www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i5.70

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Correlation between Corneal Sensitivity and Peripheral Neuropathy in Patients with Diabetes Mellitus

Authors
Dr Chitra Raghavan[1], Dr V. Sahasranamam[2], Dr Blessy Jacob[3]
Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India
Corresponding Author
Dr V. Sahasranamam
Director, Regional Institute of Ophthalmology, Thiruvananthapuram, 695035, India
Phone Number: +91-9846020421, Email: *drsahasranamam@gmail.com*

Abstract

Purpose: *The objective was to quantitate the loss of corneal sensitivity in patients with diabetic peripheral neuropathy and to determine if it correlates with the stage of DM.*

Materials and Methods: *This is a cross sectional analytical study of all diabetic patients attending the Indian Institute of Diabetes, Trivandrum, outpatient clinic (Jan 2011-- Jun 2012). After detailed medical history and general examination FBS, PPBS and HBA1c were done. Patients underwent a slit lamp examination after which corneal sensitivity was measured using Cochet-Bonnet esthesiometer. The readings were taken at five different points on the cornea (at centre, 12o'clock, 3 o'clock, 6o'clock and 9o'clock) and was repeated three times. The average of all the readings in mm was noted. DPN was assessed by a neurologist using Modified Neuropathy Disability Score. A dilated fundus examination was done to assess the grade of retinopathy. All statistical analysis was performed using SPSS for windows. Pearson's correlation was estimated to explore the functional measures of neuropathy, age, duration of diabetes and HbA1c.*

Results: *Corneal sensitivity was absent, mild, moderate and severe in 26.9%, 20.9%, 31.3% and 20.9% of diabetic patients. Neuropathy was absent in 10.4%. There was a significant correlation between duration of diabetes and the decrease in corneal sensation. A strong negative correlation existed between the severity of peripheral neuropathy and reduction in corneal sensation.*

Conclusion: *Loss of corneal sensation occurring in diabetic patients is easily quantifiable and correlates with neuropathy and progresses with the severity of neuropathy. These findings have important clinical implications regarding the development of corneal abnormalities in diabetic patients and also raise the possibility that corneal sensation could be used to screen for diabetic neuropathy.*

Keywords: *Corneal sensitivity, Diabetic peripheral neuropathy, Cochet-Bonnet esthesiometer.*

Introduction

Fifty per cent of diabetic patients develop neuropathies due to progressive loss of nerve fibres which in turn leads to foot ulceration and amputations[1]. There are several theories explaining the pathogenesis of DPN like polyol pathway, accumulation of advanced glycosylation end products, low level of growth factors, free radical oxidative stress and immunologic factors[2],[3]. DPN affects both the small and large peripheral nerves. The current gold standard for diagnosis of DPN is vibration perception using biothesiometer[4]. But it measures function of large nerve fibres while DPN

primarily affects small nerve fibres[5],[6]. Assessing the small fibre damage using skin punch biopsy is invasive and non-repeatable[7].and patients are prone for infection[8]. The density of corneal epithelial nerves is 300–600 times higher than that of the skin with approximately 7000 nociceptors /m2[9]. Cornea derives its innervation from the ophthalmic division of trigeminal nerve and contains primarily A^{δ} and Unmyelinated C fibres which are impaired in diabetic neuropathy[10]. Malik et al[10] was the first to describe significant association between corneal nerve fibre damage and neuropathic severity in diabetic patients. Alterations of the corneal nerves decrease the corneal sensitivity resulting in corneal hypoesthesia that disrupts the epithelial architecture and function. Corneal sensitivity appears to be reduced in approximately 20% of diabetic patients[12], [13]. The functioning of the corneal nerve is assessed by corneal sensitivity tests. There are three main groups of receptors in the cornea: mechanical or mechano-nociceptors, chemical or polymodal nociceptors, and thermal or cold receptors[13],[14]. Although less sensitive and repeatable than NCCA, CB esthesiometry is best correlated with functional measures of peripheral neuropathy[13],[14]. Corneal sensitivity can be assessed by Cochet Bonnet (CB) esthesiometer and non-contact corneal esthesiometry (NCCA)[15],[16]. High mechanical threshold, measured using the Cochet-Bonnet esthesiometer, was reported in DM patients. Low corneal sensitivity in DM patients has been associated to the degree of sensory neuropathy and retinopathy, age, and duration of the disease.[17],[18]. Recently many studies have explored corneal sensitivity as a potential marker of DPN[19]. CB esthesiometry being minimally invasive is used as a standard method for assessing corneal sensitivity[20]. A quantitative determination of corneal sensation may diagnose early peripheral neuropathy thereby preventing sight threatening complications. This study aims to find out if there is any correlation between corneal sensitivity measured using Cochet Bonnet esthesiometer and severity of peripheral neuropathy graded according to Neuropathy Disability Scoring in patients with diabetes mellitus. It also analyse the relation of corneal sensitivity to the duration and control of diabetes; and is corneal sensitivity decreased before the onset of peripheral neuropathy.

