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The growing pains of corneal nerve loss in diabetes

Aim: To assess the relationship between corneal nerve morphology and pain severity in patients with diabetic neuropathy.
Methods: Participants with diabetes mellitus (n=118) and healthy controls (n=38) were assessed for peripheral neuropathy with the neuropathy disability score (NDS), quantitative sensory testing [vibration perception threshold (VPT), cold perception (CPT) and warm perception threshold (WPT)], heart rate variability (HRV), and nerve conduction studies [sural nerve conduction velocity (SNCV) and amplitude (SNAP)]. A visual analogue scale (VAS; mm) was used to assess for the presence and severity of neuropathic pain (0-4 'no pain', 5-44 'mild pain' and 45-100 'moderate-severe pain'). Corneal confocal microscopy (CCM) was performed to quantify corneal nerve morphology [corneal nerve fiber (CNFD), branch density (CNBD), and length (CNFL)] and corneal sensitivity was assessed.
Results: All participants with diabetes had neuropathy based on NDS >2 and 75 participants (88.5%) had painful neuropathy (NDS >2 and VAS >4). 44.3% of participants with painful neuropathy were on pain relief medication. HbA1c and triglycerides were higher in participants with pain compared to those with no pain. In participants with diabetes compared to controls there were significant alterations in large fiber measures (NDS, VPT, SNCV, SNAP) and HRV with no relationship to pain severity. However, small fiber measures (CPT, WPT, CNFD, CNBD and CNFL) were significantly altered in patients with diabetes compared to controls and were worse in patients with 'moderate-to-severe pain' compared to 'no pain' and 'mild pain'. There was a significant correlation between pain severity and measures of small fiber neuropathy. A CNFD <23.69 fibers/mm^2 had the best diagnostic performance for PDN.
Conclusions: Neuropathic pain in diabetes is associated with greater corneal nerve loss and small fiber dysfunction.

Comment. The International Diabetes Federation estimates that 493 million people have diabetes, and this is expected to exceed 700 million by 2045. Neuropathic pain occurs in 1 out of 5 adults with diabetes and is associated with depression, anxiety and irregular sleep. Efforts to develop effective pain relief therapy are hampered by the lack of biomarkers of neuropathic pain. CCM can be used to objectively quantify C-fiber damage which relates to neuropathic signs and symptoms. The present study shows that small fiber degeneration underpins pain and suggests a role for CCM as a biomarker of painful diabetic neuropathy.

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Reference. Kalteniece A, Ferdousi M, Azmi S, Khan SU, Worthington A, Marshall A, Faber CG, Lauria G, Boulton AJM, Soran H, Malik RA. Corneal nerve loss is related to the severity of painful diabetic neuropathy. Eur J Neurol. 2022 Jan;29(1):286-294. doi: 10.1111/ene.15129. Epub 2021 Oct 13.
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