoms and/or signs of peripheral neuropathy. The paucity of relevant

248 literature from our country on the corneal sensitivity in diabetics was a challenge and therefore
249 made comparison difficult. This study will help build database on the effect of diabetes in the
250 eye for future.

251 **CONCLUSION**

252 Corneal sensitivity in diabetics with peripheral neuropathy was significantly less than that in
253 diabetics without peripheral neuropathy.

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