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*CORRESPONDENCE
Yu-Chi Liu,
liuchiy@gmail.com

†These authors have contributed equally to this work

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Corneal nerve status as a biomarker for neurodegenerative and neurological diseases: a narrative review

Jiayue Li[1†], Andrew En Hsien Sim[1†], Mingyi Yu[2], Chang Liu[2], Isabelle Xin Yu Lee[2], Ansa Anam[3], Jasmine Shimin Koh[4] and Yu-Chi Liu[2,5,6*]

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [2]Regenerative Therapy Group, Singapore Eye Research Institute, Singapore, Singapore, [3]Department of Ophthalmology, MTI Khyber Teaching Hospital, Peshawar, Pakistan, [4]National Neuroscience Institute, Singapore, Singapore, [5]Department of Cornea and External Eye Disease, Singapore National Eye Centre, Singapore, Singapore, [6]Ophthalmology and Visual Sciences Academic Clinical Program, Duke-NUS Medical School, Singapore, Singapore

Corneal nerve status has gained prominence as a potential adjunctive biomarker for neurodegenerative and neurological diseases, as corneal small-fibre abnormalities can be detected in peripheral neuropathy and may precede conventional manifestations in certain conditions. Advances in in vivo confocal microscopy (IVCM) allow non-invasive, cellular-level assessments of corneal nerve alterations in real-time. Corneal nerve metrics have been associated with disease progression and severity. This review explores the role of corneal nerve status in the evaluation and monitoring of neurodegenerative and neurological diseases or conditions, including diabetic peripheral neuropathy (DPN), Parkinson's disease (PD), mild cognitive impairment (MCI) and dementia, multiple sclerosis (MS), schizophrenia, amyotrophic lateral sclerosis (ALS), migraine, tauopathies, and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The strength and maturity of evidence vary substantially between conditions. DPN has the most established evidence base, with replicated cross-sectional and longitudinal studies showing reductions in corneal nerve fibre density, branch density and length, and evidence that corneal nerve loss may precede conventional manifestations of neuropathy. In MS, longitudinal studies demonstrate progressive corneal nerve loss associated with worsening disability. In PD, the extent of corneal nerve fibre loss correlates with severity of motor deterioration, cognitive impairment and development of autonomic dysfunction, although proposed applications in prodromal detection, disease phenotyping, and prognostication remain largely dependent on small, single-centre studies. Studies in MCI and dementia suggest potential diagnostic and prognostic utility, including comparisons with neuroimaging, but are largely derived from overlapping single-centre cohorts. Evidence in CIDP, migraine, ALS, and schizophrenia remains limited or conflicting, while evidence in tauopathies is predominantly pre-clinical. Overall, current literature supports corneal nerve parameters primarily as promising adjunctive rather than established diagnostic, prognostic, treatment-response biomarkers. Direct evidence that IVCM provides incremental diagnostic or prognostic value over established biomarkers remains limited. Furthermore, heterogeneity in confocal platforms, image acquisition, image sampling, and analytical methods

must be considered in the interpretation across studies. Standardised acquisition and analysis protocols, prospective multicentre longitudinal studies, appropriate adjustment for confounders, and direct comparison with established biomarkers are necessary before broader clinical translation.

KEYWORDS
cornea, corneal nerves, corneal confocal microscopy, neurodegenerative diseases, diabetic peripheral neuropathy, Parkinson's disease, dementia, multiple sclerosis

Introduction

The cornea is a transparent, avascular tissue in the eye that plays a crucial role in vision and has dense innervation and the ability to reflect peripheral nerve changes [1]. Recent research has suggested the potential value of corneal nerve architecture as a biomarker for various neurodegenerative and neurological diseases. The nerves observed in in vivo confocal microscopy (IVCM) typically consist of peripheral C and Aδ sensory neurons originating from the trigeminal ganglion [2]. Corneal neurons have shorter axons and exist in a slightly different tissue environment at their peripheral terminals. However, they seem similarly susceptible to metabolic and toxic insults, making them a promising non-invasive biomarker for detecting sensory peripheral neuropathy [3].

Advancements in automated analysis techniques have improved the accuracy and efficiency of IVCM assessments. Fully automated IVCM analysis, such as the ACCMetrics software developed by Dabbah et al., has been instrumental in these findings. Moreover, automated analysis enables rapid image analysis, facilitating scalability for large cohort studies and longitudinal assessments [4].

Emerging evidence has supported the use of corneal nerve fibre parameters as diagnostic and prognostic biomarkers for neurodegenerative and neurological diseases, including but not limited to diabetic peripheral neuropathy (DPN), Parkinson's disease (PD), and multiple system atrophy (MSA). Quantitative changes in corneal nerve metrics, evaluated by IVCM, have been associated with disease progression and severity. This review synthesises current research findings and evaluates corneal nerve status as a potential biomarker for various neurodegenerative and neurological diseases. Through a comprehensive analysis of the literature, we aim to underscore the role of corneal nerve fibre assessments in advancing our understanding of neurodegenerative and neurological diseases and potentially improving clinical practice.

Search strategy and selection criteria

This article is a narrative review. To provide an overview of the role of corneal nerve status as a diagnostic and monitoring marker for neurodegenerative and neurological diseases, an electronic literature search of the PubMed database was performed. The PubMed search initially focused on articles published from 2015 to June 2025. Relevant earlier publications and newer papers encountered during revision were also included.

We employed a combination of keywords and medical subject headings (MeSH) to capture a broad yet focused range of relevant studies. The search terms included but were not limited to "corneal nerves" AND "diabetic peripheral neuropathy", "peripheral neuropathy", "corneal nerves" AND "neurodegenerative diseases", "corneal confocal microscopy" AND "Parkinson's disease", "corneal nerve fibre" AND "dementia" OR "Alzheimer's disease", "corneal neuropathy" AND "multiple sclerosis", "*in vivo* confocal microscopy" AND "schizophrenia" OR "amyotrophic lateral sclerosis", "*in vivo* confocal microscopy" AND "motor neuron disease", "corneal sensitivity" AND "migraine", "tauopathies" AND "corneal nerves", "chronic inflammatory demyelinating polyradiculoneuropathy" AND "corneal nerves".

The authors included only articles published in English with full texts available, and restricted the date range to the most recent 10 years (2015–2025) to ensure the inclusion of current and relevant research. The authors also manually reviewed the bibliographies of the selected articles to identify additional pertinent studies that might not have appeared in the initial database search. Both observational and interventional studies that provided qualitative or quantitative data on corneal nerve changes in these conditions were identified. Large language models were used for language editing only; all scientific content was reviewed and verified by the authors.

Consistent with the narrative design of this review, articles were selected by the authors on the basis of relevance to each disease section rather than through a formal screening protocol. No PRISMA framework, duplicate independent screening or standardised risk-of-bias instrument was applied. Studies were instead appraised qualitatively, with attention to study design, sample size, the availability of longitudinal follow-up and whether findings had been replicated by independent groups. These appraisals are presented at the end of each disease section, are compared across conditions in the section comparing the

Abbreviations: IVCM, *In vivo* confocal microscopy; DPN, Diabetic peripheral neuropathy; PD, Parkinson's disease; MSA, Multiple system atrophy; UMSARS, Unified multiple system atrophy rating scale; DCN, Diabetic corneal neuropathy; CNFD, Corneal nerve fibre density; CNFL, Corneal nerve fibre length; CNBD, Corneal nerve branch density; DM, Diabetes mellitus; AUC, Area under the curve; AI, Artificial intelligence; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TD, Tremor dominant; ROC, Receiver operating characteristic; MCI, Mild cognitive impairment; AD, Alzheimer's disease; MRI, Magnetic resonance imaging; MTA, Medial temporal lobe atrophy; MS, Multiple sclerosis; CNFrD, Corneal nerve fractal dimension; CNFA, Corneal nerve fibre area; CNFW, Corneal nerve fibre width; EDSS, Expanded disability status scale; MSSS, Multiple sclerosis severity score; ALS, Amyotrophic lateral sclerosis; CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy.

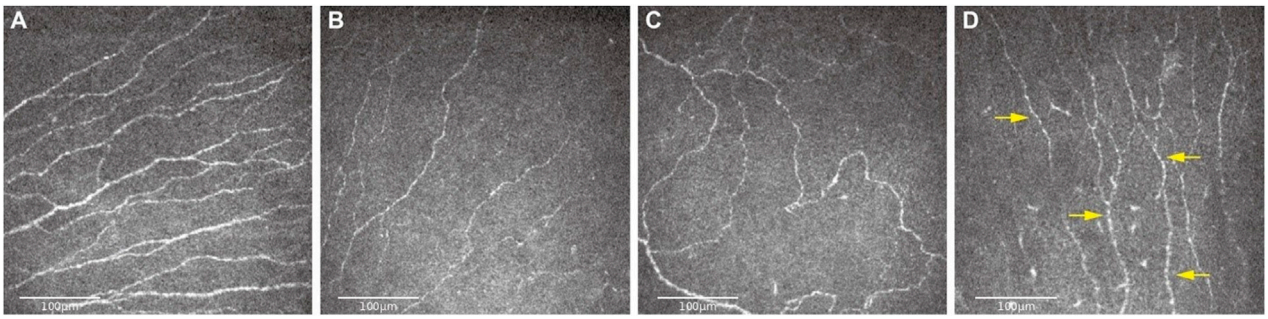


FIGURE 1
Representative IVCM images of the corneal sub-basal nerve plexus from a healthy subject and a patient with DPN (Heidelberg Retina Tomograph III with Rostock Cornea Module; Heidelberg Engineering GmbH, Heidelberg, Germany). Original image size, 400 × 400 µm (384 × 384 pixels). Images are original to this study and have not been published previously. **(A)** Corneal nerves appear as well-defined, densely anastomosed linear structures with Y- or H-shaped branches. **(B)** Decreased CNFD and CNFL in DPN. **(C)** Increased corneal nerve tortuosity in DPN. **(D)** Corneal nerve beadings (arrows) in DPN manifested as focal enlargement along the nerve fibres.

strength of evidence across diseases, and the limitations of this approach are acknowledged under Limitations and Future Directions.

Corneal nerve status in relation to diabetic peripheral neuropathy (DPN)

Introduction

DPN is the most frequent long-term complication of diabetes [5], characterised by damage to the peripheral nerves, leading to neuropathic pain, loss of sensation, and in severe cases, limb amputation. The diagnosis and monitoring of DPN pose significant challenges due to the insidious onset and slow progression of the disease [6]. Recently, IVCM has emerged as a promising non-invasive technique to detect early signs of DPN by examining corneal nerve status. This technique offers unique advantages in the early detection and monitoring of DPN progression and severity [7].

