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

Rayaz A. Malik[1,2]

[1] Weill Cornell Medicine-Qatar, Education City, Qatar Foundation, Doha, Qatar.
[2] University of Manchester, Division of Cardiovascular Sciences, Manchester, United Kingdom.

Arq. Neuropsiquiatr. 2022;80(8):767–769.

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 study[2] 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 metanalysis[3] 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 utility[5] 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 tolerance[8] 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 study[11] 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 with[13] and without[14] 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 $\sim$ 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

Address for correspondence
Rayaz A Malik
(e-mail: ram2045@qatar-med.cornell.edu).

DOI https://doi.org/10.1055/s-0042-1756169.
ISSN 0004-282X.

received
June 30, 2022
accepted
July 27, 2022

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

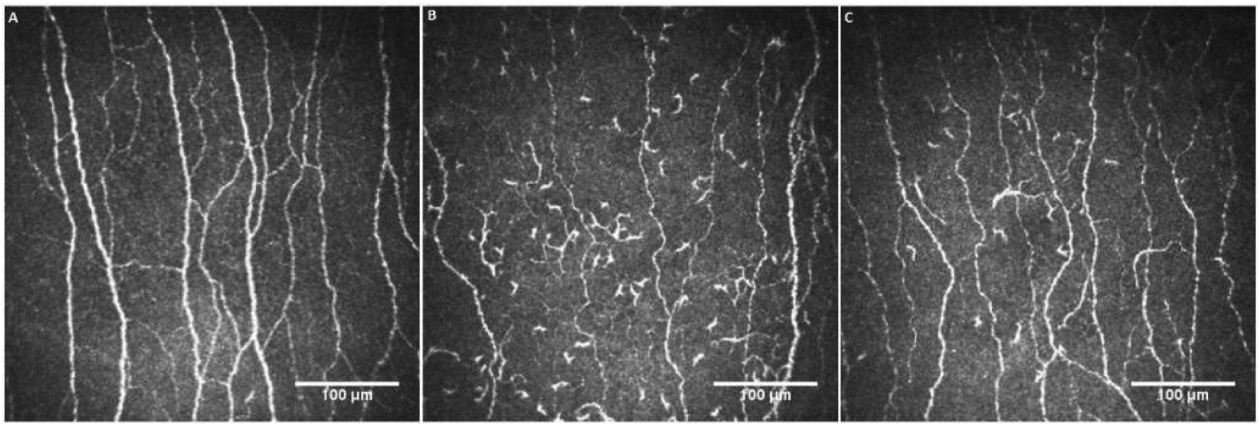

Figure 1 Representative corneal confocal microscopic images of the central corneal sub-basal nerve plexus in a healthy control participant (**A**), a patient with long COVID showing loss of corneal nerves and increased Langerhans cells (**B**), and a patient without long COVID (**C**).

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 disease[21] 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, B_{12} 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.

