Assessment of corneal nerve structure and peripheral nerve function in detection of diabetic peripheral neuropathy

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Introduction

- Diabetic peripheral neuropathy (DPN) is a progressive complication of diabetes that leads to lower limb sensory and motor dysfunction.
- Standard nerve conduction studies may not be sensitive enough to detect early changes in nerve function that occur prior to the onset of structural change.[1]
- Nerve excitability is a non-invasive technique that allows the assessment of sodium and potassium ion-channel function in the nodal and internodal regions of the axon (Figure 1).[2]
- Previous studies have shown that patients with type 1 diabetes have impaired ion-channel activity in the axonal membrane.[2]
- Structural changes to the corneal nerves have been observed using *in vivo* corneal confocal microscopy (Figure 2) and serve as a **biomarker** for nerve fiber damage in diabetic peripheral neuropathy.[3]
- There have been no controlled studies which compared the diagnostic ability of these two techniques.

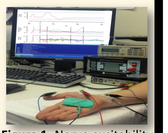

Figure 1. Nerve excitability studies

Figure 2. *In vivo* corneal confocal microscopy

Purpose

- To compare the ability of corneal nerve fiber assessment and axonal ion-channel function to diagnose DPN in type 1 diabetes.

Methods

- **Study design:**
  - A total of 49 subjects with type 1 diabetes and 19 age-matched controls (mean age of 35 ± 15 and 32 ± 7 years, respectively) were enrolled.
  - Average glycosylated hemoglobin and body mass index of diabetes group was 64.15 ± 16.34 mmol/mol and 25.44 ± 3.45 kg/m^2, respectively.
  - Participants with Type 1 diabetes were classified based on the total neuropathy scores (TNS): those with neuropathy group (DPN+; TNS > 1; n = 14) and without neuropathy group (DPN-; TNS < 1; n = 35).
- **Exclusion criteria:** Medical illnesses and treatment associated with neuropathy, current eye infections, corneal abrasions, history of refractive surgery or anterior segment trauma.
- **Corneal confocal microscopy:** All participants underwent corneal confocal microscopy in both eyes to assess fiber length, density, branch density, total branch density, width and inferior whorl length (corneal nerve length at the inferior whorl).
- **Nerve excitability studies:** Motor excitability studies were conducted on the median nerve to assess axonal ion-channel function in nodal and internodal regions of the axonal membrane. Parameters obtained included threshold electrotonus and recovery cycle.
- **Statistical analysis:**
  - One-way ANOVA or Kruskal-Wallis to assess differences between groups.
  - Receiver operating characteristic curves (ROCs) analyses to estimate of area under curve (AUC) and define the optimal cut offs to diagnose DPN. Statistical significance was defined as $P < 0.05$.

Results

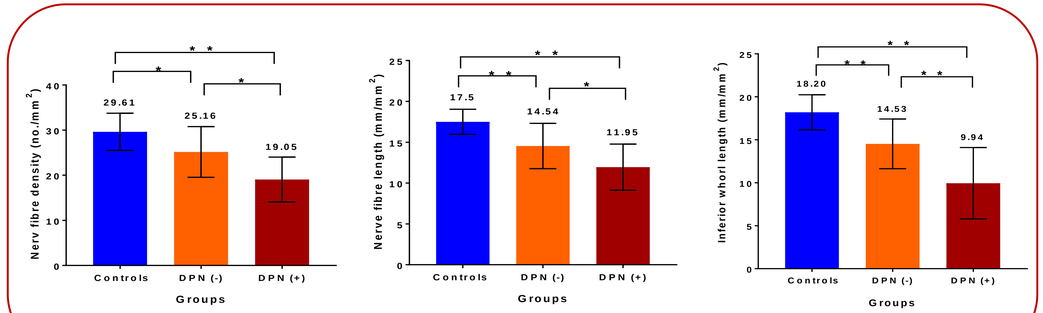

Figure 3. Corneal nerve morphology in control subjects and diabetic patients with DPN(+) and without neuropathy, DPN(-). **P<0.001; *P< 0.05

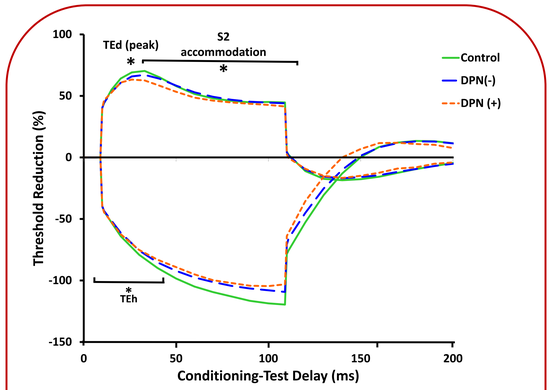

Figure 4. Mean excitability data in controls and in patients with DPN(+) and DPN(-); *P<0.05; TE illustrating the reductions in S2 accommodation, TEd and TEh; TE provides information on internodal properties and axonal membrane potential; DPN = Diabetic peripheral neuropathy; TEd = depolarizing threshold electrotonus; TEh = hyperpolarizing threshold electrotonus