Mechanisms underlying corneal nerve changes and DPN

The mechanisms underlying corneal nerve changes in DPN are largely driven by hyperglycaemia-induced metabolic and vascular disturbances. Chronic hyperglycaemia leads to the accumulation of advanced glycation end-products, oxidative stress, and inflammation, causing neuronal damage and loss [8]. Metabolically, excess glucose shunted through the polyol pathway leads to the accumulation of harmful by-products such as sorbitol and fructose, increasing osmotic and oxidative stress. Additionally, microvascular dysfunction reduces blood supply to nerves, exacerbating ischaemia and nerve degeneration [9]. Inflammatory mediators further worsen neurodegeneration [10]. While both diabetic corneal neuropathy (DCN) and DPN share these mechanisms, IVCM provides an imaging modality to directly visualise small-fibre nerve changes in the cornea, which are often the earliest detectable signs of neuropathy, making DCN a valuable adjunctive biomarker for DPN.

In-vivo confocal microscopy findings in DPN

On IVCM evaluation, corneal sub-basal nerves appear as well-defined, densely anastomosed, thin and linear structures with homogeneous reflectivity and Y-shaped or H-shaped branches [11]. IVCM presentations in DPN are characterised by decreased Corneal Nerve Fibre Density (CNFD), Corneal Nerve Fibre Length (CNFL), tortuous nerves, and nerve beading (Figure 1).

Early detection of peripheral nerve damage in DPN

In the early stages of DPN, IVCM can detect subclinical corneal nerve alterations before traditional diagnostics become abnormal: patients with diabetes show reduced CNFD, corneal nerve branch density (CNBD), and CNFL compared to healthy controls, with these deficits preceding both clinical symptoms and nerve conduction changes in DPN [7, 12–14]. In a longitudinal rat model of prediabetes and type 2 diabetes, animals fed a high-fat diet exhibited significant early reductions in CNFL and corneal sensitivity, even before alterations in intraepidermal nerve fibre density or thermal nociception, thereby corroborating IVCM's superior sensitivity for detecting subclinical DPN [15]. Among IVCM parameters, reduced CNFL, particularly within the inferior whorl region, has emerged as the most sensitive early marker of diabetic sensorimotor polyneuropathy, often preceding overt symptoms by years and outperforming conventional nerve conduction studies in subclinical detection [16].

DCN in relation to diagnosis of DPN

Corneal nerve parameters are reliable and reproducible biomarkers for detecting and staging DPN. Quantitative corneal nerve parameters, including CNFL, CNFD, and CNBD, are significantly reduced in patients with DPN compared to those without [17, 18]. A meta-analysis that included 13 studies and 1680 participants concluded that corneal nerve parameters were significantly reduced in patients with diabetes mellitus (DM), especially when the DM status was complicated with DPN, implying that corneal nerve morphology assessment is useful for

the detection and evaluation of early nerve damage in patients with DM [19]. CNFL has demonstrated good reproducibility as a potential biomarker of early DPN [20]. This was corroborated by a longitudinal assessment study examining 396 participants across three groups, which found CNFL was significantly lower in the DPN group versus diabetics without neuropathy (14.0 ± 6.4 mm/mm^2 vs. 19.1 ± 5.8 mm/mm^2, P < 0.001) [21].

Conventional DPN diagnostics, such as nerve conduction studies, demonstrate limited sensitivity for detecting small-fibre pathology. Skin biopsy, the current gold standard for diagnosing small fibre neuropathy, is invasive and hence less appealing as a diagnostic and screening tool [22]. In contrast, IVCM provides direct visualisation of small unmyelinated C-fibres and Aδ-fibres, which are the first neural structures affected by hyperglycaemia-induced metabolic toxicity. Corneal nerve parameters demonstrate substantial diagnostic utility, with Ahmed et al. reporting area under the curve (AUC) values of 0.88 for CNFL and 0.84 for CNFD for distinguishing participants with diabetes with versus without DPN [23]. Ferdousi et al. also reported a CNFD AUC of 0.81 [24]. Moreover, CNFD had a higher diagnostic AUC than intraepidermal nerve fibre density in the same cohort (0.81 versus 0.73) [25].

Corneal nerve metrics also provide predictive value for DPN development. A CNFL threshold of <14.9 mm/mm^2 predicted diabetic peripheral neuropathy development with a sensitivity of 0.82 and a specificity of 0.69 [26]. Furthermore, CNFL provided prognostic information up to 6 years before DPN diagnosis, with an optimal cut-off of 14.1 mm/mm^2, yielding a sensitivity of 67% and specificity of 71% [13]. A sustained abnormal CNFL for at least 50% of a 2-year observation period demonstrated superior predictive capacity for incident DPN (AUC: 0.763, p < 0.0001) compared to single measurements, emphasising the value of serial monitoring [27].

Disease progression and severity in DPN

Corneal nerve parameters correlate closely with DPN severity, providing both functional and structural assessments of disease progression. Functionally, corneal sensitivity decreases significantly with advancing DPN, showing strong correlations with clinical neuropathy scores (r = 0.441, P < 0.001) and quantitative sensory thresholds, including cold, vibration, and warm sensation [28, 29]. Structurally, CNFD, CNBD, and CNFL progressively decline with increasing DPN severity, as assessed by neuropathy scores and nerve conduction studies (P < 0.001), enabling stratification of patients across mild, moderate, and severe neuropathy stages [30, 31]. CNFD correlated inversely with the Total Neuropathy Score (ρ = −0.783, P < 0.01) [32]. Separately, cross-sectional evidence suggests that CCM can detect small-fibre abnormalities at earlier clinical stages of diabetic neuropathy than skin-biopsy-derived intraepidermal nerve fibre assessment, while providing a rapid, non-invasive examination [30].

These corneal metrics show significant negative correlations with neuropathic symptom severity scores and pain intensity, with CNFD, CNBD, and CNFL all declining with increasing pain severity on visual analogue scale ratings [33].

The progressive corneal nerve changes enable identification of patients at risk for serious DPN complications. CNFD demonstrates high specificity for early-stage small fibre neuropathy (84%), DPN diagnosis (75%), and individuals at risk for foot ulceration (72%), serving as an objective marker for complication stratification [34]. Furthermore, patients developing diabetic neuroosteoarthropathy show significantly reduced corneal nerve metrics compared to non-diabetic controls, and corneal nerve changes correlate with neuropathic pain severity [35, 36]. Thus, IVCM assessment of corneal nerve status enables risk stratification across the spectrum of DPN severity and complications, guiding the optimal timing of therapeutic interventions.

AI-based diagnostic approaches

Recent advances have harnessed artificial intelligence (AI) to automate and enhance IVCM analysis for DPN detection, addressing limitations of manual quantification, including inter-observer variability and time-intensive processing.

Deep learning algorithms have significantly improved diagnostic performance. A convolutional neural network (CNN)-based algorithm employing data augmentation enabled rapid quantification of multiple nerve parameters, including fibre length, branch points, tail points, nerve segments, and fractal dimensions, without manual intervention. This approach achieved an AUC of 0.83, specificity of 0.87, and sensitivity of 0.68 for DPN diagnosis, outperforming the ACCMetrics tool [37]. Another CNN trained on IVCM images achieved 96% accuracy in separating healthy controls from diabetics with neuropathy, without the need for manual nerve tracing or parameter extraction [38]. Advanced ResNet-50 models incorporating Grad-CAM (gradient-weighted class activation mapping) visualisation achieved sensitivity of 0.91, specificity of 0.93, and AUC of 0.95 in patients with Type 1 DM (T1DM), Type 2 DM (T2DM), and prediabetes using IVCM images of the sub-basal nerve plexus, without requiring prior manual quantification of corneal nerve parameters [39]. In a cross-sectional study of 369 participants, including healthy controls and people with T1DM, T2DM or prediabetes, a CNN classifier was developed to process single corneal images for DPN severity stratification, achieving F1-scores of 0.91 for healthy controls, 0.88 for participants without peripheral neuropathy, and 0.91 for participants with peripheral neuropathy [40].

U2Net-based segmentation tools outperformed ACCMetrics in consistency with manual annotation and achieved an AUC of 0.75 for DPN diagnosis, further improving the reliability of automated nerve quantification [41].

Transformer-based models represent recent advances. A Swin transformer network outperformed traditional CNNs with an AUC of 0.94 for DPN diagnosis, highlighting the potential of transformer architectures for rapid, accurate screening [42], while Vision Transformer models achieved an AUC of 0.99, sensitivity of 98%, and specificity of 92% for DPN diagnosis from IVCM images without manual segmentation [43]. Hybrid approaches combining deep learning with an adaptive neuro-fuzzy inference system for DPN diagnosis achieved an AUC of 0.95 with 92% sensitivity and 80% specificity, demonstrating the potential for rapid, automated, and accurate diagnosis [44].

A recent deep learning model extracted features directly from corneal images and, when combined with HbA1c, achieved an AUC of 0.94 for predicting diabetic foot risk [45]. Integration with serum

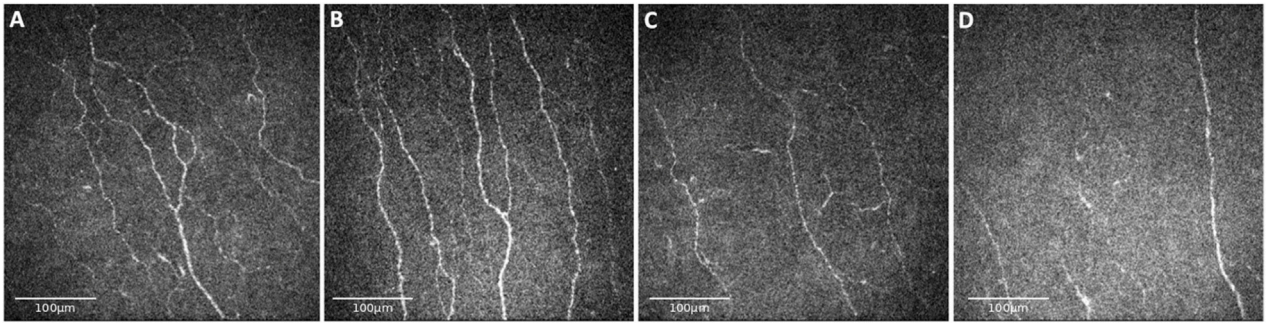


FIGURE 2
Representative IVCM images of the corneal sub-basal nerve plexus in controls and patients with diabetic foot at differing risk levels (Heidelberg Retina Tomograph III with Rostock Cornea Module; Heidelberg Engineering GmbH, Heidelberg, Germany). Original image size, 400 × 400 µm (384 × 384 pixels). Images are original to this study and have not been published previously. Controls **(A)**, patients with low-risk diabetic foot **(B)**, moderate-risk diabetic foot **(C)**, and high-risk diabetic foot **(D)**. Corneal nerve status deteriorated with the progression of diabetic foot risk.

creatinine produced an AUC of 0.93 for identifying high-risk patients with diabetic foot (Figure 2). Notably, quantitative nerve parameters did not enhance performance compared with raw images, indicating that deep learning can capture diagnostically relevant features without manual extraction. This approach provides a novel screening methodology for diabetic foot risk categories.