Research

Design and Method

This is a cross sectional analytical study of all diabetic patients attending the Indian Institute of Diabetes, Trivandrum, outpatient clinic (Jan 2011--Jun 2012). Subjects who have undergone previous ocular surgeries and those with conditions known to affect corneal sensitivity viz .Connective tissue disorders, corneal dystrophies, history of viral keratitis, contact lens wearers were excluded. A sample size of 67 was obtained using the formula N=8/r2+ 2 assuming the correlation between corneal sensitivity and peripheral neuropathy is r=--0.35. After detailed medical history and general examination FBS, PPBS and HBA1c were done. Patients underwent a slit lamp examination after which corneal sensitivity was measured using Cochet-Bonnet esthesiometer. Its filament was extended to 60 mm. The tip of the fibre was steadily advanced towards the cornea. When the end plate of nylon filament was found to be in contact with cornea, a mild pressure was exerted such that fibre had the slightest bend just visible. The response was assessed either by subjective response of patient or by objective blinking or withdrawal response. If there was no response the fibre length was shortened in steps of 5 mm each time and procedure was repeated till a response was elicited. The readings were taken at five different points on the cornea (at centre, 12o'clock, 3o'clock, 6o'clock and 9o'clock) and were repeated three times. The average of all the readings in mm was noted. At times 'blanks' were given to test patient's reliability and only reliable data was included. DPN was assessed by a neurologist using Modified Neuropathy Disability Score (table 1). A dilated fundus examination was done to assess the grade of retinopathy. All statistical analysis was performed using SPSS for windows (version 17.0; SPSS, Chicago, IL). The following tests were performed:

Chi-- square test and Pearson's correlation coefficient.

Results

Of the subjects 57.40% were males. Age distribution is shown in table 2. The percentage of patients with different risk factors is shown in table 3. Duration of diabetes in the subjects are shown in table 4. HbA1c was greater than 7 in 55.2%. Corneal sensation measured is tabulated in table 5.Correlation between age and corneal sensation was not significant as shown in table 6. Peripheral neuropathy score is shown in table 7. There was a significant correlation between duration of diabetes and the decrease in corneal sensation (chi square = 26.31; $p < 0.05$) (Table 8). Corneal sensation significantly correlated with retinopathy (Table 9). A strong negative correlation existed between the severity of peripheral neuropathy and reduction in corneal sensation($r = -0.773$, $p<0.0001$) (Table 10). Pearson's correlation estimated to explore the functional measures of neuropathy, age, duration of diabetes, HbA1c are shown in (Table 11).