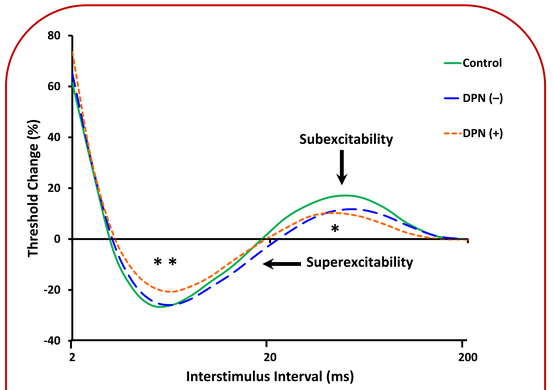

Figure 5. Mean excitability data of recovery cycle in control subjects and in patients with DPN(+) and DPN(-); *P<0.001; *P<0.05; Recovery cycles illustrating the reductions in superexcitability and subexcitability; Recovery cycle provides indirect information on sodium and potassium ion-channel activity at the nodal and paranodal regions of the axon; DPN = Diabetic peripheral neuropathy

Table 1.ROC of neuropathy measures for the diagnosis DPN in type 1 diabetes

Variable	AUC	Sensitivity	Specificity	Cut-off value	*P* value
IWL (mm/mm^2)	0.880	84	78	12.53	<0.001
CNFD (no./mm^2)	0.827	75	78	23.63	0.002
CNFL (mm/mm^2)	0.794	71	89	14.28	0.005
Peak response (mV)	0.761	67	66	10.25	0.014
TEd (peak) (%)	0.744	73	67	63.54	0.024

Abbreviations: ROC, receiver operating characteristic curves; AUC, area under curve; IWL, inferior whorl length; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; TEd, depolarizing threshold electrotonus; mm, millimetre; mV, millivolt; no., number

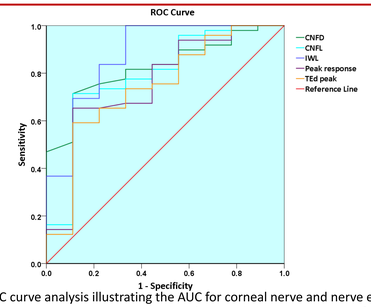

Figure 6. ROC curve analysis illustrating the AUC for corneal nerve and nerve excitability parameters: ROC curves = Receiver operating characteristic curves ; IWL = Inferior whorl length, CNFD = Corneal nerve fiber density, CNFL = Corneal nerve fiber length, TEd = Depolarizing threshold electrotonus, AUC = Area under curve

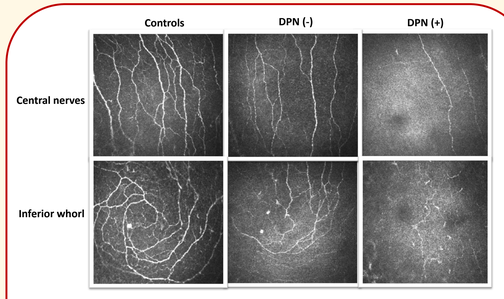

Figure 7. Central and IWL mages for a control subject and a DPN (-)and DPN (+) patient demonstrating nerve depletion affecting both areas and the IW particularly in DPN(+).

Conclusions

- Participants with DPN had a significant reduction in corneal nerve fiber density, nerve fiber length and inferior whorl length compared to DPN- and controls.
- Reduction in threshold electrotonus measures in DPN+ compared to controls is suggestive of reduced nodal and internodal conductances. Superexcitability, a marker of nodal and juxta paranodal sodium and potassium ion channel function is markedly reduced in DPN+ compared to DPN- and controls.
- Inferior whorl length had the highest area under curve (0.880) in distinguishing the DPN+ from controls and DPN-, with an optimal cut off value of 12.53 mm/mm^2 (Table 1 and Figure 6).
- Corneal inferior whorl length, nerve fiber density and nerve fiber length were able to diagnose DPN with higher sensitivity than measures of nerve excitability studies.
- The assessment of corneal nerve structure may provide an indication of early nerve damage prior to the onset of clinical signs and symptoms of diabetic peripheral neuropathy. Therefore, this may provide a window of opportunity to intervene and prevent the progression of early neuropathy in type 1 diabetes.

References

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