References

1 Pupe C, Dieckmann G, Dornas R, Nascimento O. Corneal confocal microscopy in patients with symptomatic diabetic poly-neuropathy compared to controls. Arq Neuropsiquiatr 2022;80(08): 812–821
2 Malik RA, Kallinikos P, Abbott CA, et al. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. Diabetologia 2003;46(05):683–688
3 Gad H, Petropoulos IN, Khan A, et al. Corneal confocal microscopy for the diagnosis of diabetic peripheral neuropathy: A systematic review and meta-analysis. J Diabetes Investig 2022;13(01):134–147
4 Chen X, Graham J, Dabbah MA, et al. Small nerve fiber quantification in the diagnosis of diabetic sensorimotor polyneuropathy: comparing corneal confocal microscopy with intraepidermal nerve fiber density. Diabetes Care 2015;38(06):1138–1144
5 Perkins BA, Lovblom LE, Bril V, et al. Corneal confocal microscopy for identification of diabetic sensorimotor polyneuropathy: a pooled multinational consortium study. Diabetologia 2018;61 (08):1856–1861
6 Perkins BA, Lovblom LE, Lewis EJH, et al. Corneal Confocal Microscopy Predicts the Development of Diabetic Neuropathy: A Longitudinal Diagnostic Multinational Consortium Study. Diabetes Care 2021;44(09):2107–2114
7 Ferdousi M, Romanchuk K, Mah JK, et al. Early corneal nerve fibre damage and increased Langerhans cell density in children with type 1 diabetes mellitus. Sci Rep 2019;9(01):8758
8 Asghar O, Petropoulos IN, Alam U, et al. Corneal confocal microscopy detects neuropathy in subjects with impaired glucose tolerance. Diabetes Care 2014;37(09):2643–2646
9 Ziegler D, Papanas N, Zhivov A, et al; German Diabetes Study (GDS) Group. Early detection of nerve fiber loss by corneal confocal microscopy and skin biopsy in recently diagnosed type 2 diabetes. Diabetes 2014;63(07):2454–2463
10 Tavakoli M, Ferdousi M, Petropoulos IN, et al. Normative values for corneal nerve morphology assessed using corneal confocal microscopy: a multinational normative data set. Diabetes Care 2015; 38(05):838–843
11 Ferdousi M, Kalteniece A, Azmi S, et al. Diagnosis of Neuropathy and Risk Factors for Corneal Nerve Loss in Type 1 and Type 2 Diabetes: A Corneal Confocal Microscopy Study. Diabetes Care 2021;44(01):150–156
12 Azmi S, Jeziorska M, Ferdousi M, et al. Early nerve fibre regeneration in individuals with type 1 diabetes after simultaneous pancreas and kidney transplantation. Diabetologia 2019;62 (08):1478–1487
13 Adam S, Azmi S, Ho JH, et al. Improvements in Diabetic Neuropathy and Nephropathy After Bariatric Surgery: a Prospective Cohort Study. Obes Surg 2021;31(02):554–563
14 Azmi S, Ferdousi M, Liu Y, et al. Bariatric surgery leads to an improvement in small nerve fibre damage in subjects with obesity. Int J Obes 2021;45(03):631–638

15 Ponirakis G, Abdul-Ghani MA, Jayyousi A, et al. Effect of treatment with exenatide and pioglitazone or basal-bolus insulin on diabetic neuropathy: a substudy of the Qatar Study. BMJ Open Diabetes Res Care 2020;8(01):e001420
16 Lewis EJH, Perkins BA, Lovblom LE, Bazinet RP, Wolever TMS, Bril V. Effect of omega-3 supplementation on neuropathy in type 1 diabetes: A 12-month pilot trial. Neurology 2017;88(24):2294–2301
17 Britten-Jones AC, Kamel JT, Roberts LJ, et al. Investigating the Neuroprotective Effect of Oral Omega-3 Fatty Acid Supplementation in Type 1 Diabetes (nPROOFS1): A Randomized Placebo-Controlled Trial. Diabetes 2021;70(08):1794–1806
18 Petropoulos IN, Ponirakis G, Khan A, et al. Corneal confocal microscopy: ready for prime time. Clin Exp Optom 2020;103 (03):265–277
19 Bitirgen G, Korkmaz C, Zamani A, et al. Corneal confocal microscopy identifies corneal nerve fibre loss and increased dendritic cells in patients with long COVID. Br J Ophthalmol 2021:bjophthalmol-2021-319450
20 Bitirgen G, Akpinar Z, Malik RA, Ozkagnici A. Use of Corneal Confocal Microscopy to Detect Corneal Nerve Loss and Increased Dendritic Cells in Patients With Multiple Sclerosis. JAMA Ophthalmol 2017;135(07):777–782
21 Lim SH, Ferdousi M, Kalteniece A, et al. Corneal confocal microscopy detects small fibre neurodegeneration in Parkinson's disease using automated analysis. Sci Rep 2020;10(01):20147
22 Ponirakis G, Al Hamad H, Sankaranarayanan A, et al. Association of corneal nerve fiber measures with cognitive function in dementia. Ann Clin Transl Neurol 2019;6(04):689–697
23 Verdugo RJ, Matamala JM, Inui K, et al. Review of techniques useful for the assessment of sensory small fiber neuropathies: Report from an IFCN expert group. Clin Neurophysiol 2022; 136:13–38