Table 1 provides a comprehensive overview of studies evaluating corneal nerve status in relation to DPN.

Counter-evidence: limitations of corneal nerve metrics

Despite the preponderance of data supporting the diagnostic value of using corneal nerve status, not all studies corroborate its reliability as a DPN biomarker. A recent meta-analysis found that standard corneal nerve parameters (CNFL, CNFD and CNBD) do not significantly differ between patients with painful and painless DPN, indicating that these metrics cannot distinguish between pain subtypes and are therefore limited as pain-specific biomarkers in DPN [48]. Furthermore, a lack of association was found between corneal nerve density and clinical measures of DPN, including neuropathy symptoms and disability scores, nerve conduction studies, and quantitative sensory tests [49]. These results underscore the need for cautious interpretation of IVCM findings and highlight the importance of developing more accurate quantitative tools and multimodal diagnostic approaches for DPN assessment.

Overall appraisal of the evidence in DPN

The evidence base in DPN is the strongest of any condition considered in this review. It comprises large cross-sectional cohorts, prospective longitudinal studies with follow-up of two to 6 years, and meta-analytic synthesis. The core findings - reduction of CNFD, CNBD and CNFL in diabetes, and the predictive value of CNFL for incident DPN, have been reproduced by independent groups in different countries. Several caveats nonetheless apply. Most diagnostic accuracy estimates derive from single-centre cohorts analysed with a common software pipeline, few studies report blinded assessment or pre-specified diagnostic thresholds, and the artificial intelligence studies in particular are susceptible to optimistic performance estimates where external validation datasets were not used. Findings relating to the detection and progression of DPN may therefore be regarded as robust, whereas the pain-specific and artificial intelligence-based applications remain exploratory.

Corneal nerve status in relation to Parkinson's disease

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterised by motor symptoms such as tremors, bradykinesia, and rigidity. However, non-motor symptoms, including hyposmia, sleep disorders, and autonomic dysfunction, are increasingly recognised as significant contributors to the disease burden and often precede other motor manifestations [50]. Emerging data indicate that both dopaminergic and non-dopaminergic pathology underlie these non-motor features, with the alpha-synuclein pathology starting in the gastrointestinal autonomic plexus and spreading along the neuronal pathways [51]. There is also accumulating evidence demonstrating early α-synuclein deposition and small-fibre degeneration within the skin, autonomic nervous system, and enteric plexus [52, 53]. Given that corneal nerves are predominantly small, unmyelinated sensory fibres, analogous to those affected in cutaneous and autonomic neuropathy, corneal nerve involvement in PD is biologically plausible. This provides a mechanistic rationale for evaluating corneal nerve alterations as an adjunctive biomarker of peripheral small-fibre neurodegeneration in PD. To support this, recent studies have suggested that corneal nerve fibre alterations could serve as a novel biomarker for diagnosing and monitoring PD.

Evidence of corneal neuropathy in early PD and disease progression

Multiple studies have demonstrated that corneal nerve fibre loss is present in early and even prodromal PD, preceding overt motor symptoms. In a clinical cross-sectional study including 26 patients

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TABLE 1 Corneal nerve changes in relation to DPN.

Authors	Study design	Sample size (total N)	Study population	Findings
Petropoulos et al. [12]	Review Paper	-	-	Diabetic patients showed reduced CNFD, CNBD, CNFL, with these deficits preceding both clinical symptoms and nerve conduction changes in DPN
So et al. [7]	Review Paper	-	-	Reduced CNFD, CNBD, CNFL in diabetic patients with these deficits preceding both clinical symptoms and nerve conduction changes in DPN.
Perkins et al. [13]	Prospective cohort study	261	T1DM n = 203; T2DM n = 58; all without DPN at baseline; mean follow-up 5.8 years (IQR 4.2–7.0)	Reduced CNFD, CNBD, CNFL in diabetic patients with these deficits preceding both clinical symptoms and nerve conduction changes in DPN. Baseline CNFL <14.1 mm/mm^2 predicted new-onset DPN with 67% sensitivity and 71% specificity
Carmichael et al. [14]	Observational, retrospective	35	T1DM n = 20; healthy controls n = 15	Reduced CNFD, CNBD, CNFL in diabetic patients with these deficits preceding both clinical symptoms and nerve conduction changes in DPN.
Coppey et al. [15]	Experimental	108	Healthy control n = 36, high-fat-diet/prediabetes n = 36, T2DM n = 36; 12 rats/group assessed at each time point	IVCM has superior sensitivity for detecting subclinical DPN
Petropoulos et al. [16]	Cross-sectional	68	Diabetes with DPN n = 25; without DPN n = 28; healthy controls n = 15	Reduced CNFL in inferior whorl region appears to be most sensitive early marker and precedes symptoms by years
Wang et al. [17]	Cross-sectional	220	T2DM n = 172 (DPN n = 100; no DPN n = 72); healthy controls n = 48	CNFL, CNFD, CNBD were significantly reduced in patients with DPN vs. without DPN
Li et al. [18]	Cross-sectional	152	T2DM n = 128; healthy controls n = 24	CNFL, CNFD, CNBD reduced in DPN patients compared to healthy controls
Jiang MS et al. [19]	Meta-analysis	13 studies; pooled N = 1,680	Patients with DPN, without DPN, healthy controls	Corneal nerve parameters were significantly reduced in the patients with DPN compared with healthy controls
Hertz et al. [20]	Cross-sectional	46	T1DM n = 26; healthy controls n = 20	CNFL was established as reproducible biomarker predictive of DPN development
Pritchard et al. [21]	Prospective cohort study	396	T1DM with DPN n = 76; T1DM without DPN n = 166; healthy controls n = 154; 4-year follow-up (annual assessments)	CNFL was significantly lower in the DPN patients compared to diabetic patients without neuropathy
Ahmed et al. [23]	Cross-sectional	153	T1DM n = 89 (DPN n = 33; no DPN n = 56); healthy controls n = 64	CNFL demonstrated an AUC of 0.88 for distinguishing DPN patients from controls, while CNFD achieved an AUC of 0.84
Ferdousi et al. [24]	Cross-sectional	490	Healthy controls n = 72; T1DM n = 149; T2DM n = 269	CNFD had an AUC of 0.81
Alam et al. [25]	Cross-sectional	88	T1DM without DPN n = 30; T1DM with DPN n = 31; healthy controls n = 27	CNFD demonstrated better diagnostic ability than intraepidermal nerve fibre density for patients with DPN (AUC 0.81 versus 0.73)

(*Continued*)

TABLE 1 Continued

Authors	Study design	Sample size (total N)	Study population	Findings
Lovblom et al. [26]	Prospective cohort study	65	T1DM patients without DPN; mean follow-up 3.5 ± 0.9 years	CNFL threshold of <14.9 mm/mm^2 predicted DPN development with sensitivity of 0.82 and specificity of 0.69
Ponirakis et al. [27]	Prospective cohort study	107	T2DM patients; median follow-up 4 years (range 1–7)	Sustained abnormal CNFL persisting for at least 50% of a 2-year observation period demonstrated superior predictive capacity for incident DPN with an AUC of 0.76, compared to single-point measurements
Tavakoli et al. [28]	Cross-sectional	118	Diabetes n = 101; healthy controls n = 17	Corneal sensitivity correlated with neuropathy scores and quantitative sensory thresholds
Pritchard et al. [29]	Cross-sectional baseline analysis within a prospective cohort	300	Diabetes with DPN n = 93; diabetes without DPN n = 146; healthy controls n = 61; 5-year longitudinal study; baseline assessment reported	Corneal sensitivity correlates with neuropathy scores and quantitative sensory thresholds
Quattrini et al. [30]	Cross-sectional	69	Diabetes n = 54; healthy controls n = 15	CNFL progressively declines with increasing DPN severity, enabling stratification of patients across mild, moderate, and severe neuropathy stages
Petropoulos et al. [31]	Cross-sectional	241	T1/T2DM n = 186; healthy controls n = 55	Reduction in CNFD, CNBD, CNFL significantly correlates with neuropathy severity scores
Tummanapalli et al. [32]	Cross-sectional	79	T1DM n = 50; healthy controls n = 29	CNFD correlated with comprehensive neuropathy assessment. IVCM detects these changes earlier than skin biopsy
Azmi et al. [46]	Cross-sectional	104	Men with T1DM: erectile dysfunction n = 41, no erectile dysfunction n = 29; healthy controls n = 34	CNFD, CNBD and CNFL were lower in men with T1DM and erectile dysfunction than in those without erectile dysfunction
De Clerck et al. [47]	Cross-sectional	134	Normal glucose metabolism n = 87; prediabetes n = 20; T2DM n = 27	CNFL was significantly lower in T2DM than in normal glucose metabolism, with a significant trend across worsening glucose metabolism status
Kalteniece et al. [33]	Cross-sectional	156	DPN n = 118; healthy controls n = 38	CNFD, CNBD and CNFL declined with increasing pain severity in DPN, correlating significantly with visual analogue scale pain scores
Quattrini et al. [34]	Cross-sectional	55	DM patients, no control group	CNFD demonstrates high specificity for early-stage small fibre neuropathy (84%), DPN diagnosis (75%), and individuals at risk for foot ulceration (72%), serving as an objective marker for complication stratification
Herlyn et al. [35]	Pilot study	26	Diabetic neuro-osteoarthropathy n = 13; healthy controls n = 13	Reduced corneal nerve metrics in diabetic neuroosteoarthropathy patients correlated with neuropathic pain severity
Kalteniece et al. [36]	Cross-sectional	170	Painful DPN n = 78; painless DPN n = 62; healthy controls n = 30	Corneal nerve alterations correlated with neuropathic pain severity

(*Continued*)

