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

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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, 12 o'clock, 3 o'clock, 6 o'clock and 9 o'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\textsuperscript{[5,6]}\textsuperscript{[5,6]}. Assessing the small fibre damage using skin punch biopsy is invasive and non-repeatable\textsuperscript{[7]}\textsuperscript{[7]} and patients are prone for infection\textsuperscript{[8]}\textsuperscript{[8]}. The density of corneal epithelial nerves is 300–600 times higher than that of the skin with approximately 7000 nociceptors /m\textsuperscript{2}\textsuperscript{[9]}. Cornea derives its innervation from the ophthalmic division of trigeminal nerve and contains primarily A\textsuperscript{δ} and Unmyelinated C fibres which are impaired in diabetic neuropathy\textsuperscript{[10]}\textsuperscript{[10]}. Malik et al\textsuperscript{[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\textsuperscript{[12,13]}\textsuperscript{[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\textsuperscript{[13,14]}\textsuperscript{[13,14]}. Although less sensitive and repeatable than NCCA, CB esthesiometry is best correlated with functional measures of peripheral neuropathy\textsuperscript{[13,14]}\textsuperscript{[13,14]}. Corneal sensitivity can be assessed by Cochet Bonnet (CB) esthesiometer and non-contact corneal esthesiometry (NCCA)\textsuperscript{[15,16]}\textsuperscript{[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\textsuperscript{[17,18]}\textsuperscript{[17,18]}. Recently many studies have explored corneal sensitivity as a potential marker of DPN\textsuperscript{[19]}\textsuperscript{[19]}. CB esthesiometry being minimally invasive is used as a standard method for assessing corneal sensitivity\textsuperscript{[20]}\textsuperscript{[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/r\textsuperscript{2}+ 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 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 extended to 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, 12\’o’clock, 3\’o’clock, 6\’o’clock and 9\’o’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

![Figure 1](image_url)

**Table 1:** NDS to assess peripheral neuropathy

| NDS | Right | Left |
|-----|-------|------|
| **VPT**<br>128 Hz tuning fork; apex of big toe:<br>normal = can distinguish vibrating/not vibrating | | |
| **Temperature perception on dorsum of the foot**<br>Use tuning fork with beaker of ice/warm water | Normal = 0; abnormal = 1 | |
| **Pin prick**<br>Apply pin proximal to big toenail just enough to deform the skin; trial pair = sharp, blunt; normal = can distinguish sharp/not sharp | | |
| **Achilles reflex**<br>Present = 0<br>Present with reinforcement = 1<br>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      | Normal | Mild | Moderate | Severe | Total |
|----------|--------|------|----------|--------|-------|
| < 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        |        | 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% |      |          |        |       |
| 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      | 17    |
|                           | 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% |      |          |        |       |
| 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
Table 11: 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 Correlation | -588** | -466** | -466** | -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 | .530** | .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 et al and Murphy PJ 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, 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 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 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 et al and Petropoulos 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 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 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.

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