

Editorial

Corneal confocal microscopy for the assessment of diabetic neuropathy and beyond in Brazil

Microscopia confocal da córnea para a avaliação de neuropatia diabética no Brasil

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The study by Pupe et al.¹ is the first paper from Brazil and indeed South America showing that corneal confocal microscopy (CCM) can identify small nerve fiber damage and increased Langerhans cells in patients with diabetic neuropathy. Despite the inclusion of only 35 patients with diabetes and overall good glycemic control, corneal nerve loss was evident in patients with ‘mild neuropathy’ based on symptoms and nerve conduction, which progressively worsened with increasing severity of the diabetic neuropathy. Furthermore, corneal nerve fiber loss correlated with the severity of neuropathy assessed using NDS and fibular nerve conduction velocity.

Our pioneering study² published in 2003 in Manchester, United Kingdom, also showed that CCM could be used to identify early nerve damage in subclinical diabetic neuropathy, which presented a progressive worsening in patients with moderate and severe diabetic neuropathy. A Web of Science search on June 30th, 2022, with *corneal confocal microscopy* and *diabetic neuropathy* as the primary terms, returned 470 publications from Europe, Canada, Australia, Japan, China and now Brazil. We have recently undertaken a systematic review and meta-analysis³ including 38 studies and over 4,000 patients with diabetes which showed that CCM identifies corneal nerve fiber loss in patients with subclinical and clinical diabetic neuropathy.

We have previously shown that corneal nerve loss has a diagnostic utility comparable to that of intraepidermal nerve fiber density in patients with diabetic neuropathy.⁴ In a large multi-center study funded by the National Institutes of Health (NIH), we confirmed that CCM has excellent diagnostic utility⁵ and also predicts the development of clinical

diabetic neuropathy.⁶ Consistent with the study by Pupe et al.,¹ early subclinical corneal nerve loss has been shown in children with type-1 diabetes,⁷ and subjects with impaired glucose tolerance⁸ and recently-diagnosed type-2 diabetes.⁹ Normative values for corneal nerves have been established, and they show a small age-dependent decrease but no impact of height, weight, or body mass index (BMI).¹⁰ This is reassuring, as the study by Pupe et al.¹ showed corneal nerve loss in patients with diabetic neuropathy, despite the controls being significantly older. In our recent study¹¹ of 490 participants with diabetes, corneal nerve loss was associated with low-density lipoprotein (LDL) cholesterol and triglycerides values in type-1 diabetes, and with age, weight and hemoglobin A1c (HbA1c) in type-2 diabetes. This suggests that treating these modifiable risk factors may lead to nerve regeneration.

We have shown that simultaneous pancreas and kidney (SPK) transplantation in patients with type-1 diabetes normalized HbA1c and was associated with corneal nerve regeneration after 6 months, with an improvement in neuropathic symptoms after 24 months and nerve conduction after 36 months.¹² We have also shown evidence of corneal nerve regeneration after bariatric surgery in obese subjects with¹³ and without¹⁴ diabetes. In a randomized clinical trial,¹⁵ a weekly glucagon-like peptide-1 (GLP-1) agonist with pioglitazone or basal bolus insulin led to an ~ 3% improvement in HbA1c and was associated with corneal nerve regeneration over 12 months, but with no change in vibration perception or sudomotor function. Two recent trials^{16,17} with omega-3 fatty acid in patients with type-1 diabetes have demonstrated corneal nerve regeneration

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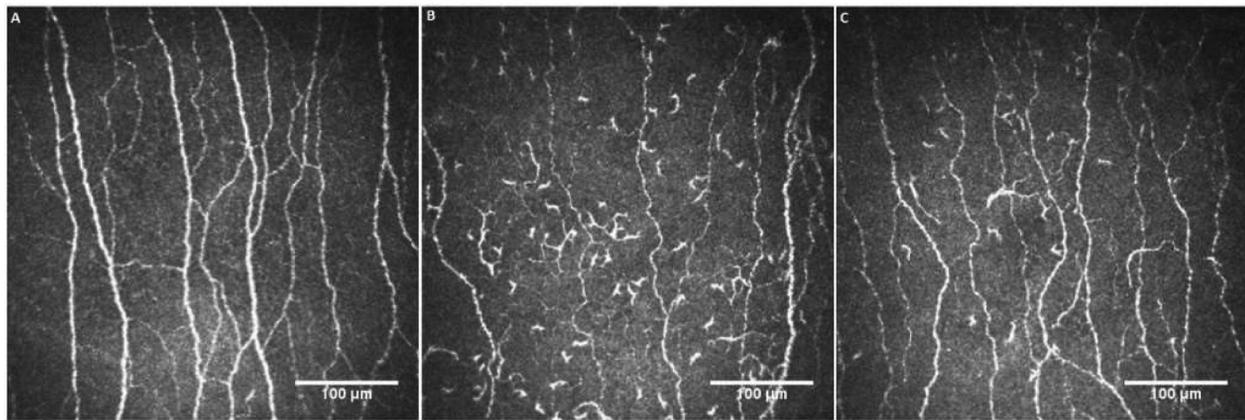


Figure 1 Representative corneal confocal microscopic images of the central corneal sub-basal nerve plexus in a healthy control participant (A), a patient with long COVID showing loss of corneal nerves and increased Langerhans cells (B), and a patient without long COVID (C).

with no change in nerve conduction velocity, thermal thresholds or autonomic nerve function. Thus, CCM could be used as an end-point in clinical trials of therapies for diabetic neuropathy and other peripheral neuropathies.

Corneal confocal microscopy also has a much wider application in the assessment of other neuropathies, such as chemotherapy-induced peripheral neuropathy (CIPN), HIV neuropathy, chronic inflammatory demyelinating polyneuropathy, Fabry disease, neurofibromatosis, Friedreich ataxia, transthyretin familial amyloid polyneuropathy, and amyloid protein immunoglobulin light chain (AL) amyloidosis.¹⁸ We have also recently shown loss of corneal nerve fibers and increased antigen-presenting Langerhans cells in people with long coronavirus disease 2019 (COVID-19)¹⁹ (→ **Figure 1**). This is important, as it provides an objective means to assess patients with long COVID. Corneal confocal microscopy has also been used to show corneal nerve loss in central neurodegenerative diseases, including multiple sclerosis,²⁰ Parkinson's disease²¹ and dementia.²²

In conclusion, the study by Pupe et al.¹ reinforces the results of many other studies showing that CCM is a robust end point for the assessment of neurodegeneration in diabetic neuropathy and other peripheral neuropathies, as well as central neurodegenerative diseases. Brazil is home to an epidemic of diabetes and diabetic neuropathy, as well as many other neuropathies, such as leprosy, B₁₂ deficiency, HIV, amyloidosis and, of course, long COVID. Corneal confocal microscopy could be easily deployed to help to diagnose and monitor these neurological diseases and the effect of the therapies.²³

Conflict of Interest

The author has no conflict of interests to declare.

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