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Review

Diabetic corneal neuropathy as a surrogate marker for diabetic peripheral neuropathy

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From the Contents

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Abstract

Diabetic neuropathy is a prevalent microvascular complication of diabetes mellitus, affecting nerves in all parts of the body including corneal nerves and peripheral nervous system, leading to diabetic corneal neuropathy and diabetic peripheral neuropathy, respectively. Diabetic peripheral neuropathy is diagnosed in clinical practice using electrophysiological nerve conduction studies, clinical scoring, and skin biopsies. However, these diagnostic methods have limited sensitivity in detecting small-fiber disease, hence they do not accurately reflect the status of diabetic neuropathy. More recently, analysis of alterations in the corneal nerves has emerged as a promising surrogate marker for diabetic peripheral neuropathy. In this review, we will discuss the relationship between diabetic corneal neuropathy and diabetic peripheral neuropathy, elaborating on the foundational aspects of each: pathogenesis, clinical presentation, evaluation, and management. We will further discuss the relevance of diabetic corneal neuropathy in detecting the presence of diabetic peripheral neuropathy, particularly early diabetic peripheral neuropathy; the correlation between the severity of diabetic corneal neuropathy and that of diabetic peripheral neuropathy; and the role of diabetic corneal neuropathy in the stratification of complications of diabetic peripheral neuropathy.

Key Words: corneal nerve quantification; corneal nerves; diabetic cornea; diabetic corneal neuropathy; diabetic microvascular complications; diabetic peripheral neuropathy; *in vivo* confocal microscopy; neurotrophic keratopathy; ocular surface

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by systemic hyperglycemia. The disease manifests in either of two forms: a primary insulin production deficiency in type 1 DM (T1DM) or a gradual development of insulin resistance and decreased sensitivity towards insulin secretion in type 2 DM (T2DM) (Association, 2010). In 2013, the total number of diabetics in the world was 382 million (Alaboud et al., 2016). This figure has been projected to reach 366 million by 2030 (Khalil, 2017) and 693 million by 2045 (Alwin Robert and Al Dawish, 2019). Besides adversely affecting one's health, DM has demonstrated debilitating effects that scale beyond the individual level – enormous healthcare costs were inflicted upon the economy in 2007, amounting to a staggering US$174 billion and US$58 billion arising from loss of productivity (Khalil, 2017; Alwin Robert and Al Dawish, 2019). Meanwhile, the worldwide economic burden of DM is poised to hit US$2.1 trillion by 2030 (Bommer et al., 2018). Given the far-reaching implications of DM as an international health challenge, it is imperative for us to understand how to actively prevent or manage the complications that are associated with DM.

DM, especially if uncontrolled over a prolonged period, is linked to the development of both macrovascular and microvascular complications. Microvascular complications can be primarily categorized into diabetic nephropathy, diabetic retinopathy, and diabetic peripheral neuropathy (DPN) (Khalil, 2017). DPN presents as a length-dependent sensorimotor polyneuropathy, resulting in systemic structural and functional changes in neuronal cells. Of burgeoning interest is a plausible relationship that may be established between DPN and diabetic corneal neuropathy (DCN), which is separate ocular sequelae from diabetic retinopathy (Pritchard et al., 2011). In this review, we will discuss the clinical features of DCN and DPN. We will further discuss the relevance of DCN in detecting the presence of DPN, the correlation between the severity of DCN and that of DPN, and the role of DCN in the stratification of complications of DPN.

Search Strategy and Selection Criteria

The authors conducted a search on the online database PubMed Central, Embase, Cochrane, and Scopus for relevant articles that describe the characteristics of DCN and DPN or explore the association between both. Articles were included up to June 2021. Keywords included but were not limited to "diabetes" AND "corneal neuropathy" AND "peripheral neuropathy" OR "keratopathy", "corneal sensitivity" AND "diabetes", "*in-vivo* confocal microscopy" AND "diabetes", "corneal nerves" AND "diabetes". Only papers written in English were incorporated in our review, and we restricted the date of publication to the most recent ten years as much as possible. Supplementary relevant articles were also extracted from the bibliographies of the existing articles. After duplicate removal, the authors independently screened the abstracts and shortlisted papers based on our inclusion criteria. We later examined the full-text version of all selected articles. Out of the 319 articles identified and screened from the preliminary database search, a result of 102 articles was included in the final manuscript.