Figure 1: Association between corneal sensation and peripheral neuropathy

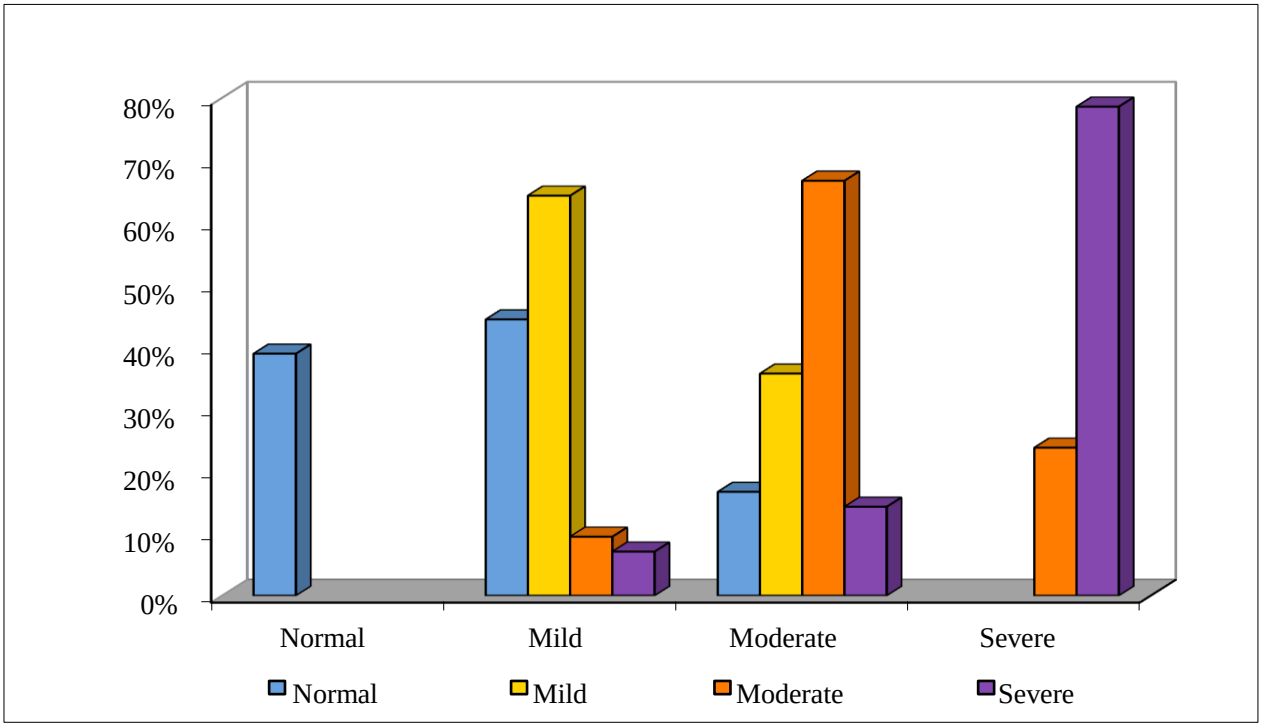

Table 1: NDS to assess peripheral neuropathy

NDS			
		Right	Left
VPT 128 Hz tuning fork; apex of big toe: normal = can distinguish vibrating/not vibrating	Normal = 0; abnormal = 1		
Temperature perception on dorsum of the foot Use tuning fork with beaker of ice/warm water			
Pin prick Apply pin proximal to big toenail just enough to deform the skin; trial pair = sharp, blunt; normal = can distinguish sharp/not sharp			
Achilles reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS total out of 10		

Table 2: Age distribution

Age (Code)	Percent
< 50 yrs.	11.90%
50 --- 59	41.80%
60 --- 69	29.90%
70 --- 79	13.40%
>= 80 yrs.	3%

Table 3: Frequency of associated risk factors

Risk factors	Percentage
Smoking	29.90%
Hypertension	73.1%
Hyperlipidaemia	58.2%
Coronary artery disease	23.90%

Table 4: Frequency of duration of diabetes

DM duration	Frequency	Per cent
< 5 years	3	4.5%
6-10	24	35.8%
11-15	29	43.3%
16-20	6	9%
>20	5	7.5%
Total	67	100%

Table 5: Grades of loss of corneal sensation

Corneal sensation	Frequency	Per cent
Normal	18	26.9%
Mild	14	20.9%
Moderate	21	31.3%
Severe	14	20.9 %
Total	67	100%