TABLE 1 Continued

Authors	Study design	Sample size (total N)	Study population	Findings
Williams et al. [37]	Cross-sectional	222 participants (development cohort); external image datasets used for validation	DPN n = 132; no DPN n = 90 in development cohort	A CNN-based algorithm achieved an AUC of 0.83, specificity of 0.87, and sensitivity of 0.68 for DPN diagnosis and demonstrated superior intraclass correlation compared to ACCMetrics
Scarpa et al. [38]	Cross-sectional	100	DPN n = 50; healthy controls n = 50	A CNN trained on IVCM images achieved 96% accuracy in distinguishing healthy controls from diabetes with neuropathy without the need for manual nerve tracing or parameter extraction
Meng et al. [39]	Cross-sectional	279	T1DM n = 88; T2DM n = 141; prediabetes n = 50	An advanced ResNet-50 model incorporating Grad-CAM visualisation achieved sensitivity of 0.91, specificity of 0.93, and AUC of 0.95 in detecting DPN using IVCM images of the sub-basal nerve plexus without requiring prior manual quantification of corneal nerve parameters
Preston et al. [40]	Cross-sectional	369	Healthy controls n = 90; T1DM n = 88; T2DM n = 141; prediabetes n = 50	A CNN classifier processing single corneal IVCM images for peripheral neuropathy classification achieved F1-scores of 0.91 for healthy controls, 0.88 for participants without peripheral neuropathy, and 0.91 for participants with peripheral neuropathy
Qiao et al. [41]	Cross-sectional	175	Healthy controls n = 64; diabetes n = 111	A U2Net-based segmentation tool outperformed ACCMetrics and achieved an AUC of 0.75 for DPN diagnosis
Chen et al. [42]	Cross-sectional	94	DPN n = 57; no DPN n = 37	A Swin transformer network outperformed traditional CNNs with an AUC of 0.94 for DPN diagnosis
Ben Rabah et al. [43]	Cross-sectional	106	DPN n = 29; healthy controls n = 77	Vision transformer models achieved an AUC of 0.99, sensitivity of 98%, and specificity of 92% for DPN diagnosis from IVCM images without manual segmentation
Salahouddin et al. [44]	Cross-sectional	108	Healthy controls n = 21; DPN n = 25; no DPN n = 62	A hybrid approach combining deep learning with an adaptive neuro-fuzzy inference system for DPN diagnosis achieved an AUC of 0.95 with 92% sensitivity and 80% specificity
Liu et al. [45]	Cross-sectional	471	Healthy controls n = 205; low-risk diabetic foot n = 187; moderate-risk n = 42; high-risk n = 37	A deep learning model achieved an AUC of 0.94 when combined with HbA1c and an AUC of 0.93 when integrated with serum creatinine for predicting diabetic foot risk
Vidyasagar et al. [48]	Systematic review	7 studies; pooled N = 803	Painful DPN n = 213, non-painful DPN n = 275, diabetes without neuropathy n = 99 and healthy controls n = 216	Corneal nerve parameters (CNFL, CNFD, CNBD) cannot reliably distinguish between patients with painful and painless DPN.

(*Continued*)

TABLE 1 Continued

Authors	Study design	Sample size (total N)	Study population	Findings
Badian et al. [49]	Cross-sectional	77	T2DM n = 41; healthy controls n = 36	A lack of association was found between CNFD and clinical measures of DPN, including neuropathy symptom and disability scores, nerve conduction studies, and quantitative sensory tests, suggesting that corneal nerve fibres may not accurately reflect clinical severity or symptoms

Abbreviations: ACCMetrics, Automated Corneal Confocal Microscopy Metrics; AUC, area under the curve; CNN, convolutional neural network; CNBD, corneal nerve branch density; CNFD, corneal nerve fibre density; CNFL, corneal nerve fibre length; DPN, diabetic peripheral neuropathy; DM, diabetes mellitus; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; Grad-CAM, Gradient-weighted Class Activation Mapping; IVCM, in vivo confocal microscopy.

with newly diagnosed PD and 22 control subjects, these patients presented with significantly reduced CNFD and CNFL as compared to controls. Skin biopsies showed similar epidermal nerve densities between groups, indicating that IVCM is more sensitive for detecting early small fibre neuropathy in PD. The authors thus concluded that corneal nerve metrics provided evidence of pre-clinical peripheral neuropathy in newly diagnosed PD patients, aiding in the early diagnosis and management of PD [54].

The deterioration of corneal nerve metrics shows a consistent pattern across the disease spectrum, from healthy individuals to prodromal and manifest PD. A cross-sectional study demonstrated that CNFD and CNFL values declined progressively from healthy controls through prodromal PD to manifest PD, supporting their application as early screening markers for PD [55].

In a systematic review of IVCM and its applications in PD assessment, Che and Yang comprehensively analysed findings from multiple IVCM studies and consistently identified significantly reduced CNFD in PD patients relative to healthy controls [56]. Notably, the magnitude of corneal nerve fibre loss showed progressive worsening with advancing disease severity. The authors concluded that IVCM might serve as a supplementary tool for assessing PD progression. Through highlighting the sensitivity of IVCM in detecting early nerve fibre alterations, they proposed its use as a diagnostic tool for PD-related neuropathy.

Corneal nerve fibre loss and cognitive impairment in PD

Research has demonstrated a link between corneal nerve fibre loss and cognitive impairment in patients with PD. A study by Che et al. demonstrated that patients with PD exhibited significant corneal nerve fibre loss compared to controls, with CNFD positively correlating with cognitive performance as assessed by the Montreal Cognitive Assessment, indicating that corneal nerve fibre loss is associated with the severity of cognitive dysfunction [57].

Another study observed a marked reduction in corneal sub-basal nerve plexus density in PD patients compared to healthy controls, and this reduction was significantly correlated with cognitive impairment as measured by the Addenbrooke's Cognitive Examination-Revised score [58]. This was the first study to directly demonstrate an association between corneal nerve loss and cognitive dysfunction in PD, supporting the involvement of the peripheral nervous system in what was previously considered a purely central nervous system disorder.

Differentiating PD with and without autonomic involvement using IVCM

Autonomic dysfunction is a common non-motor symptom in PD, often complicating the clinical picture. Identifying autonomic involvement early, especially before overt symptoms arise, is crucial for guiding tailored interventions.

Evidence shows that IVCM can distinguish PD patients with autonomic involvement from those without. Corneal nerve parameters, including CNFD, CNBD, CNFL, and the CNBD/CNFD ratio, were all significantly lower in PD patients exhibiting autonomic dysfunction compared to those without. These findings suggest that IVCM offers a non-invasive method for stratifying PD patients based on autonomic nervous system involvement [59].

In support of this, another study demonstrated that CNFD was reduced in PD compared to controls, while CNBD and CNFL were closely correlated with both autonomic symptoms and parasympathetic dysfunction. These findings reinforce the utility of IVCM in identifying autonomic involvement in PD, as the technique's parameters were not influenced by disease duration or levodopa dose, but rather by the presence of autonomic symptoms. This supports a pathophysiological link between small fibre degeneration and impaired autonomic regulation in PD [60].

Corneal nerve fibre density in motor progression in PD

CNFD has shown promise as a prognostic biomarker for motor progression in PD. Lim et al. conducted a prospective study evaluating the association between baseline CNFD and motor decline over 12 months in PD [61]. Using the Movement Disorder Society Unified Parkinson's Disease Rating Scale as an outcome measure, they found that patients in the lowest quartile of CNFD at baseline experienced a significantly greater worsening in motor scores compared to those in the highest quartile. These findings suggest that reduced CNFD predicts faster motor deterioration, underscoring its potential utility in identifying PD patients at risk for more rapid functional decline.

Recent investigations have demonstrated significant correlations between corneal nerve parameters and the severity of motor symptoms in PD. Notably, lower CNFD and CNFL were correlated with higher motor symptom scores, indicating that as motor impairment becomes more severe, corneal nerve loss increases [55].

Additionally, IVCM has demonstrated potential in phenotyping motor subtypes within PD. Che et al. reported that patients with the postural instability and gait disturbance subtype exhibited greater corneal nerve fibre loss than those with the tremor-dominant (TD) subtype [62]. Logistic regression analysis revealed that higher CNFD and CNFL were significantly associated with the TD phenotype (OR = 1.265 and OR = 1.706, respectively). Furthermore, receiver operating characteristic (ROC) analysis demonstrated excellent discrimination between tremor-dominant and PIGD subtypes using combined corneal nerve metrics (AUC = 0.832), indicating IVCM's broader applicability in PD phenotyping beyond autonomic classification.

Consistent with these findings, Che and Yang also demonstrated that decreased CNFD correlated with more pronounced motor symptoms, reinforcing the role of corneal nerve status as a marker of disease progression in PD [56].

Distinguishing between multiple system atrophy and PD

Multiple system atrophy (MSA) and PD share several clinical features, making differential diagnosis challenging. Niu et al. explored the use of IVCM in distinguishing MSA from PD. Results showed that both CNFD and CNFL were significantly lower in MSA patients compared to PD patients. In the combined MSA + PD group, CNFD was negatively correlated with the Orthostatic Grading Scale. In the MSA group alone, CNFD was significantly negatively correlated with both unified multiple system atrophy rating scale (UMSARS) I and II, and regression analysis confirmed that both CNFD and CNFL were inversely associated with MSA severity, demonstrating a statistically significant relationship between corneal nerve fibre loss and disease severity. ROC analysis showed that the algorithm utilising CNFL achieved an AUC of 0.72 with 73.3% sensitivity and 73.0% specificity for distinguishing MSA from PD after adjusting for age, gender, and disease duration. The algorithm combining CNFD, CNBD, and CNFL produced a similar AUC of 0.72. Although the overall discriminatory power was modest, the greater corneal nerve fibre loss in MSA indicates that IVCM can detect a quantitatively distinct pattern of peripheral denervation. When integrated with clinical and paraclinical evaluations, IVCM may provide a useful non-invasive biomarker to aid differential diagnosis in cases where MSA and PD present with overlapping features [63].

Moreover, Lim et al. found significantly lower CNFD, CNBD and CNFL in both PD and MSA than in healthy controls [64]. These comparisons with controls do not establish a direct difference between MSA and PD.

Overall appraisal of the evidence in PD

The PD literature consists predominantly of small to moderate cross-sectional and case-control studies, with a single prospective study of motor progression over 12 months. The reduction of CNFD and CNFL in PD relative to controls has been reproduced by several independent groups and may be considered reasonably established. In contrast, the applications of greatest clinical interest - detection in the prodromal phase, motor subtype phenotyping, prediction of motor progression, and discrimination of MSA from PD - each rest on one or two single-centre studies, show only modest discriminatory performance, and have not been validated in multicentre cohorts. These findings should therefore be interpreted as promising but in the preliminary stage.

Table 2 provides a summary of studies evaluating corneal nerve fibre alterations in the context of PD.

