**Corneal Nerve Morphology in Painful Diabetic Neuropathy: A Meta-Analysis of *In Vivo* Confocal Microscopy Studies**

**Aim:**   
Painful diabetic peripheral neuropathy (pDPN) is a debilitating condition that significantly impacts quality of life. While pain is inherently a subjective experience, identifying objective markers associated with its underlying mechanisms remains a critical challenge, but would improve our understanding of pDPN pathophysiology.

This systematic review and meta-analysis aimed to evaluate whether common corneal nerve morphology parameters—corneal nerve fibre length (CNFL), corneal nerve fibre density (CNFD), and corneal nerve branch density (CNBD)—imaged using *in vivo* confocal microscopy (IVCM), differ significantly based on the presence of DPN and on neuropathic pain status.

**Methods:**   
This systematic review included studies comparing individuals with pDPN to those with non-painful diabetic neuropathy (npDPN), individuals with diabetes, but without neuropathy (DPN-), and healthy controls. A search strategy was developed and conducted in MEDLINE, EMBASE, Web of Science, and Cochrane Library databases for studies published from 2000 onward. Outcomes compared were based on IVCM-assessed corneal nerve morphology. Risk of bias was evaluated using the Newcastle-Ottawa Scale and evidence certainty was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework.

**Results:**   
Seven observational studies comprising 803 participants (213 pDPN, 275 npDPN, 99 DPN-, 216 healthy controls) revealed no significant differences in CNFL, CNFD, or CNBD between pDPN and npDPN cohorts with moderate quality evidence. However, all parameters were significantly reduced in pDPN patients compared to DPN- and healthy controls (high quality evidence).

**Conclusion:**  
These findings suggest that corneal nerve morphology parameters are not significantly different between individuals with pDPN and npDPN. While corneal nerve metrics effectively identify diabetic neuropathy, their association with pain remains unclear. Emerging evidence points to mechanisms beyond structural abnormalities—such as central sensitization, inflammation, and subtle nerve changes like micro-neuromas and axonal swelling—that may contribute to pDPN symptoms. Future research should explore these alternative parameters to improve our understanding of pDPN pathophysiology and identify potential biomarkers for pain pathophysiology.