Ophthalmology Research: An International Journal
6(3): 1-9, 2016; Article no.OR.30326
ISSN: 2321-7227

SCIENCEDOMAIN *international*
www.sciencedomain.org

Correlation between Corneal Sensitivity and Peripheral Neuropathy in Type 2 Diabetics Attending the Endocrinology Clinic of University of Port Harcourt Teaching Hospital (UPTH), Nigeria

Rhoda D. Komolafe[1*], Chinyere N. Pedro-Egbe[2] and Elizabeth A. Awoyesuku[2]

[1]Department of Ophthalmology, Braithwaite Memorial Specialist Hospital, Rivers State, Nigeria.
[2]Department of Ophthalmology, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author RDK designed the study. Author CNPE wrote the protocol and first draft of the manuscript. Author EAA managed the literature searches and author RDK carried out the study, collated data and analyzed the data. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/OR/2016/30326
Editor(s):
(1) Stephen G. Schwartz, Department of Clinical Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, USA.
Reviewers:
(1) Thiago Gonçalves dos Santos Martins, Federal University of São Paulo, Brazil.
(2) Italo Giuffre, University of Rome, Italy.
(3) Iman M. Eissa, Cairo University, Egypt.
Complete Peer review History: http://www.sciencedomain.org/review-history/17027

Original Research Article

Received 2nd November 2016
Accepted 19th November 2016
Published 25th November 2016

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. Diabetes-free controls were recruited simultaneously. Data of each participant was documented on standard proforma and subsequently had ocular examinations. Central corneal sensitivity was assessed

**Corresponding author: E-mail: drkomolafer@yahoo.com;*

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: 54.5 ±10.1 years). Corneal sensitivity in the right eye of diabetics was: 52.4±6.7 mm and 55.5±4.9mm 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/mm^2 and 0.47±0.09 gm/mm^2 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 <25mV (p-value <0.001).

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

Keywords: Corneal sensitivity; type 2 diabetics; peripheral neuropathy.

1. 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 criteria for DM which includes symptoms of DM plus random blood sugar greater than 11.1 mmol/l (200 mg/dl) or fasting plasma glucose greater than 7.0 mmol/l (126 g/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].

1.1 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].

Not only can corneal diseases develop in diabetic patients, but also they are very 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 entity with diabetes mellitus being the commonest cause. The diagnosis of peripheral neuropathy is often subjective compounded by the absence of relevant instruments in developing countries such as Nigeria, thus, this study will provide a quick and effective means of

identifying diabetics at risk of peripheral neuropathy sparing them a life time of pain.

2. MATERIALS AND METHODS

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

2.1 Inclusion Criteria for Patients

Patients with Type 2 DM attending the Endocrinology Clinic, who gave written informed consent or thumb print.

2.2 Inclusion Criteria for Control

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

2.3 Exclusion Criteria for Patients and Control

1. Patients who did not give informed consent
2. Corneal scarring, thinning, abrasions or vascularisation from other causes.
3. History of ocular surgery or trauma.
4. History of chronic ocular disease or recurrent infection example: herpetic keratitis.
5. Use of anti-glaucoma eye drops and Non steroidal anti-inflammatory.
6. Contact lens wear.
7. Patients who have had any laser treatment (Refractive, Retinal photocoagulation, Yttrium Aluminium Garnet etc).
8. Diabetics with HIV infection- tested using Rapid HIV test kit (determine^{R}Alere).
9. Severe (critical) medical illness that will interfere with the ability to carry out the study.
10. Patients on neuro-toxic medications such as Isoniazide.
11. Type 2 diabetics with past history of Cerebro Vascular Accident and/or Multiple Sclerosis.
12. Type 2 diabetics with a history of substance abuse and/or chronic alcoholism (>21 units/week/year for men and >14 units/week/year for women- one bottle of local beer equivalent to 2 units).
13. Patients with Type 1 DM and gestational DM.

2.4 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.

2.5 Sampling Technique

The study involved consecutive recruitment of diabetics as they presented to the Endocrinology Clinic. 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 (Luneau Ophthalmologie, 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).