Corneal nerve status in relation to cognitive impairment and dementia

Introduction

Dementia and mild cognitive impairment (MCI) represent a continuum of neurodegenerative disorders characterised by progressive cognitive and functional decline, with the most common subtype being Alzheimer's disease (AD). MCI represents a stage at which cognitive decline exceeds normal ageing but does not yet meet the criteria to diagnose dementia [65]. MCI may be a precursor to dementia, and brain changes underlying AD occur at least 20 years prior to the onset of symptoms, providing an optimal window for early diagnosis and effective interventions [66]. Early diagnosis and intervention have emerged as one of the key components of the national dementia strategy in certain European countries [67]. Currently, well-established biomarkers for dementia due to AD are visualisation of beta-amyloid (Aβ) and tau deposition in cerebrospinal fluid studies and magnetic resonance imaging (MRI) or radionuclide imaging to assess the degree of atrophy, hypometabolism, or hypoperfusion [68]. IVCM is now gaining prominence in the context of neurodegenerative diseases such as dementia.

Corneal nerve fibre loss and mild cognitive impairment

The medial temporal lobe atrophy (MTA) scoring has been a well-established biomarker for dementia due to its ease of application in clinical practice [69], together with its ability to differentiate between AD and healthy controls and predict the progression of MCI to AD [70]. However, its diagnostic relevance to MCI is still indeterminate and conflicting [68].

In recent times, several studies have shown that there is an association between corneal nerve measures and cognitive impairment. In a comparison between IVCM and the widely used MTA scoring, the diagnostic accuracy of corneal nerve measures was reported to be non-inferior to MTA scoring for dementia, and higher than MTA scoring in MCI, with a higher sensitivity (81% versus 70%) and specificity (81% versus 75%) [71]. Between IVCM and brain volumetry, IVCM also had a higher diagnostic capability in identifying MCI compared to brain volumetry within the studied cohort [72].

In a study conducted by Ponirakis et al. that focused on the predictive value of IVCM parameters versus brain volumetry for progression from MCI to dementia, MCI patients who progressed to dementia had both significantly lower IVCM parameters, including CNFD, CNBD, CNFL, and lower hippocampal volume compared to

TABLE 2 An overview of studies evaluating corneal nerve fibre alterations in the context of PD.

Authors (Year)	Study design	Sample size (total N)	Study population	Results
Podgorny et al. [54]	Case-control	48	PD n = 26; healthy controls n = 22	Significant reductions in CNFD and CNFL were observed in PD patients, indicative of peripheral neuropathy at a pre-clinical stage. IVCM is more sensitive for detecting pre-clinical small fibre neuropathy
Yaisawang et al. [55]	Cross-sectional	53	Prodromal PD n = 17; manifest PD n = 18; healthy controls n = 18	Progressive decline seen in CNFD and CNFL from controls through prodromal to manifest PD, supporting early disease screening. Lower CNFD and CNFL were associated with worse motor scores
Che and Yang [56],	Systematic review	-	-	IVCM consistently demonstrates reduced CNFD in PD and is proposed as a supplementary diagnostic tool for PD-related neuropathy with sensitivity for early nerve fibre alterations. Decreased CNFD correlated with more pronounced motor symptoms
Che et al. [57]	Observational	95	PD n = 65; healthy controls n = 30	PD patients showed corneal nerve loss compared with controls, with nerve parameters correlating with the severity of cognitive and motor dysfunction
Misra et al. [58]	Case-control	30	PD n = 15; healthy controls n = 15	Marked reduction was seen in corneal sub-basal nerve plexus density in PD. Significant correlation seen with cognitive impairment
Che et al. [62]	Cross-sectional	73	TD n = 29; PIGD n = 34; mixed subtype n = 10	CNFD, CNBD and CNFL were lower in PIGD than TD; combined corneal nerve metrics discriminated TD from PIGD (AUC 0.832)
Che et al. [59]	Cross-sectional	101	PD n = 71; healthy controls n = 30	IVCM parameters differentiate PD patients with autonomic involvement from those without
Kass-Iliyya et al. [60]	Case-control	52	PD n = 26; healthy controls n = 26	CNFD correlated with autonomic symptoms and parasympathetic dysfunction independent of disease duration and levodopa dose
Lim et al. [61]	Longitudinal	89 at baseline; 64 in longitudinal PD cohort	PD n = 64; healthy controls n = 25 at baseline; PD participants followed for 12 months	Lowest CNFD quartile showed greater motor deterioration than highest quartile. CNFD predicts motor progression
Niu et al. [63]	Cross-sectional	124	PD n = 63; MSA n = 30; healthy controls n = 31	CNFD and CNFL lower in MSA than PD. ROC analysis shows AUC of 0.72, 73.3% sensitivity, 73.0% specificity for MSA/PD discrimination
Lim et al. [64]	Cross-sectional	56	PD n = 19; PSP n = 11; MSA n = 8; healthy controls n = 18	CNFD, CNBD and CNFL were lower in both PD and MSA than in controls. In PSP, CNFD was lower than in controls, whereas CNBD and CNFL did not differ significantly.

Abbreviations: AUC, area under the curve; CNBD, corneal nerve branch density; CNFD, corneal nerve fibre density; CNFL, corneal nerve fibre length; IVCM, in vivo confocal microscopy; MSA, multiple system atrophy; PD, Parkinson's Disease; ROC, receiver operating characteristic.

those who did not [73]. IVCM parameters were significantly associated with cognitive function and functional independence in both MCI and dementia in a similar study [74].

Additionally, further evidence from Gundogan et al. showed significantly lower CNFL, CNFD, and CNBD in AD patients compared to healthy controls. Corneal sensitivity, the clinical functionality of corneal nerve metrics, was also significantly lower in AD patients compared to healthy controls, in conjunction with the aforementioned IVCM parameters [75].

Overall appraisal of the evidence in dementia and MCI

Existing studies provide preliminary evidence that IVCM parameters may represent a non-invasive biomarker of neurodegeneration and could potentially complement established cognitive and neuroimaging assessments. However, available evidence remains largely derived from single-centre cohorts with substantial overlap in investigators, limiting independent validation

TABLE 3 An overview of studies evaluating corneal nerve Status in dementia or MCI.

Authors (Year)	Study design	Sample size (total N)	Study population	Results
Ponirakis et al. [74]	Cross-sectional study	76	MCI n = 30; dementia n = 26; healthy controls n = 20	1. MCI patients had significantly lower CNBD and CNFL than controls 2. CNBD, CNFL, and CNFD were significantly reduced in dementia patients than controls 3. CNFD and CNFL were significantly lower in the dementia group compared to the MCI group 4. CNFD and CNBD were significantly associated with cognitive function, duration of cognitive impairment, and functional independence
Al-Janahi et al. [71]	Cross-sectional study	182	Healthy controls n = 36; MCI n = 80; dementia n = 66	The diagnostic accuracy of IVCM was high and comparable with MTA scoring for dementia and superior to MTA scoring for MCI.
Ponirakis et al. [72]	Cross-sectional study	208	Healthy controls n = 42; MCI n = 98; dementia n = 68	For MCI, the AUC of IVCM (76%–81%) was higher than brain volumetry (52%–70%). For dementia, the AUC of IVCM (77%–85%) was comparable to brain volumetry (69%–93%)
Ponirakis et al. [73]	Prospective cohort study	119	MCI n = 107 (progressed n = 33; did not progress n = 74); healthy controls n = 12; 2.6-year follow-up	Among 107 participants with MCI, 33 progressed to dementia over 2.6 years. Baseline CCM measures were lower in progressors; reported prognostic accuracy was 72%–75% for CCM versus 68%–69% for brain volumetry
Gundogan et al. [75]	Cross-sectional study	40	AD n = 22; healthy controls n = 18	1. AD patients had significantly lower CNFL and CNFD compared to controls 2. AD patients had significantly lower CNBD compared to controls

Abbreviations: AD, Alzheimer's disease; AUC, area under the curve; CNBD, corneal nerve branch density; CNFD, corneal nerve fibre density; CNFL, corneal nerve fibre length; IVCM, *in vivo* confocal microscopy; MCI, mild cognitive impairment; MTA, medial temporal atrophy.

and generalisability of the reported diagnostic and prognostic performance.

Table 3 shows a summary of studies on corneal nerve status associated with dementia and MCI.

Corneal nerve status in relation to multiple sclerosis

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system, particularly affecting young women [76]. It commonly involves the optic nerves, brainstem, cerebellum, and spinal cord. Axonal loss occurs early in the disease course and is a major determinant of progressive neurological disability, highlighting the need for biomarkers that facilitate early diagnosis and treatment [77].

MRI is an important imaging endpoint in MS clinical trials and is used to assess disease activity and progression [78]. Retinal nerve fibre layer thickness measured by optical coherence tomography has also been investigated as a marker of neuroaxonal damage [79], although its correlation with clinical disability remains limited. IVCM may provide an additional means of quantifying corneal axonal loss and assessing disease severity.

IVCM applications in MS

In a study of 26 patients with MS and 23 healthy controls, total corneal nerve fibre density was reduced in MS [80]. In a separate study, CNFD, CNBD and CNFL were reduced in MS, and CNFD was inversely associated with the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Severity Score (MSSS) [81]. In another study comparing clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS, and healthy controls, CNFD, CNFL, and corneal nerve fractal dimension (CNFrD) were significantly reduced across MS disease courses [82].

Among IVCM parameters, CNBD showed the highest discriminative performance between healthy controls and patients with relapsing-remitting MS, while CNFD showed the highest discriminative performance between healthy controls and secondary progressive MS [83].

Monitoring of disease progression

Serial IVCM may detect changes associated with disability progression. In a 2-year prospective cohort of patients with relapsing-remitting MS, corneal nerve fibre area (CNFA) and corneal nerve fibre width (CNFW) decreased

significantly as expanded disability status scale increased. Changes in CNFD and CNFL also correlated with changes in expanded disability status scale and multiple sclerosis severity score [84].

Similarly, Petropoulos et al. followed patients with relapsing-remitting MS, secondary progressive MS, and healthy controls over 2 years. CNFD, CNBD, and CNFL decreased significantly in relapsing-remitting MS, while CNFD and CNBD decreased significantly in secondary progressive MS [83].

These findings suggest that corneal nerve abnormalities are detectable across MS disease courses and may change with disability progression, supporting further evaluation of IVCM as a complementary imaging biomarker.

Overall appraisal of the evidence in MS

The MS literature includes two prospective cohort studies and several cross-sectional studies, giving it one of the stronger evidence bases for IVCM after DPN. Longitudinal studies demonstrate progressive corneal nerve loss over 2 years in association with worsening disability, suggesting that IVCM may reflect dynamic neuroaxonal change.