Diabetic Microvascular Complications

Diabetic microvascular complications manifest mainly as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy (Alaboud et al., 2016; Khalil, 2017; Khanam et al., 2017; Alwin Robert and Al Dawish, 2019). Diabetic neuropathy commonly presents as a symmetrical sensorimotor neuropathy (Gupta and Gupta, 2014; Alwin Robert and Al Dawish, 2019), affecting nerves in all parts of the body including those on the cornea, leading to DCN. As diabetic neuropathy is a systemic nervous disorder, patients with DCN may also suffer from DPN. Therefore, the evaluation for DCN not only presents a window to diagnose DCN early, it also could serve as a surrogate marker for DPN (Zhao et al., 2019).

Diabetic Peripheral Neuropathy

With the incidence of DM increasing across the world, the incidence of complications that follows is also expected to rise accordingly (Sun et al., 2020). DPN is a well-documented complication of DM, affecting up to 50% of patients during the clinical course (Bikbova et al., 2018). It usually manifests itself late into the disease or in uncontrolled DM, with as many as 39% of patients experiencing painful DPN when left untreated (Snyder et al., 2016). An estimated 236 million persons worldwide have been diagnosed with DPN (Tesfaye and Selvarajah, 2012). DPN is also a significant contributor to morbidity and mortality in diabetic patients (Tesfaye and Selvarajah, 2012) – patients with DPN are 10 to 20 times more likely to undergo a limb amputation than patients without DPN (Sun et al., 2020), with a lower

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limb lost as a result of DPN every 30 seconds (Selvarajah et al., 2019). In the United States, the annual cost per patient to visit various healthcare institutions for DPN increased by 46%, with total healthcare costs channeled to manage this complication adding up to an astonishing US$10.91 billion a year (Liu et al., 2019).

Pathogenesis of diabetic neuropathy

To date, the pathophysiology of diabetic neuropathy has yet to be fully elucidated – the presentation of neuropathic symptoms differs from patient to patient and is far from uniform. Though, the underlying pathophysiological mechanisms may be similarly heterogeneous, likely attributed to the metabolic and microvascular processes from chronic hyperglycemia (**Figure 1**). The metabolic pathways related to the pathogenesis include formation and accumulation of advanced glycation end products (AGE), activation of the aldose reductase (polyol) pathway, activation of protein kinase C (PKC) and mitogen-activated protein kinases, as well as the production of reactive oxygen species (ROS) (Singh et al., 2014). Collectively, these processes culminate in direct nerve axonal injury, ischemia, and eventual neuronal cell loss (Hicks and Selvin, 2019). The hypoxic and ischemic environment also promotes cytokine proliferation (tumor necrosis factor-α and interleukin-6) that contributes to the role of inflammation in diabetic neuropathy (Ristikj-Stomnaroska et al., 2019). However, serum nerve growth factor has been reported to be uninvolved in the development of DPN. In fact, it has been found to be negatively associated with the severity of DPN (Kim et al., 2009).