Table 6: Correlation between corneal sensation and age

Age	Corneal Sensation Grade				Total
	Normal	Mild	Moderate	Severe	
< 50 yrs.	6	1	1		8
	33.30%	7.10%	4.80%		11.90%
50 --- 59	10	9	5	4	28
	55.60%	64.30%	23.80%	28.60%	41.80%
60 --- 69	2	3	8	7	20
	11.10%	21.40%	38.10%	50.00%	29.90%
70 --- 79		1	6	2	9
		7.10%	28.60%	14.30%	13.40%
>= 80 yrs.			1	1	2
			4.80%	7.10%	3.00%
Total	18	14	21	14	67
Chi Square; 27.711; P < 0.01					

Table 7: Peripheral neuropathy as assessed by NDS

Peripheral neuropathy score	Frequency	Per cent
Normal	7	10.4%
Mild	20	29.9%
Moderate	21	31.3%
Severe	19	28.4 %
Total	67	100%

Table 8: Correlation between corneal sensitivity and duration of DM

Duration of DM	Corneal Sensation Grade				Total
	Normal	Mild	Moderate	Severe	
<= 5 yrs.	3				3
	16.70%				4.50%
06 --- 10	10	8	3	3	24
	55.60%	57.10%	14.30%	21.40%	35.80%
11 --- 15	5	5	12	7	29
	27.80%	35.70%	57.10%	50.00%	43.30%
16 --- 20			3	3	6
			14.30%	21.40%	9.00%
> 20 yrs.		1	3	1	5
		7.10%	14.30%	7.10%	7.50%
Total	18	14	21	14	67
Chi Square; 26.313; P < 0.05					

Table 9: Correlation between corneal sensitivity and diabetic retinopathy

Diabetic retinopathy stage	Corneal Sensation Grade				Total
	Normal	Mild	Moderate	Severe	
No Diabetic Retinopathy	10	9	2		21
	47.61	42.85	9.50%		31.30%
Mild	7	4	8	2	21
	33.33%	19.04%	38.09%	9.5%	31.30%
Moderate	1	1	9	6	17
	5.88%	5.88%	52.90%	35.29%	25.40%
Severe			2	5	7
			28.57%	71.40%	10.40%
P. Diabetic Retinopathy				1	1
				100%	1.50%
Total	18	14	21	14	67
Chi Square; 42.295; P < 0.001					

Table 10: Correlation between corneal sensitivity and peripheral neuropathy

Peripheral Neuropathy Score	Corneal Sensation				Total
	Normal	Mild	Moderate	Severe	
Normal	**7**				**7**
	38.90%				**10.40%**
Mild	8	9	2	1	20
	44.40%	64.30%	9.50%	7.10%	29.90%
Moderate	3	5	13		21
	16.70%	35.70%	61.90%		31.30%
Severe			6	13	19
			28.60%	92.90%	28.40%
Total	18	14	21	14	67
Chi Square; 72.807; P < 0.001					

Table11: Pearson Correlations

		Age (yrs.)	DM: Duration	rbs	hba1c	fundus	Corneal Sensation: Score	Peripheral Neuropathy: Score (Code)
Age (yrs.)	Pearson Correlation	1.000	.797**	.340**	.307*	.394**	-.588**	.520**
	Sig. (2-tailed)	.	.000	.005	.012	.001	.000	.000
	N	67	67	67	67	67	67	67
DM: Duration	Pearson Correlation	.797**	1.000	.454**	.347**	.336**	-.464**	.440**
	Sig. (2-tailed)	.000	.	.000	.004	.005	.000	.000
	N	67	67	67	67	67	67	67
rbs	Pearson Correlation	.340**	.454**	1.000	.789**	.474**	-.460**	.524**
	Sig. (2-tailed)	.005	.000	.	.000	.000	.000	.000
	N	67	67	67	67	67	67	67
hba1c	Pearson Correlation	.307*	.347**	.789**	1.000	.476**	-.453**	.465**
	Sig. (2-tailed)	.012	.004	.000	.	.000	.000	.000
	N	67	67	67	67	67	67	67
fundus	Pearson Correlation	.394**	.336**	.474**	.476**	1.000	-.680**	.602**
	Sig. (2-tailed)	.001	.005	.000	.000	.	.000	.000
	N	67	67	67	67	67	67	67
Corneal Sensation: Score	Pearson	-.588**	-.464**	-.460**	-.453**	-.680**	1.000	-.773**
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.	.000
	N	67	67	67	67	67	67	67
Peripheral Neuropathy: Score (Code)	Pearson Correlation	.520**	.440**	.524**	.465**	.602**	-.773**	1.000
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.
	N	67	67	67	67	67	67	67