However, the longitudinal cohorts remain relatively small with limited follow-up. Whether IVCM provides additional information beyond MRI or retinal nerve fibre layer assessment by optical coherence tomography has not been formally established. Its diagnostic, prognostic, and disease-monitoring roles therefore remain investigational, and larger prospective multicentre studies comparing IVCM with established MS biomarkers are required before routine clinical use.

Table 4 shows a summary of studies on corneal nerve status associated with MS.

Corneal nerve status in relation to schizophrenia

IVCM applications in schizophrenia

Schizophrenia is a chronic, debilitating psychiatric condition characterised by positive, negative and cognitive symptoms most commonly attributable to genetic susceptibility and environmental influences [85]. While no objective diagnostic markers are available at present, well-accepted diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, are commonly used [86]. This reliance on clinical assessment may limit diagnostic accuracy. Changes in ocular physiology, including corneal nerve alterations, are therefore being investigated as potential biomarkers [87].

In a cross-sectional study involving 62 subjects, there were significant reductions in CNFD, CNFL, CNBD and the CNBD: CNFD ratio in patients with schizophrenia compared with healthy controls [88]. The ratio is CNBD:CNFD MRI brain volumetry also showed a significant decrease in cingulate gyrus volume in schizophrenia patients. The area under the ROC curve for distinguishing schizophrenia from healthy controls was 88% for CNFL, 84% for CNBD, 79% for CNFD and 73% for cingulate gyrus volume.

Comparison of IVCM with existing biomarkers

Neither IVCM parameters nor cingulate gyrus volume correlated with symptom severity or cognitive dysfunction [88]. Structural MRI findings may also be confounded by treatment-related factors such as antipsychotic-associated brain volume changes [89], and have limited correlations with clinical outcomes other than cognitive impairment [90], with no established diagnostic or prognostic role in psychosis [91]. Although IVCM showed greater discriminative accuracy than cingulate gyrus volumetry in a single study, further validation is required before its diagnostic utility can be established.

Overall appraisal of the evidence in schizophrenia

The evidence synthesised in this review regarding schizophrenia is confined to a single cross-sectional study of 62 participants. Although the reported discriminative performance was high, possible confounding factors including dry eye, antipsychotic exposure and metabolic syndrome were not formally assessed or adjusted for. Current limited evidence should be regarded as preliminary and hypothesis-generating rather than as evidence of diagnostic utility.

Corneal nerve status in relation to amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting upper and lower motor neurons, leading to muscle weakness, bulbar dysfunction and, in advanced disease, respiratory failure [92]. Diagnosis remains largely clinical and is supported by electrodiagnostic findings, due to clinical heterogeneity and the lack of reliable objective biomarkers [93]. CSF, biochemical and neurophysiological tests may support diagnosis, but none are sufficiently robust to serve as the primary outcome measure in clinical trials [94]. Although traditionally considered a motor disease, ALS is increasingly recognised to involve subclinical C-fibre sensory dysfunction [95], providing a rationale for IVCM assessment of corneal nerve degeneration.

In a cross-sectional study of ALS patients and healthy controls [96] conducted to assess corneal nerve parameters and dendritic cell densities, CNFL was significantly lower, while corneal dendritic cell densities were significantly higher in patients with ALS than in controls. In addition, inferior whorl corneal length was significantly associated with disease severity and progression in ALS. Patients with bulbar involvement also showed significantly lower inferior whorl corneal length and higher inferior whorl dendritic cell density compared to patients without bulbar involvement. In a study of a similar design, there was a significant reduction in total corneal nerve length (CNL) and an increase in nerve tortuosity in ALS patients compared to healthy controls. Importantly, there was a significant correlation between CNL and the ALS functional rating scale bulbar subscore as well as the ALS severity score bulbar subscore [97], which are commonly used clinical measures to quantify the degree of bulbar dysfunction through assessments of speech and swallowing. Use CNL for total corneal nerve length and

TABLE 4 An overview of studies evaluating corneal nerve fibre alterations in the context of MS.

Authors (Year)	Study design	Sample size (total N)	Study population	Results
Mikolajczak et al. [80]	Cross-sectional study	49	MS n = 26; healthy controls n = 23	Total corneal nerve fibre density was reduced in MS and associated with clinical severity.
Bitirgen et al. [81]	Cross-sectional study	87	RRMS n = 57; healthy controls n = 30	CNFD, CNBD and CNFL were reduced in patients with MS compared to healthy controls Inverse correlations were found between EDSS and nerve fibre density, and between MSSS and nerve fibre density
Bitirgen et al. [84]	Prospective cohort study	31	RRMS n = 31; 2-year follow-up	There was a significant reduction in CNFA and CNFW with increasing EDSS. The changes in CNFD and CNFL correlated with the changes in EDSS.
Petropoulos et al. [82]	Cross-sectional study	72	CIS n = 9; RRMS n = 20; SPMS n = 22; healthy controls n = 21	There was a significant reduction in CNFD, CNFL, and CNFrD in MS patients compared to healthy controls
Petropoulos et al. [83]	Prospective cohort study	103	RRMS n = 68; SPMS n = 15; healthy controls n = 20; 2-year follow-up	Corneal nerve parameters show excellent capacity to distinguish healthy controls from relapsing-remitting MS and secondary progressive MS patients, and relapsing-remitting MS from secondary progressive MS. CNFD and CNBD decreased over 2 years in RRMS and SPMS; CNFL also decreased in RRMS.

Abbreviations: CNBD, corneal nerve branch density; CNFA, corneal nerve fibre area; CNFD, corneal nerve fibre density; CNFL, corneal nerve fibre length; CNFW, corneal nerve fibre width; CNFrD, corneal nerve fractal dimension; EDSS, expanded disability status scale; MS, multiple sclerosis; MSSS, multiple sclerosis severity score.

for the bulbar-score correlations. In contrast, Turhan et al. found significantly higher corneal dendritic cell density in ALS patients than healthy controls, but no significant differences in CNFD, CNFL or CNBD [95].

Overall, the three small cross-sectional studies in this review demonstrate discordant results: two reported corneal nerve loss, while one found no difference in IVCM parameters apart from dendritic cell density. No longitudinal data are available, and no study has examined whether IVCM parameters can predict functional decline. The evidence is therefore best described as conflicting and preliminary.

Table 5 shows an overview of studies on corneal nerve status associated with ALS.

Corneal nerve status in relation to migraine

Introduction and application of IVCM

Migraine is a common, chronic neurological disorder characterised by recurrent disabling attacks of headache, and continues to be one of the world's leading causes of disability [98] and poor quality of life. The aetiology of migraine is not well understood at present, but is believed to be due to a constellation of genetic, environmental, and neurological factors. Currently, the diagnosis of migraine is largely clinical, and is based on a comprehensive history and clinical examination [99]. The lack of objective biomarkers, together with the clinical heterogeneity of migraine, poses significant challenges to the development of effective and individualised management. The cornea receives its sensory supply from the ophthalmic division of the trigeminal nerve. The close association between the trigeminal nerve and the pathogenesis of migraine underscores the potential value of corneal nerve neuropathic changes as objective biomarkers for migraine diagnosis, disease progression, and treatment response [100].

Corneal nerve alterations have been reported in migraine, with Kinard et al. finding significantly lower CNFD in patients with chronic migraine than in healthy controls [101]. This is further corroborated by a study by Guldiken et al. who also demonstrated a significant decrease in CNFD, CNBD, and CNFL in patients with migraine compared to healthy controls, regardless of variables such as number of headache days or the presence of dry eyes. There was no significant difference in IVCM parameters for various migraine durations, number of headache days over the recent three months or pain intensity [102]. The significant corneal neuropathic changes reported in the above studies are consistent with the trigeminovascular hypothesis [103] in the pathogenesis of migraines, and suggest that corneal nerve parameters merit further evaluation as candidate biomarkers in migraine.

Overall appraisal of the evidence in migraine

Two cross-sectional studies form the basis of this section. Both report reductions in corneal nerve parameters relative to controls, but neither demonstrated a consistent relationship with headache frequency, migraine duration or pain intensity. Dry eye disease, which is more prevalent among patients with migraine and independently reduces corneal nerve

TABLE 5 An overview of studies on corneal nerve status in relation to ALS.

Authors (Year)	Study design	Sample size (total N)	Study population	Results
Ferrari et al. [97]	Cross-sectional study	15	ALS n = 8; healthy controls n = 7	Reduced corneal small-fibre nerve number and branching in ALS patients ALS patients showed significantly reduced total corneal nerve length (CNL) and increased nerve tortuosity compared with controls.
Fu et al. [96]	Cross-sectional study	130	ALS n = 66; healthy controls n = 64	ALS patients had significantly lower CNFL and higher dendritic cell densities in peripheral and inferior whorl regions than controls. IWL was significantly associated with disease severity and progression in patients with ALS. Patients with bulbar involvement showed significantly lower IWL and higher inferior whorl dendritic cell densities than those without
Turhan et al. [95]	Cross-sectional study	51	ALS n = 31; healthy controls n = 20	CNFD, CNFL, and CNBD do not differ between ALS patients and controls ALS patients showed significantly higher dendritic cell density and a greater number of patients with increased dendritic cell density than controls

Abbreviations: ALS, amyotrophic lateral sclerosis; CNFL, corneal nerve fibre length; CNFD, corneal nerve fibre density; CNBD, corneal nerve branch density; IWL, inferior whorl length.

metrics, was not consistently accounted for. Current evidence therefore supports an association between migraine and corneal nerve alterations rather than an established biomarker role.

Corneal nerve status in relation to tauopathies

Introduction

Tauopathies are chronic, progressive neurodegenerative disorders characterised by abnormal tau deposition in the central nervous system [104]. Tau aggregates form neuropathological inclusions within neurons, causing neuronal death [105]. Clinical manifestations include movement, cognitive and behavioural disorders with substantial heterogeneity [106]. Diagnosis is confirmed by neuropathological assessment at autopsy, except in inherited autosomal dominant tauopathies or clinically defined syndromes such as progressive supranuclear palsy (PSP) [105].

Application of IVCM in tauopathies

As substantial neuronal damage often precedes overt symptoms and approximately one-third of disease-modifying therapies in development target tau aggregation or synthesis [106], early detection of tauopathies is increasingly important [107]. Peripheral tissues may provide accessible biomarkers. Skin has emerged as a minimally invasive marker of neurodegeneration because of its bidirectional interaction with the central nervous system through the skin-brain axis [108]. Vacchi et al. demonstrated tau immunoreactivity along somatosensory and autonomic cutaneous nerve fibres in patients with degenerative tauopathies [109]. Given the similar embryological origins of skin and corneal fibres, corneal nerve degeneration has also been investigated in tauopathies.