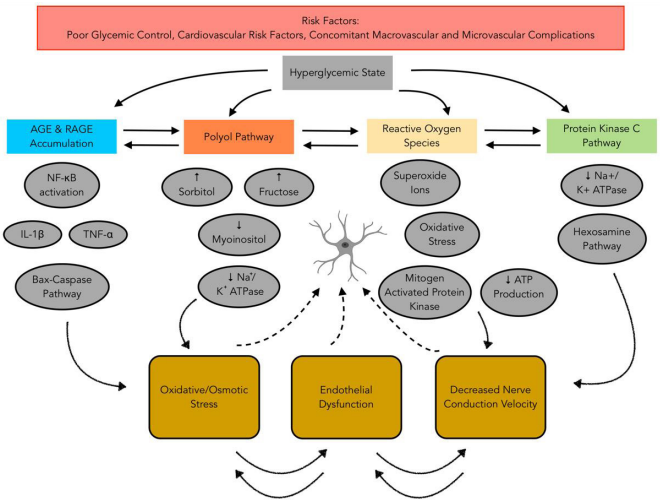

Figure 1 | **Pathogenesis of diabetic neuropathy.**
A chronic hyperglycemic state predisposes downstream metabolic processes of AGE/receptor for AGE, polyol pathway activation, production of ROS, and the induction of the PKC pathway. The subsequent activation of the nuclear factor kappa B, elevation in mitogen-activated protein kinase as well as the induction of hexosamine pathway heralds the onset of cytokine-mediated pro-inflammatory reactions. Collectively, this culminates in functional and structural aberrations of peripheral neuropathy via several established mechanisms – oxidative stress to nerve cells induced by ischemia, endothelial microangiopathy, and increased neuronal dysfunction. AGE: Advanced glycation end products; ATP: adenosine triphosphotase; IL-1β: interleukin-1 beta; Na^+/K^+ ATPase: sodium-potassium adenosine triphosphatase; NF-κB: nuclear factor kappa B; RAGE: receptor for advanced glycation end products; TNF-α: tumor necrosis factor alpha.

Advanced glycation end products

When blood glucose is chronically elevated, glucose is shunted into alternative metabolic pathways, including the non-enzymatic addition of sugar moieties onto various adducts such as arginine and lysine residues of proteins, free amino groups on lipids, or guanine nucleic acids (Peppa et al., 2009), producing a group of molecules termed as AGE. AGEs were shown to accumulate in perineurial collagen, Schwann cells, and the axoplasm of nerve fibers (Markoulli et al., 2018). Within these target cells, they alter intracellular protein function, interfere with the physiological interaction between the extracellular matrix and their receptors, and result in the production of ROS via plasma protein binding to receptors for AGE (Ryle and Donaghy, 1995). The nuclear factor kappa B transcription pathway is subsequently activated by AGE-receptor for AGE interactions, leading to pro-inflammatory gene expression and apoptosis of neuronal cells (Kim et al., 2011).

Aldose reductase pathway (polyol pathway)

Likewise to the formation and accumulation of AGEs, excess blood glucose could be shunted to the aldose reductase pathway, otherwise known as the polyol pathway. The enzymes aldose reductase and sorbitol dehydrogenase catalyze the conversion of the excess glucose to sorbitol and fructose (Oates, 2002). As sorbitol and fructose are unable to pass through the nerve cell membrane, their intracellular accumulation leads to increasing osmotic stress (Markoulli et al., 2018). This is further compounded by the depleting action of sorbitol and fructose on myoinositol, an intracellular carbocyclic sugar imperative for normal nerve functioning (Dyck et al., 1988). Decreasing myoinositol levels correspondingly decrease membrane sodium-potassium adenosine triphosphate (Na^+/K^+ ATPase) activity, inducing abnormal structural modifications such as axonal swelling and progressive axonal atrophy (Xia et al., 1995). With impaired endoneurial blood supply, nerve perfusion deteriorates (Markoulli et al., 2018). This culminates in overall decreased nerve conduction velocity and eventual neuronal breakdown (Mansoor et al., 2020).

Protein kinase C pathway

Hyperglycemia induces the production of diacylglycerol, which is an activator of PKC. PKC is a serine/threonine-related protein kinase that takes on an integral role in cellular signal transduction. When it is activated, it leads to injurious effects on target nerve cells that manifest as various diabetic complications (Hempel et al., 1997). It has been postulated that activated PKC leads to diminished Na^+/K^+ ATPase activity, leading to an electrolyte imbalance that affected nerve conduction velocity and neuronal regeneration (Xia et al., 1995). Clinical trials of selective and non-selective PKC inhibitors, such as Ruboxistaurin, have been shown to restore nerve conduction rates and neuronal blood flow (Geraldes and King, 2010). Such findings are evidence that PKC pathway activation is indeed a key metabolic process that mediates changes in membrane potential, neuronal function, and nerve conductivity in diabetic neuropathy (Mansoor et al., 2020).