2.6 Corneal Sensation

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

2.7 Vibration Perception Threshold

Vibration Perception Threshold was tested using the hand held biothesiometer at the dorsum of the hallux on the on the lateral malleolus. The voltage of the vibrator was increased until the

patient could feel a vibration on three separate occasions at 2 minute intervals. The mean of these values was used to determine the vibration perception threshold. There was blinding (done by the assistant) of the patients to avoid bias. The vibration perception was considered abnormal when the mean voltage of three readings exceeded 25 milliVolts.

2.8 Blood Glucose Estimation

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

Fasting blood sugar: Normal ≤ 6.9 mmol/l

Glycosylated haemoglobin:

4-6.5%: Normal for patients without diabetes mellitus (average blood glucose: 3-8 mmol/l)
6.5-7.5%: Target range for those with diabetes mellitus (average blood glucose: 8-10 mmol/l)
8-9.5%: High (average blood glucose: 11-14 mmol/l)
>9.5%: Very high (average blood glucose: ≥15 mmol/l)

Data obtained were analyzed using commercially available statistical data management software-Statistical Package for Social Sciences Package version 17 (SPSS-17). Age groups, gender and features of peripheral neuropathy amongst others were presented using frequency tables. The proportion of diabetics with peripheral neuropathy was expressed in tables and Pearson non parametric chi-square test was used for tests of analysis at 95% confidence level. Fishers tests was used in place of Pearson's chi-square test in cases when the number within each cell was less than 5 or the sum of the numbers in the entire cells was less than 20. Continuous variables- Age was expressed in mean and the relationship between the values in diabetics and control was tested using two-tailed independent t-test at 95% confidence level.

Level of cornea sensitivity was compared between the study groups using two tailed independent t-test. Relationship between peripheral neuropathy and some characteristics of diabetes was tested using multi-nominal logistic regression analysis to determine the wald statistics, odd's ratio (O.R) and 95% confidence interval of O.R while bivariate correlation analysis was used to determine the coefficient of correlation (r-value), strength of correlation (R^2). The level of statistical significance for all the analysis was set at p-value <0.05.

3. RESULTS

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

3.1 Age and Sex Distribution of Subjects

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

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

3.2 Features of Peripheral Neuropathy among Diabetic Subjects

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

3.3 Level of Corneal Sensitivity In Study Subjects

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

3.4 Frequency of Study Subjects at Different Levels of Corneal Sensitivity

Seventy (58.3%) of control had corneal sensitivity of less than 60 mm which was less

than diabetics (n= 90;75%). Six subjects (0.8%) had corneal sensitivity level of 35 mm and were all diabetics (X^2= 6.00 df=1, p-value 0.0143).

3.5 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).

3.6 Relationship between Corneal Sensitivity and Vibration Pressure Threshold (Peripheral Neuropathy) in Diabetics

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

4. 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.