Experimental studies have demonstrated corneal nerve abnormalities in tauopathy models. In an animal study comparing mouse models of tauopathy (P301L) and wild type [110], CNFL and CNFD were significantly decreased compared with wild-type mice, while corneal regeneration after injury was significantly impaired [110]. In another murine model, mice overexpressing human non-mutated tau showed significantly decreased stromal corneal nerve occupancy at 4 months, with no change in sub-basal plexus nerve occupancy compared with wild-type mice. Htau mice experienced corneal nerve degeneration before any memory deficit or learning impairment was apparent [111].

Overall appraisal of evidence in tauopathies

Evidence supporting IVCM as a biomarker for tauopathies remains predominantly pre-clinical. Experimental studies demonstrate corneal nerve degeneration and impaired regeneration, with some abnormalities preceding neurological deficits, suggesting potential sensitivity to early tau-associated neurodegeneration. However, human evidence remains extremely limited. Although corneal nerve abnormalities have been reported in small cohorts including patients with PSP [64], there is insufficient evidence that these changes are specific to tau pathology or correlate directly with tau burden. Longitudinal human studies incorporating tau-PET, CSF or plasma phosphorylated tau are needed to determine whether IVCM can distinguish tauopathies from other neurodegenerative disorders and detect pre-clinical disease.

Corneal nerve status in relation to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic, progressive immune-mediated neuropathy affecting peripheral nerves and nerve roots. The disease course is generally slow and progressive, but approximately one-third of patients with CIDP may experience a relapsing-remitting course [112]. CIDP can manifest as different clinical forms. The classical

presentation is characterised by both proximal and distal symmetrical weakness with sensory loss predominantly affecting proprioception and vibration sense [113].

Diagnosis and treatment of CIDP remain challenging because reliable disease biomarkers are lacking, limiting patient stratification and individualised treatment. Although disease activity can be assessed using established severity scores, objective measures remain limited [114]. Early axonal loss has been associated with clinical outcomes and shown to predict long-term disability and muscle strength [115, 116]. Given this association, corneal nerve assessment may provide an objective measure of axonal loss in CIDP (Figure 3).

In a prospective cohort of 17 patients, IVCM was used to assess corneal nerve degeneration and immune cell infiltration over 18 months [117]. Baseline total cell infiltrates >30/mm^2 demonstrated 100% sensitivity and 100% specificity for predicting clinical progression over 18 months. However, total cell infiltrates did not change subsequently in either progressive or stable CIDP, raising uncertainty about their ability to monitor treatment response. Corneal parameters also did not correlate with disease duration or severity.

Among the studies included in this review, the evidence in CIDP consists of a single prospective cohort of 17 patients. A limited sample size renders the reported sensitivity and specificity of 100% for predicting clinical progression statistically fragile. The absence of correlations between corneal parameters and disease duration or severity is difficult to reconcile with a straightforward biomarker interpretation. Replication in substantially larger cohorts is required before clinical inference can be drawn.

Comparison of the evidence base across diseases

The quantity and quality of evidence supporting corneal nerve status as a biomarker vary substantially across the conditions reviewed. Amongst all conditions reviewed, DPN has the broadest and most independently replicated evidence base. Multiple independent groups have reported concordant findings in large cohorts. Prospective longitudinal follow-up extends up to 6 years and predictive thresholds for incident neuropathy have been proposed and tested. MS is also supported by two prospective cohorts with 2-year follow-up, which demonstrate that corneal nerve loss parallels disability progression. However, the longitudinal evidence base remains relatively small and includes overlapping investigators, limiting the extent of fully independent replication. In PD, the core cross-sectional observation of corneal nerve loss is well replicated, but evaluation of clinically important applications such as prognostication and phenotyping still largely rests on single-centre studies. Evidence in dementia and MCI mostly originates from one research group, with only one independent Alzheimer's disease cohort, although findings are internally consistent. CIDP, migraine, ALS, schizophrenia and tauopathies are each supported by one to three small studies, with conflicting results in ALS and predominantly pre-clinical data in tauopathies; the evidence in these conditions should be regarded as exploratory.

Table 6 summarises the evidence according to the number and design of included publications, the largest study sample, availability and duration of longitudinal follow-up, and evidence of independent replication or multicentre validation.

Comparison between IVCM and existing biomarkers across diseases

A related and largely unanswered question is whether IVCM parameters provide incremental value over existing biomarkers. Direct comparisons are available in only a small number of contexts. In DPN, CNFD had a higher AUC than intraepidermal nerve fibre density obtained by skin biopsy within the same cohort (0.81 versus 0.73) [25], and IVCM detects abnormality earlier than nerve conduction studies [16]. In MCI, IVCM parameters showed higher diagnostic AUCs than medial temporal lobe atrophy scoring and brain volumetry within the studied cohorts, whereas performance in dementia was broadly comparable; one MCI cohort also reported higher apparent prognostic accuracy for progression to dementia than brain volumetry [71–73]. In schizophrenia, the single available study reported a higher AUC for CNFL than for cingulate gyrus volume on magnetic resonance imaging within the same cohort, although neither measure correlated with symptom severity [88]. In MS, corneal nerve measures and retinal nerve fibre layer thickness have been compared using ROC analyses in the same cohort [83], but incremental clinical value over established imaging remains unproven; and in PD no comparison has been made with dopamine transporter imaging or with skin biopsy for phosphorylated α-synuclein. In CIDP, a single 17-patient cohort reported 100% sensitivity and 100% specificity for baseline corneal immune-cell infiltration greater than 30/mm^2, compared with 80% sensitivity and 88% specificity for nerve ultrasound, but this has not been externally validated [117]. Demonstrating incremental value over existing modalities, rather than simply a difference from healthy controls, is the principal evidential gap facing the field.

Table 7 shows an overview of direct comparisons between IVCM and existing biomarkers across diseases.

Limitations and future directions

Limitations of the present review

This article is a narrative rather than a systematic review. Studies were identified through a single database and were selected on the basis of relevance rather than by duplicate independent screening; no formal risk-of-bias instrument was applied; and the appraisals of evidence strength presented at the end of each disease section represent the qualitative judgement of the authors. Publication bias is likely to favour positive findings, particularly in the smaller literatures such as schizophrenia, migraine and CIDP where few studies exist. In addition, several disease areas are dominated by a small number of research groups, so that apparent consistency of findings may in part reflect shared methodology rather than biological reproducibility.

A further limitation lies in the current evidence base for tauopathies, where current data are predominantly derived from animal models, with very limited human evidence. Although pre-clinical models provide valuable insight into the mechanisms of tau-related neurodegeneration, they may not fully reflect the complexity of human disease. Human data presently available are limited, and the clinical relevance of corneal nerve findings in tauopathies

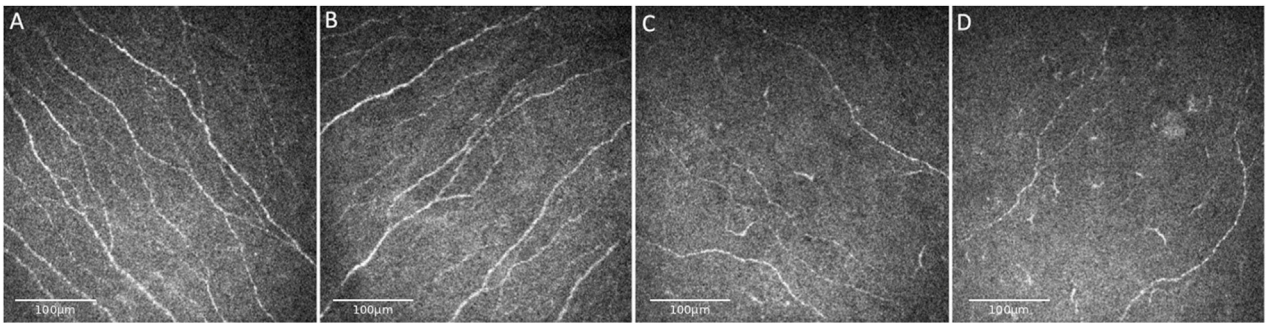


FIGURE 3
Representative IVCM images of the corneal sub-basal nerve plexus in controls and patients with CIDP (Heidelberg Retina Tomograph III with Rostock Cornea Module; Heidelberg Engineering GmbH, Heidelberg, Germany). Original image size, 400 × 400 µm (384 × 384 pixels). Images are original to this study and have not been published previously. Controls **(A,B)**. Patients with CIDP **(C,D)**. CIDP patients show reduced corneal nerve fibre density and length, accompanied by increased immune cell (IC) count (total number of ICs per frame) and density (cells/mm^2).

therefore largely remains unestablished. This limitation should be borne in mind when interpreting the section on tauopathies.

Ocular and systemic confounders of corneal nerve measurement

Ageing, ocular surface inflammation, dry eye disease, DM without neurological involvement, contact lens wear and prior ocular surgery may confound corneal nerve measurements. Ageing is associated with reduced corneal nerve fibre density and length [118], while ocular surface inflammation and dry eye disease alter corneal nerve morphology. Neuropathic corneal pain, which may be confused with dry eye disease, is associated with corneal microneuromas that could be mistaken for disease-related neurodegeneration [119].

DM may alter corneal nerve parameters before neuropathy is clinically apparent. In 37 individuals with impaired glucose tolerance compared with 20 healthy controls, CNFD, CNBD and CNFL were all significantly reduced, and 40.5% had CNFD below a neuropathy-consistent threshold despite no clinical diabetes or peripheral neuropathy [120]. Diabetic corneal neuropathy also correlates with diabetic peripheral neuropathy severity [121] and independently predicts diabetic foot risk, with corneal changes preceding clinical foot complications [45, 122]. Keratorefractive surgery [123, 124], cataract surgery [125] and orthokeratology contact lens wear may also induce corneal denervation and alter the normal architecture of the sub-basal nerve plexus [126].