Production of reactive oxygen species

Hyperglycemic-induced oxidative free radical formation is considered as the coalescing principle of all the pathways of diabetic neuropathy. Elevated blood glucose levels increase the amount of sugar entry into the mitochondria, correspondingly increasing the rate of oxidative metabolism of glucose within the mitochondria (Giacco and Brownlee, 2010). This results in excessive formation of reactive oxygen species and superoxide ions, the primary oxygen free radical produced in the mitochondria (Niedowicz and Daleke, 2005). With a persistent increase in the concentration of ROS across the mitochondrial electron transport chain and a corresponding decrease in cellular antioxidative capacity, this imbalance puts the body in a state of oxidative stress – a characteristic picture seen in hyperglycemia (Oyenihi et al., 2015).

Nerve cells are the most susceptible to such mitochondrial oxidative injury as they possess a relatively larger mitochondrial volume (Mansoor et al., 2020). This decreases the generation of energy required for cellular processes, inhibiting nerve conduction and causing demyelination of axons (Kim et al., 2011). Hyperglycemia-induced oxidative stress is also known to trigger apoptosis of tissue cells by specifically activating the Bax-caspase pathway. This diminishes the electrochemical gradient across the mitochondrial membrane, allowing for the leakage of cytochrome c into the cytoplasm and hence apoptosis to occur (Oyenihi et al., 2015). In addition, ROS are strong activators of mitogen-activated protein kinases that manifest themselves as signal transducers of various pro-inflammatory pathways to produce cytokines (interleukin-1, tumor necrosis factor, interleukin-6) (Du et al., 2010), contributing to the role of inflammation in the pathogenesis of diabetic neuropathy (Ristikj-Stomnaroska et al., 2019).

Clinical manifestations of diabetic peripheral neuropathy

DPN has been defined as a symmetrical, length-dependent sensorimotor polyneuropathy attributed to metabolic and microvascular alterations (Tesfaye and Selvarajah, 2012). Classically, affected regions of the body demonstrate reduced sensation in a distal-to-proximal fashion of progression, also described as a "glove-and-stocking" pattern of sensory loss (Javed et al., 2014). 10–30% of diabetic patients experience sensory symptoms and present with painful DPN, depending on the population demographics (Hicks and Selvin, 2019). Most patients experience pain that is burning in character, accompanied by prickling, itching, and tingling sensations that are mainly felt in the lower extremities (Javed et al., 2014). Allodynia, which is the experience of painful stimuli that are not normally elicited, may also be present.

In addition to sensory dysfunction, autonomic neuropathy and motor deficits are also manifestations of DPN (Callaghan et al., 2012). Autonomic dysfunction in DPN affects the nerves innervating the cardiovascular, gastrointestinal, urogenital systems as well as sudomotor function (Hicks and Selvin, 2019). Motor symptoms usually manifest late into the disease (Tesfaye and Selvarajah, 2012). Patients may present with difficult mobility, lack of motor coordination, progressive weakness, and distal palsies, with decreased or absent ankle reflexes (Roszkowska et al., 2020).

As the onset of sensory symptoms is insidious (Callaghan et al., 2012), it is imperative to diagnose DPN early so that limb-threatening sequelae, such as foot ulceration, gangrene, can be prevented. The established risk factors are listed in **Table 1** (Zhao et al., 2016; Callaghan et al., 2018; Pai et al., 2018; Liu et al., 2019; Alam et al., 2020; Kaewput et al., 2020; Lu et al., 2020).

Evaluation and diagnosis of DPN

The diagnosis of DPN can be attained with both subjective and objective approaches. Routine diagnosis largely remains clinical, with elaborate history taking and a standardized physical examination. Clinical assessment is done via careful history taking and testing for changes in sensation to temperature or pin-prick (small-fiber function) and vibration. Simple screening maneuvers such as the Semmes-Weinstein monofilament examination, superficial pain sensation and vibration testing are performed in the consultation session (Perkins et al., 2001). Tools such as the 128-Hz tuning fork (large-fiber function) and the 10-g monofilament are typically used to assess the risk for ulceration and amputation (Pop-Busui et al., 2017). However, these methods