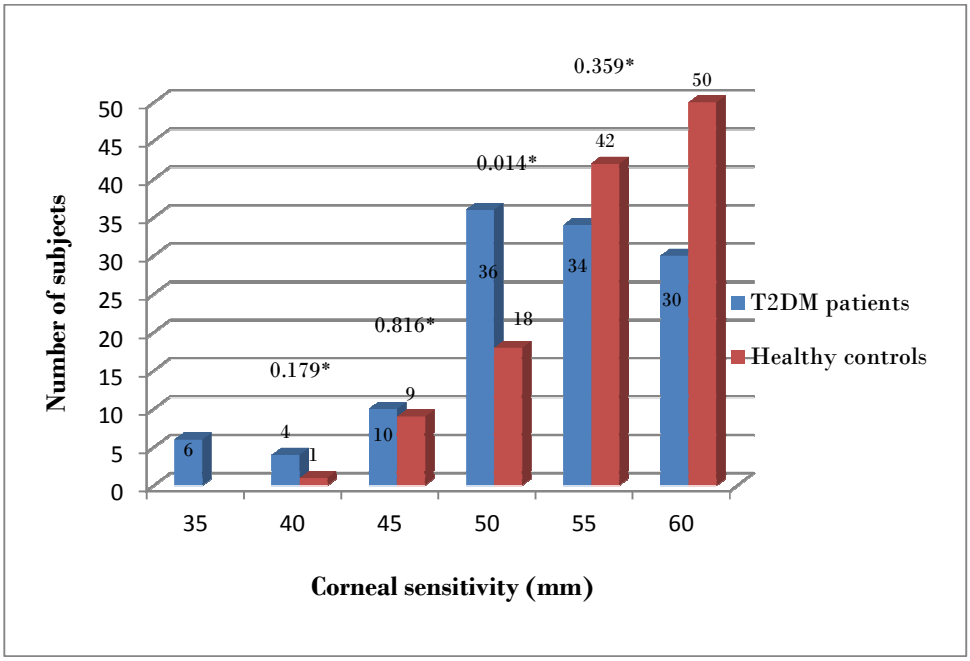

Fig. 1. Frequency of study subjects at different levels of corneal sensitivity
*Key * represents the p-values using non parametric chi-square test*

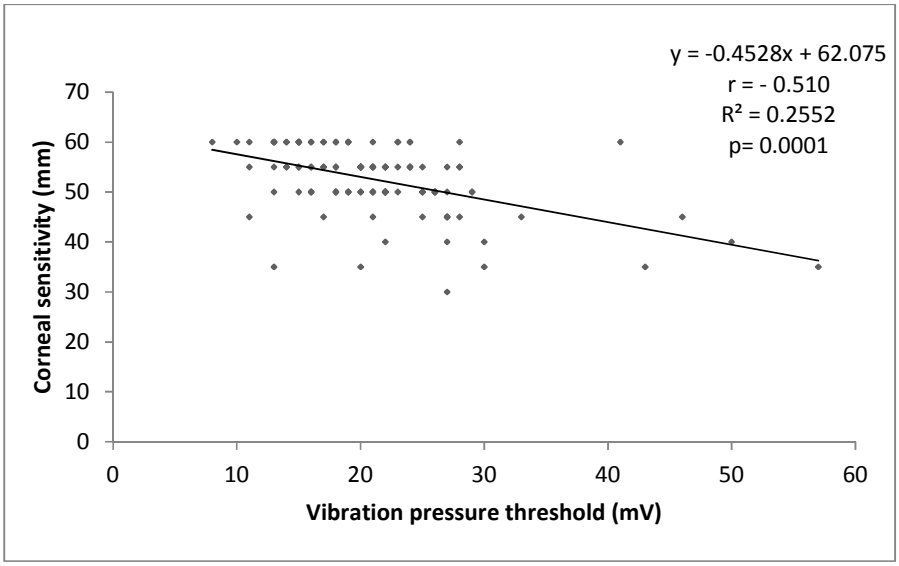

Fig. 2. Relationship between corneal sensitivity and vibration perception threshold (peripheral neuropathy) in diabetics

4.1 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.

4.2 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 60 mm. 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.

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

Non parametric chi-square tests

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 limbs				
Yes	74	61.7	6.53	0.011
No	46	38.3		
Pricking sensation of 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	71.1		
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		

Non parametric chi-square tests

Table 3. Level of corneal sensitivity in study subjects

Variables	Mean ± S.D.	Range	Mean diff ± 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 ± 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 ±0.1	- 4.8 to – 1.0	- 3.019	0.003
Mean value pressure (gm/mm^2)						
Right eye						
Diabetic	0.54 ± 0.16	0.4 to 1.4				
Control	0.47 ±0.09	0.0 to 0.7	0.07 ±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 ± 0.03	0.06 to 0.19	3.855	<0.001

Independent t-tests

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
Mean diff		*-4.5± 0.2*	*0.09 ± 0.04*
p-value		*0.014*	*0.044*
Peripheral neuropathy			
Present	29	46.5 ± 7.2	0.70 ± 0.22
Absent	91	54.2 ± 5.4	0.50 ± 0.11
Mean diff		*-7.7 ± 0.1*	*0.09 ± 0.04*
p-value		*<0.001*	*<0.001*

Two tailed Independent t-tests of analyses
MVP=mean value pressure (gm/mm^2), AVPT = average vibration pressure threshold

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

5. CONCLUSION

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

COMPETING INTEREST

Authors have declared that no competing interests exist.