Methodological heterogeneity between studies

Methodological heterogeneity across studies may affect the comparability and reproducibility of corneal nerve measurements. Different confocal microscopy platforms, such as the Nidek ConfoScan 4 and the Tandem Scanning confocal microscope, differ in resolution, field of view, and image acquisition characteristics, and have been shown to yield subbasal nerve density estimates that differ by two-to three-fold for the same tissue [127]. Laser scanning platforms, such as the Heidelberg Retina Tomograph II, provide high-resolution imaging of the corneal subbasal nerve plexus and may detect smaller-calibre nerve fibres [128]. Acquisition protocols also contribute to variability between studies. The number of images sampled per cornea affects measurement accuracy, with as many as eight non-overlapping central images required to bring nerve branch density estimates within 30% of the true mean [129], while the precise location of images sampled within the central cornea can independently produce significant differences in nerve parameter values, reflecting the heterogeneous, whorl-centred distribution of the subbasal nerve plexus [130]. In addition, manual and automated (or semi-automated) analysis software packages, such as CCMetrics and ACCMetrics, do not produce equivalent results. Automated analysis has been shown to systematically underestimate corneal nerve fibre length relative to manual tracing, despite preserving good reproducibility [131], and automated analysis has shown a non-significant tendency to underestimate corneal nerve measurements relative to manual tracing following refractive surgery-induced corneal reinnervation, attributed to thin, short regenerating fibres being more readily missed by automated software [132].

Future directions

Future research should prioritise the development of consensus-based, standardised protocols for image acquisition, sampling, parameter definition, and analysis. Moreover, studies should also report the confocal platform, image acquisition protocol, and analysis software used, adopt a fixed and consistent image-selection strategy, and, where possible, validate findings using more than one analysis method, so that results can be compared reliably across the field. Larger prospective multicentre cohorts with longitudinal follow-up should subsequently apply these standardised methods to establish robust normative reference ranges, validate diagnostic and prognostic thresholds, and assess the value of IVCM parameters over existing biomarkers. Further refinement of IVCM image acquisition may additionally improve the precision and representativeness of corneal nerve measurements. Integration of validated automated or artificial intelligence-based analysis may facilitate reproducible assessment across centres. As corneal nerve imaging becomes more widely applied as a biomarker for neurodegenerative and neurological disease, future studies should screen for and document ocular and systemic factors, such as ageing, ocular surface inflammation, dry eye disease, DM without neurological involvement, contact lens wear,

TABLE 6 Comparison of the evidence base for corneal nerve status as a biomarker across neurodegenerative and neurological conditions.

Condition	Publications included in this review (design)	Largest sample	Longitudinal data	Independent cohorts/cohort overlap	Independent replication/ multicentre data
DPN	38 unique publications listed in Table 1: predominantly cross-sectional, with longitudinal cohorts, reviews/meta-analysis, one animal model and multiple AI development studies	490 participants in the largest primary clinical cohort; meta-analysis included 1,680 participants	Yes – follow-up to 6 years	≥12 clearly distinguishable cohorts. Exact number cannot be reliably determined as several publications represent follow-up, secondary analyses or reuse of overlapping clinical/image datasets	Yes – multiple independent groups; multinational data available
MS	5 publications: cross-sectional and prospective cohort studies	103 participants	Yes - two cohorts with 2-year follow-up	3 independent cohorts, with partial overlap in subsequent longitudinal publications	Partial – multiple cohorts, with overlapping investigators in longitudinal studies
PD	11 publications: case-control/cross-sectional studies, one prospective longitudinal study and one review	124 participants	Limited - one 12-month study	≥8 independent cohorts	Partial – core finding of corneal nerve loss replicated across multiple independent cohorts. Phenotyping and prognostic applications remain supported largely by single-centre studies
Dementia and MCI	5 studies: cohort and cross-sectional	208 participants	Yes – MCI progression cohort followed for a mean 2.6 years	2 independent cohorts	Limited – predominantly one research group; one independent AD cohort
CIDP	1 prospective cohort	17 participants	Yes - 18 months	1 independent cohort	None amongst included studies
Migraine	2 cross-sectional studies	80 participants	No	2 independent cohorts	Yes – two independent cross-sectional cohorts
ALS	3 cross-sectional studies	130 participants	No	3 independent cohorts	Yes – three independent cohorts, but findings are conflicting
Schizophrenia	1 cross-sectional study	62 participants	No	1 independent cohort	No
Tauopathies	2 studies; evidence reviewed here is pre-clinical and derived from transgenic murine models	Not applicable	No	2 independent pre-clinical murine studies/models	Pre-clinical replication only – two murine studies

Abbreviations: AUC, area under the curve; CNBD, corneal nerve branch density; CNFD, corneal nerve fibre density; CNFL, corneal nerve fibre length; IVCM, *in vivo* confocal microscopy; DPN, diabetic peripheral neuropathy; MS, multiple sclerosis; PD, Parkinson's disease; MCI, mild cognitive impairment; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; ALS, amyotrophic lateral sclerosis.

Table 6 summarises the maturity of the evidence base according to publication number and study design, number and independence of participant cohorts, largest sample size, availability of longitudinal follow-up, and independent or multicentre replication. A formal evidence grade was not assigned because this narrative review did not apply a validated risk-of-bias or evidence-certainty framework. Publication number should not be interpreted as equivalent to the number of independent patient populations.

Independent cohort was defined as a distinct participant population. Publications reporting follow-up, extension, secondary analyses or clearly overlapping recruitment programmes were grouped as a single cohort family. Pooled multicentre studies were evaluated according to their contributing cohort sources where these could be identified. Reviews and meta-analyses were included in publication counts but were not counted as independent cohorts. Pre-clinical studies were considered separately from human cohorts. Where participant-level overlap could not be determined confidently from the published reports, the minimum number of clearly distinguishable independent cohorts (≥n) is reported.

and prior ocular surgery and either exclude affected individuals or statistically adjust for these variables, so that observed corneal nerve changes can be attributed to the disease under investigation.

Collectively, these developments will be critical for establishing corneal nerve status not only as a diagnostic adjunct, but also as a reliable and generalisable adjunctive biomarker in future studies of neurodegenerative and neurological diseases.

TABLE 7 Direct comparisons between IVCM and existing biomarkers across diseases.

Condition	Clinical purpose	Comparator/reference test	Reported direct comparison	Same cohort?	External validation/ incremental value
DPN	Diagnostic	Skin biopsy (IENFD)	CNFD AUC 0.81 versus IENFD 0.73 for DPN diagnosis [25]	Yes	Thresholds/performance not externally validated in that study; incremental value beyond established testing was not formally tested
Dementia	Diagnostic	MRI medial temporal lobe atrophy (MTA) score and brain volumetry	For MCI, CCM AUCs exceeded MTA and brain-volumetry AUCs within the studied cohorts; for dementia, performance was broadly comparable [71, 72]	Yes	No external validation of the comparative performance; no formal incremental-value analysis
MCI	Prognostic	MRI brain volumetry	At study-derived cut-offs, classification accuracy was 72%–75% for CCM versus 68%–69% for hippocampal/whole-brain volumetry; however, AUCs were 0.71–0.74 for CCM versus 0.78 for hippocampal and whole-brain volume [73]	Yes	Single-centre cohort; no external validation and no formal demonstration of incremental value
Schizophrenia	Diagnostic discrimination	MRI cingulate gyrus volume	CNFL AUC 0.88 versus cingulate gyrus volume AUC 0.73 for distinguishing schizophrenia from controls [88]	Yes	Cross-sectional cohort; no external validation; neither measure correlated with symptom severity
CIDP	Prognostic/risk stratification	High-resolution nerve ultrasound (Bochum ultrasound score)	Baseline total corneal cells >30/mm^2: Sensitivity/specificity 100%/100% in this cohort; maximum BUS of 4: 80%/88% for clinical progression [117]	Yes	Pilot cohort of 17 patients; thresholds were not externally validated; incremental value was not tested
PD	Diagnostic/ prognostic	Dopamine transporter imaging; skin biopsy for phosphorylated α-synuclein	No direct head-to-head diagnostic or prognostic comparison identified in the studies reviewed	No	Incremental clinical value remains untested
MS	Diagnostic/ monitoring	MRI lesion burden; retinal nerve fibre layer by OCT	Corneal nerve measures and retinal nerve fibre layer thickness were compared using ROC analyses in the same cohort [83].	Yes	Incremental clinical value remains untested
ALS	Diagnostic/ monitoring	Clinical/electrodiagnostic assessment	No formal head-to-head diagnostic or monitoring performance comparison with clinical/ electrodiagnostic assessment was identified in the reviewed studies	No	Incremental clinical value remains untested
Migraine	Diagnostic/ monitoring	Clinical diagnostic criteria	No head-to-head diagnostic-performance comparison; clinical criteria were used to define migraine cases	No	Incremental clinical value remains untested

(*Continued*)

TABLE 7 Continued

Condition	Clinical purpose	Comparator/reference test	Reported direct comparison	Same cohort?	External validation/ incremental value
Tauopathies	Diagnostic/early detection	Molecular tau biomarkers (e.g., tau-PET and CSF/plasma phosphorylated tau; established primarily in AD)	No human head-to-head comparison identified; IVCM evidence in this review is predominantly preclinical	No	Clinical incremental value cannot currently be assessed

Abbreviations: AUC, area under the curve; BUS, bochum ultrasound score; CCM, corneal confocal microscopy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNFD, corneal nerve fibre density; DPN, diabetic peripheral neuropathy; IENFD, intraepidermal nerve fibre density; IVCM, *in vivo* confocal microscopy; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCT, optical coherence tomography; PD, Parkinson's disease.

Conclusion

IVCM has emerged as a promising non-invasive approach for evaluating corneal nerve alterations across a broad spectrum of neurodegenerative and neurological diseases. Based on the available literature, reductions in corneal nerve fibre density, length, and branching have been associated with disease presence, severity, progression, and, in selected conditions, future clinical deterioration. However, the strength of this evidence is highly disease-dependent. The most robust support currently exists in diabetic peripheral neuropathy and multiple sclerosis, where findings have been reproduced across independent cohorts and supported by longitudinal data. In Parkinson's disease and dementia, corneal nerve alterations are consistently reported and show potential diagnostic and prognostic value, although several clinically important applications remain dependent on small, single-centre cohorts and require external validation. Evidence in ALS, migraine, schizophrenia, CIDP, and tauopathies remains comparatively limited, conflicting, or predominantly pre-clinical and should therefore be considered exploratory.

Although IVCM shows promise as a non-invasive biomarker, future large-scale, multicentre longitudinal studies using standardised imaging and analysis protocols, with appropriate adjustment for confounders are needed. Advances in wide-field imaging, automation, and artificial intelligence may further improve reproducibility and scalability [133], supporting the potential integration of IVCM into the diagnosis and longitudinal monitoring of neurological diseases.

Author contributions

Y-CL conceived the study. JL and AS contributed equally to this work. JL, AS, MY, CL, IXYL, and AA conducted the literature search and wrote the manuscript. JKS and Y-CL supervised the study and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this work, the author(s) used GPT-4 to edit the language and improve readability. Large language models were only used for language editing.

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