Table 1 | **Risk factors of diabetic peripheral neuropathy**

Risk factors
Age > 50 years
Duration of diabetes
Poor glycemic control
Cardiovascular risk factors: hypertension, hypertriglyceridemia, hyperlipidemia, decreased high-density lipoprotein cholesterol
Concomitant microvascular complications: diabetic nephropathy, diabetic retinopathy
Concomitant macrovascular complications: cardiovascular disease, cerebrovascular disease, peripheral vascular disease
High body mass index (Obesity)
Raised thyroid-stimulating hormone levels
Raised serum uric acid levels
Vitamin D deficiency

may only identify neuropathies in the advanced and irreversible stages (Malik, 2020). Moreover, subjective clinical testing does not propose the best validity, predictive value, and reproducibility as opposed to undertaking an objective elucidation of symptoms and signs.

To circumvent this limitation, several objective screening tools have been adopted for universal usage.

Composite scoring systems

Many variations of assessment frameworks have been validated, but the most frequently accepted scores include the Michigan Neuropathy Screening Instrument, neuropathy disability score (NDS), and the neuropathy impairment score in the lower limbs. The Michigan Neuropathy Screening Instrument is a two-part screening assessment, consisting of a 15-item self-administered questionnaire and a thorough lower limb physical examination that covers inspection, vibration sensation, and ankle reflexes. 13 items of the questionnaire evaluated symptoms of DPN, 1 item assessed peripheral vascular disease and the last item assessed the presence of general asthenia. A score of ≥ 7 for the questionnaire is considered abnormal. On the other hand, a physical examination score of ≥ 2.5 would be sufficient to diagnose a patient with DPN (Feldman et al., 1994).

The NDS instrument is a 35-item checklist that examines cranial nerves, muscle weakness, reflexes, and sensation, scoring the modalities as "present" or "absent" for each leg. Vibration, pin-prick, and temperature perceptions in both great toes as well as ankle reflexes are scored accordingly (normal = 0, present with reinforcement = 1, absent = 2; Weintrob et al., 2007).

Lastly, the neuropathy impairment score in the lower limbs is a quantitative neurological examination framework that assesses various components of the neurological spectrum, encompassing muscle power grading, sensory and reflex activity grading. The scale is graded on a range of 0 points (normal) to the maximum value of 88 points for the complete absence of all motor, sensory, and reflexes in the lower extremities (Bril, 1999).

For symptomatic assessment of neuropathic pain, the Leeds assessment of neuropathic symptoms and signs has been incorporated into clinical usage. The Leeds assessment of neuropathic symptoms and signs is focused on the evaluation of patient sensory description using a self-administered pain questionnaire. It also consists of a bedside physical examination to elicit sensory dysfunction, specifically allodynia and altered pinprick threshold (Bennett, 2001). Douleur Neuropathique en 4 (DN4) is another 10-item questionnaire that seeks to detail particular features of the patient's perceived neuropathic pain – 7 items pertaining to the quality of pain (burning, painful cold, electric shocks, tingling, pins and needles, numbness, itching) and the remaining 3 items based on clinical examination (hypoesthesia to touch, hypoesthesia to pinprick, painful brushing) (Perez et al., 2007). Likewise, painDETECT is also a screening questionnaire that was initially used to assess the quality of neuropathic pain felt by chronic lower back pain patients, gradually extending its applicability to other neuronal diseases. It is fully patient-reported, measuring responses on a dichotomous scale (yes/no) with a maximum score of 35 points (Freynhagen et al., 2006).

Nerve conduction studies and electromyography

In the context of clinical research, nerve conduction studies (NCS) and electromyography (EMG) are regarded as the gold-standard tools for diagnosing DPN. However, these methods are not routinely adopted in clinical practice due to their time-consuming nature and the need for specialized equipment (Won and Park, 2016). Moreover, these methods detect mainly large-fiber neuropathy, while patients with DPN may be affected by the disease of the small myelinated and unmyelinated nerve fibers which are responsible for the transmission of pain from nociceptive stimuli (Chong and Hester, 2007). Hence, NCS and EMG may underdiagnose DPN patients with predominantly small fiber pathology, especially in those who are asymptomatic.