REFERENCES

1. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20(7):1183–97.
2. American Diabetes Association. Standards of medical care in diabetes--2008. Diabetes Care. 2008; 31(Supplement 1):S12–54.
3. Zimmet PZ, McCarty DJ, de Courten MP. The global epidemiology of non-insulin-dependent diabetes mellitus and the metabolic syndrome. J Diabetes Complications. 1997;11(2):60–8.
4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53.
5. Nyenwe EA, Odia OJ, Ihekwaba AE, Ojule A, Babatunde S. Type 2 diabetes in adult Nigerians: A study of its prevalence and risk factors in Port Harcourt, Nigeria. Diabetes Res Clin Pract 2003;62(3):177–85.
6. Unachukwu C, Uchenna D, Young E. Mortality among diabetes in-patients in Port-Harcourt, Nigeria. African J Endocrinol Metab. 2010;7(1):1–4.
7. Iyagba M. Comparison of clinical scoring systems for the diagnosis of diabetic distal symmetrical poly neuropathy at the University of Port Harcourt Teaching Hospital. A dissertation submitted to the National Post Graduate Medical College of Nigeria; 2013.
8. Vishwanath BS, Darshan MV, Shekar MA. Prevention of chronic complications of diabetes mellitus-does patient education score over treatment? Curr Sci. 2002; 83(12):1435–6.
9. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy and nephropathy in a population-based cohort: The rochester diabetic neuropathy study. Neurology. 1993;43(4):817–24.
10. Smith AG, Ramachandran P, Tripp S, Singleton JR. Epidermal nerve innervation in impaired glucose tolerance and diabetes-associated neuropathy. Neurology. 2001;57(9):1701–04.
11. Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of

diabetic complications. N Engl J Med. 1988;318(20):1315–21.

12. Zochodne DW. Neurotrophins and other growth factors in diabetic neuropathy. Semin Neurol. 1996;16:153–61.
13. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J. 2012;12(1):5–18.
14. Tavakoli M, Kallinikos PA, Efron N, Boulton AJM, Malik RA. Corneal sensitivity is reduced and relates to the severity of neuropathy in patients with diabetes. Diabetes Care. 2007;30:1895–97.
15. Bikbova G, Oshitari T, Tawada A, Yamamoto S. Corneal changes in diabetes mellitus. Curr Diabetes Rev. 2012;8:294–302.
16. McLaughlin PJ, Sassani JW, Klocek MS, Zagon IS. Diabetic keratopathy and treatment by modulation of the opioid growth factor (OGF)-OGF receptor (OGFr) axis with naltrexone: A review. Brain Res Bull. 2010;81(2-3):236–47.
17. Adeoti C, Isawumi M, Ashaye A, Olomola B. The anterior segment of the eye in diabetes. Clin Ophthalmol. 2012;6:667–71.
18. Nwosu SN. Low vision in Nigerians with diabetes mellitus. Doc Ophthalmol. 2000;101(1):51–7.
19. Boberg-Ans J. On the corneal sensitivity. Acta Ophthalmol. 2009;34:149–62.
20. Schultz RO, Van Horn DL, Peters MA, Klewin KM, Schutten WH. Diabetic keratopathy. Trans Am Ophthalmol Soc. 1981;79:180–99.
21. Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology. 2001;108:586–92.
22. Nielsen NV. Corneal sensitivity and vibratory perception in diabetes mellitus. Acta Ophthalmol. 1978;56:406–11.
23. Nuho A, Subekti I, Ismail D, Sitompul R. Correlation of neuropathy with corneal sensitivity and lacrimal gland secretion in type 2 diabetes mellitus patient. Acta Med Indones. 2004;36(3):130–35.
24. Pritchard N, Edwards K, Vagenas D, Russell AW, Malik RA, Efron N. Corneal sensitivity is related to established measures of diabetic peripheral neuropathy. Clin Exp Optom 2012;95: 355–61.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/17027