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Discussion

In this study corneal sensation was shown to be reduced in diabetics and correlated with the duration of diabetes ($p<0.01$) with the severity increasing with duration greater than 11 yrs. This is in accordance with the studies done by Tavakoli[13] et al and Murphy PJ[21] et al. Tavakoli et al suggested using confocal microscopy in longitudinal studies to assess progression of diabetic neuropathy that patients with diabetic autonomic neuropathy had a progressive and significant reduction of corneal nerve fiber density, branch density, and length compared to healthy control subjects. In the study by Nielsen[23], it was demonstrated that corneal sensitivity (determined using Cochet and Bonnet's esthesiometer) in 83% of diabetic patients was reduced below 60 mm against 38% of the controls alongside with reduced perception of vibrations (vibratory perception of the left index finger and great toe by biothesiometer). Dogru M[24] et al showed that the mean corneal sensitivity was significantly lower in diabetic patients, diabetic patients with peripheral neuropathy, and poorly controlled diabetes compared with control subjects ($P < 0.001$). Edwards[7] et al showed that patients with diabetic peripheral neuropathy had significantly reduced corneal nerve fiber length and branch density compared to controls and patients with diabetes but without diabetic peripheral neuropathy.

Ziegler[25]et al and Petropoulos[26] et al showed a reduction in corneal nerve fiber length, corneal nerve fiber density, and nerve fiber branch density has been found with increasing neuropathic severity in both types 1 and type 2 diabetes. Rosenberg[12] et al using confocal microscopy found that patients with diabetes had fewer nerve fiber bundles in sub basal nerve plexus than healthy control subjects possibly due to the presence of polyneuropathy. Also Pritchard[16] et al reported application of

confocal microscopy in assessment of diabetic polyneuropathy by measuring the corneal nerve fiber length, ability of confocal microscopy to predict the development of diabetic polyneuropathy with 63% sensitivity and 74% specificity, for a corneal nerve fiber length threshold cut-off of 14.1 mm/mm2 was demonstrated. Mishra[27] et al also described a clinical application of in vivo confocal microscopy in patients with diabetes mellitus type 1. They also found a significant relationship between corneal neuropathy and systemic neuropathy. They concluded that corneal neuropathy might be an early indicator of diabetic neuropathy because it preceded other clinical and electrophysiology tests of neuropathy. GAO[28] et al considered that DM damaged the neural communications of dendritic cells and impaired sensory nerve regeneration resulting in diabetic neuropathy. Diabetic-induced denervation of the cornea, damage the integrity of corneal epithelial cells and their ability to recover from injury. DM decreases the density of sensory nerve in the cornea. They found decreased number of dendritic cells is in tune with a decrease nerve fibers density. DM impairs communication between dendritic cells and nerve causing diabetic peripheral neuropathy. Mylonas[29] et al proved a decrease in corneal sensitivity may cause a delay in epithelial wound healing and be the cause of recurrent erosions. This is because the corneal nerves release epitheliotropic substances that promote the maintenance of the integrity of corneal surface. Abbott CA[30] et al showed NDS to be clinically useful in detecting neuropathy and in particular to help predict those at risk of foot ulceration. Malik RA[11] et al has established Impaired glucose tolerance (IGT)-related neuropathy may represent the earliest stage of diabetic neuropathy, because several groups have demonstrated that up to 40% of individuals with idiopathic neuropathy have IGT compared with <15% in the age-matched general population. Early detection is important because effective intervention must be aimed at a stage when there is a capacity for the nerve to repair, specifically in the subclinical or early phase of identifiable nerve damage.