Quantitative sensory testing

Unlike nerve conductive studies, quantitative sensory testing (QST) detects changes in both large and small nerve fibers (Backonja et al., 2009). QST stimulates temperature and vibration to assess the patient's response accordingly, quantifying their sensory thresholds. Its advantages include patient comfort because of its non-invasive nature, and the operator's relative ease of usage. However, the variability of QST results is significantly large. This may be attributed to inconsistent patient cooperation, or diverse types of equipment used leading to differing algorithms employed (Krumova et al., 2012). Essentially, this explains poor reproducibility of results due to multiple factors that influence the outcome of the test (Petropoulos et al., 2018).

Measurement of intra-epidermal nerve fiber density via skin punch biopsy

The measurement of intra-epidermal nerve fiber density (IENFD) (per length of section (IENF/mm), alongside corneal nerve fiber density evaluation, are both considered as objective quantitative assessments to determine the extent of small nerve fiber pathology in early DPN (Himeno et al., 2020). Skin punch biopsies are used to visualize nerve fibers via a 3-mm diameter skin retrieval. This allows accurate and quantifiable evaluation of early changes in small fiber morphology and provides a greater diagnostic performance compared to the previously discussed tools. However, a skin punch biopsy is an invasive procedure and predisposes patients to bleeding and infection.

Management of diabetic peripheral neuropathy

Currently, there are three main principles to be followed in the treatment of DPN: to address the underlying cause of neuropathy, to relieve the debilitating effects of symptomatic neuropathic pain, and to employ pathogenesis-oriented therapy. Management methods are primarily conservative, consisting of non-pharmacological and pharmacological interventions instituted as long-term measures for managing the patient's underlying diabetes.

Optimizing metabolic control

Poor glycemic control, high blood glucose variability, uncontrolled hypertension, and dyslipidemia are independent risk factors of DPN (**Table 1**) (Jaiswal et al., 2017; Khanam et al., 2017; Huang et al., 2019; Liu et al., 2019). In 1993, the Diabetes Control and Complications Trial Research Group (DCCT) conducted a prospective study to assess the outcomes of intensive insulin therapy in a population of 1441 diabetic patients, publishing a 60% reduction in the prevalence of clinical neuropathy in the treatment group after a 6.5 year mean follow-up period (Diabetes Control and Complications Trial Research Group et al., 1993). These findings are subsequently corroborated by another randomized 5-year prospective study that evaluated the effects of enhanced glycemic control on 49 diabetic patients, reporting a 70% decrease in the prevalence of neuropathy at the end of the study period (Linn et al., 1996). Thus, optimizing systemic metabolic control through pharmacological and lifestyle intervention remains as the cornerstone of diabetes management, preventing the progression and alleviating the prognosis of DPN (Chong and Hester, 2007; Pop-Busui et al., 2017). Depending on the type of diabetes and HbA1c level, a combination of lifestyle modification and oral hypoglycemic agents or insulin-based therapy is often instituted.

Symptomatic treatment of diabetic peripheral neuropathy

Symptoms from severe DPN can be debilitating, and effective symptomatic relief is critical in the treatment of DPN. Pharmaceutical agents such as tricyclic antidepressants, selective serotonin-norepinephrine reuptake inhibitors, and anticonvulsants have been used but with variable outcomes (Iqbal et al., 2018; Khdour, 2020). Analgesics such as oral or topical opioids can also be used as adjuvant treatment (Snyder et al., 2016).

