

IDNC

INTERNATIONAL DIABETIC NEUROPATHY CONSORTIUM

CORNEAL CONFOCAL MICROSCOPY: SURROGATE END POINT OR FALSE PROPHET?

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Formal neurological examination, including nerve conduction studies, pressure and light touch perception with monofilaments, and vibration tests have limited utility in early DPN. These tests assess large myelinated (A β) nerve fibres, which account for only 10% of peripheral nerves. In contrast, the majority of nerves are comprised of small unmyelinated C fibres and thinly myelinated A δ fibres, and these are the earliest to be damaged, before any abnormalities in the larger fibres can be demonstrated. The density of unmyelinated C fibres in the epidermis (intraepidermal nerve fibre [IENF]) is decreased early in the course of diabetes, when electrophysiology is still normal. Although skin biopsy is minimally invasive and rarely results in complications

(less than 2 per 1000), it is uncomfortable and infection and bleeding can occur. In contrast to the skin, which contains 200 nerves/mm², the nerve density in the cornea is approximately 7000/mm², making the cornea one of the most densely innervated tissues in the body. Both IENF and CCM can be used to objectively and accurately quantify small nerve fibre damage in diabetic patients. Although skin biopsy is still advocated as the 'gold standard', CCM has become the diagnostic modality of choice, because quantification of changes in the cornea is rapid, non-invasive and may be able to detect earlier stages of nerve damage than biopsy with IENF.¹⁻⁴ In a recent comparative study of CCM and IENF the area under the receiver

operating characteristic curve for identifying DPN was 0.82 for manual CNFD, 0.80 for automated CNFD, and 0.66 for IENF density.⁵ Furthermore, IENF length, corneal nerve fibre length (CNFL) and CNFD are significantly lower in patients with painful diabetic neuropathy than in those with painless neuropathy.

CCM may also have potential for predicting which individuals will later develop DPN.

In a prospective study of 65 patients with type 1 diabetes who underwent CCM with clinical and electrophysiologic examinations at baseline and after a mean of 3.5 years, 17% developed DPN during the course of follow-up. These patients with incident DPN were similar to controls in terms of baseline age, diabetes duration, gender, glycated haemoglobin levels and electrophysiologic parameters, but had significantly lower baseline CNFL and branch density. The optimal threshold for CNFL was 14.9 mm/mm² (sensitivity 0.82 and specificity 0.69).⁶

Among 30 subjects with impaired glucose tolerance who underwent CCM at baseline and annually for 3 years, 10 who developed type 2 diabetes had significantly lower CNFD, CNBD and CNFL at baseline in comparison to 17 age-matched control subjects. CNFL, IENF density and mean dendritic length (MDL) were further reduced after 3 years. In contrast, 15 IGT subjects who did not develop type 2 diabetes did not differ significantly from controls in terms of CCM parameters or IENF density at baseline. In this group, over 3 years, although there was a significant decrease in IENF density, there was no change in CCM or MDL.⁷

Nerve fibre loss is not limited to DPN and CCM may also be a useful diagnostic and monitoring tool for a variety of patients with other painful neuropathies. Using CCM, fibre loss has been demonstrated in Fabry disease, idiopathic small fibre neuropathy, Charcot-Marie-Tooth disease and neuropathies associated with chemotherapy, sarcoidosis

and CIDP. More recently CCM has also been found to be abnormal in Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease and Multiple Sclerosis.

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2. Quattrini C, Tavakoli M, Jeziorska M, et al. Surrogate markers of small fibre damage in human diabetic neuropathy. *Diabetes* 2007; 56: 2148-2154.
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