Quantitative sensory testing (QST) and electrophysiology are more sophisticated and are considered to be more sensitive for diagnosing and staging diabetic neuropathy; however, their utility in detecting early neuropathy where small fibers are damaged is limited, because they primarily measure large myelinated nerve fiber function. Several recent studies show significant small fiber abnormalities in diabetic patients with normal electrophysiology and QST [31], [32].

Conclusion

Loss of corneal sensation is easily quantifiable, occurs in diabetic patients with mild to moderate somatic neuropathy, and progresses with the severity of neuropathy. These findings have important clinical implications regarding the development of corneal abnormalities in diabetic patients and also raise the possibility that corneal sensation could be used to screen for diabetic Neuropathy.

References

1. Chawla A, Chawla R, Jaggi S. Microvasular and macro vascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016;20(4):546
2. Komolafe R, Pedro-Egbe C, Awoyesuku E. Correlation between corneal sensitivity and peripheral neuropathy in type 2 diabetics attending the Endocrinology Clinic of University of Port Harcourt Teaching Hospital (UPTH), Nigeria. Ophthalmol Res An Int J. 2016;6(3):1–9
3. Giacco F. Oxidative stress and diabetic complications. Circ Res. 2011;107(9):1058–70.
4. Albers, J.W., Brown, M.B., Sima, A.A., and Greene, D.A. Nerve conduction measures in mild diabetic neuropathy in the Early Diabetes Intervention Trial: the effects of age, sex, type of diabetes, disease duration, and anthropometric factors. Tolrestat Study Group for the Early Diabetes Intervention Trial. Neurology. 1996; 46: 85–91.

5. Sveen, K.A., Karime, B., Jorum, E., Mellgren, S.I., Fagerland, M.W., Monnier, V.M. et al. Small- and large-fiber neuropathy after 40 years of type 1 diabetes: associations with glycemic control and advanced protein glycation: the Oslo Study. Diabetes Care. 2013; 36: 3712–3717.
6. Malik, R.A., Veves, A., Tesfaye, S., Smith, G., Cameron, N., Zochodne, D. et al. Small fibre neuropathy: role in the diagnosis of diabetic sensorimotor polyneuropathy. Diabetes Metab Res Rev. 2011; 27: 678–684.
7. Edwards, K., Pritchard, N., Vagenas, D., Russell, A., Malik, R.A., and Efron, N. Utility of corneal confocal microscopy for assessing mild diabetic neuropathy: baseline findings of the LANDMark study. Clin Exp Optom. 2012; 95: 348–354.
8. Perry, J.R. and Bril, V. Complications of Sural nerve biopsy in diabetic versus non-diabetic patients. Can J Neurol Sci. 1994; 21: 34–37
9. E.Zander and G.Weddell, "Observations on the innervation of the cornea," Journal of Anatomy, vol. 85, no. 1, pp. 68–99, 1951.
10. Loseth S, Stalberg E, Jorde R, Mellgren SI. Early diabetic neuropathy: thermal thresholds and intra-epidermal nerve fibre density in patients with normal nerve conduction studies. J Neurol 2008; 255:1197–202.
11. Malik RA, Kallinikos P, Abbott CA, van Schie CH, Morgan P, Efron N, Boulton AJ. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia 2003; 46:683–8.
12. .Rosenberg ME,Tervo TM, Immonen IJ, Muller LJ, Gronhagen-Riska C, Vesaluoma MH . Corneal structure and sensitivity in type 1 diabetes mellitus. Invest Ophthalmol Vis Sci. 2000; 41:2915–2921.
13. Tavakoli M, Kallinikos PA, Efron N, Boulton AJ, Malik RA. Corneal sensitivity is reduced and relates to the severity of neuropathy in patients with diabetes. Diabetes Care. 2007;30:1895–1897
14. L. Henderson, D. Bond, and T. Simpson, "The association between eye colour and corneal sensitivity measured using a Belmonte esthesiometer," Optometry and Vision Science, vol. 82, no. 7, pp. 629–632, 2005.
15. C. Belmonte, M. C. Acosta, and J. Gallar, "Neural basis of sensation in intact and injured corneas," Experimental Eye Research, vol. 78, no. 3, pp. 513–525, 2004
16. 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(3):355–61
17. Inoue K, Kato S, Ohara C, Numaga J, Amano S, Oshika T . Ocular and systemic factors relevant to diabetic keratoepithe-liopathy. Cornea. 2001; 20:798–801.
18. Ruben ST. Corneal sensation in insulin dependent and non-insulin dependent diabetics with proliferative retinopathy. Acta Ophthalmol (Copenh). 1994; 72:576–580.
19. Rogell GD. Corneal hypesthesia and retinopathy in diabetes mellitus. Ophthalmology. 1980Mar; 87:229–233.
20. Cousen P, Cackett P, Bennett H, Swa K, Dhillon B. Tear production and corneal sensitivity in diabetes. J Diabetes Complicat. 2007; 21:371–373.
21. Murphy PJ, Patel S, Kong N, Ryder RE, Marshall J. Noninvasive assessment of corneal sensitivity in young and elderly diabetic and nondiabetic subjects. Invest Ophthalmol Vis Sci. 2004; 45:1737–1742.
22. Pritchard N, Edwards K, Vagenas D, et al. Corneal sensitivity as an ophthalmic marker of diabetic neuropathy. Optom Vis Sci. 2010;87(12):1003–8
23. Nielsen N. V. Corneal sensitivity and vibratory perception in diabetes mellitus. Acta Ophthalmologica. 1978; 56(3):406–411.

24. Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology. 2001 Mar; 108(3):586-92.
25. Ziegler, D, Papanas, N., Zhivov, A, Allgeier, S., Winter, K. Early detection of nerve fiber loss by corneal confocal microscopy and skin biopsy in recently diagnosed type 2 diabetes. 2014; 63: 2454–2463
26. Petropoulos, I.N., Alam, U., Fadavi, H., Asghar, O., Green, P., Ponirakis, G. Corneal nerve loss detected with corneal confocal microscopy is symmetrical and related to the severity of diabetic polyneuropathy. Diabetes Care. 2013; 36: 3646–3651
27. Misra SL, Crag JP, Patel DV, McGhee CN, Pradhan M, Ellyett K, Klfoyle D, Braatvedt GD. In Vivo Confocal Microscopy of Corneal nerves: An ocular biomarker for peripheral and cardiac autonomic neuropathy in type 1 diabetes mellitus. World J Diabetes. 2016 Sep 15; 7(7):406-411.
28. Nan Gao, Chenxi Yan,Fu Shin Yu. Dendritic cell dysfunction and diabetic sensory neuropathy in the cornea. J Clin Invest. 2016 May2; 126(5):1998-2011.
29. Mylonas P. G., Matsouka P. T., Papandoniou E. V., Vagianos C., Kalfarentzos F., Alexandrides T. K. Growth hormone and insulin-like growth factor I protect intestinal cells from radiation induced apoptosis. Molecular and Cellular Endocrinology. 2000;160(1-2):115–122.doi: 10.1016/S0303-7207(99)00215-4.
30. Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, Hann AW, Hussein A, Jackson N, Johnson KE, Ryder CH, Torkington R, Van Ross ER, Whalley AM, Widdows P, Williamson S, Boulton AJ. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002;19:377–384
31. Quattrini C, Tavakoli M, Jeziorska M, Kallinikos P, Tesfaye S, Finnigan J, Marshall A, Boulton AJ, Efron N, Malik RA. Surrogate markers of small fiber damage in human diabetic neuropathy. Diabetes 2007; 56:2148–54.
32. Umapathi T, Tan WL, Loke SC, Soon PC, Tavintharan S, Chan YH. Intraepidermal nerve fiber density as a marker of early diabetic neuropathy. Muscle Nerve 2007; 35:591–8.