Pathogenesis-oriented therapy

While the above-mentioned treatments are standard care administered to patients with DPN, often they are only partially effective. More effective treatments are needed, and several novel treatments directed against pathways related to DPN pathogenesis have been investigated. Aldose reductase inhibitors like Tolrestat and Sorbinil target the polyol pathway by interfering with the conversion of glucose to sorbitol and fructose, and are believed to re-establish nerve conduction velocity and promote neural regeneration in DPN (Tomlinson et al., 1994). PKC-beta inhibitors (e.g., Ruboxiastaurin) could decrease oxidative stress, a key process in the pathogenesis of DPN (Geraldes and King, 2010), and have been found to restore endoneurial blood flow and hence nerve perfusion, reduce cellular apoptosis and maintain endothelial permeability (Gálvez, 2011). Nevertheless, despite the development of the aforementioned pharmacological methods to target the pathogenetic processes of DPN, none of them have received official approval and clearance by the United States Food and Drug Administration (FDA) for clinical use to date. This is likely attributed to the inconclusive findings of previous trials, leaving the current consensus for these avenues of therapy at a stalemate. A systematic review evaluated the efficacy of aldose reductase inhibitors in the management of diabetic polyneuropathy, subsequently reporting no significant difference in treatment outcomes when compared to placebo therapy (Chalk et al., 2007). Relatively more promising is the utilization of PCK-beta inhibitors in several randomized controlled trials assessing its use in patients with DPN, revealing neuropathic pain relief in patients compared to the placebo group (Casellini et al., 2007). However, objective DPN assessments using vibration detection threshold and the Neuropathy Total Symptom Score-6 did not demonstrate any significant difference across the two treatment groups (Vinik et al., 2005).

Other pharmacological agents of management have also been looked into, including antioxidant therapies such as alpha-lipoic acid and dietary antioxidant vitamins (vitamins A, C, E). Both are believed to eliminate free radicals and negate nerve conduction abnormalities from oxidative damage (Oyenihi et al., 2015). However, similar to the findings shown in the studies

on PKC-beta inhibitors, conducted randomized controlled trials such as the SYDNEY 2 trial have also only reported a reduction in symptomatic outcomes, but no significant difference in objective neuropathic assessments such as the total symptom score (Ziegler et al., 2006). This was also preceded by another trial (alpha-lipoic acid in diabetic neuropathy III) that concluded similar findings, revealing no significant difference in total symptom score after the 7-month study period. When it comes to diagnosis of DPN, one of the biggest challenges has been that standard tools lack the sensitivity to detect early signs and symptoms of disease, limiting early identification, intervention, and monitoring of disease progression.

However, over the past decade, there have increasingly been studies suggesting that corneal neuronal complications from diabetes may be present before other clinical manifestations of DPN (Edwards et al., 2012; Papanas and Ziegler, 2013; Salahouddin et al., 2021). Most recently, an updated systematic review and meta-analysis has reported that corneal confocal microscopy has good diagnostic utility in detecting both sub-clinical and clinical DPN (Gad et al., 2021). Thus, evaluation of corneal nerve health has been actively explored as a sensitive and non-invasive approach to diagnose early DPN.

Diabetic Corneal Neuropathy

Anatomy of the corneal nerve plexus

The cornea is the most richly innervated structure in the human body (Shaheen et al., 2014), with a nerve density of approximately 7000 nociceptors/mm^2 in the epithelium, approximately 300–600 times higher than that in the skin (Zander and Weddell, 1951). Innervation of the cornea progresses from the stroma to the epithelium, and mainly consist of somatic sensory innervation originating from the ophthalmic branch of the trigeminal nerve (Müller et al., 2003). Sensory and autonomic nerve bundles from the long ciliary branches of the ophthalmic branch enter the cornea in a centripetal fashion through the corneoscleral limbus at the level of the mid-stroma, giving branches that supply it. This forms the mid-stromal plexus, which has a nerve density and complexity that increases from central to peripheral (Müller et al., 2003; **Figure 2A**). Most of the mid-stromal bundles enter into a narrow band of the anterior stroma. The posterior stroma, in contrast, is poorly innervated (Al-Aqaba et al., 2019). These anterior stromal bundles lie immediately beneath the Bowman's layer and form a flat yet dense subepithelial plexus. The subepithelial nerve bundles then advance towards the corneal surface, penetrating the Bowman's layer. Between the Bowman's layer and basal epithelium, the subepithelial nerves branch into smaller sub-basal branches, coursing parallel to the corneal surface (Müller et al., 2003). The sub-basal nerves anastomose in a complex nervous network, forming the densest plexiform arrangement in the cornea (Mansoor et al., 2020). It has a characteristic clockwise whorl pattern superficially (**Figure 2B**), innervating all layers of the corneal epithelium. These nerve terminals end as bulbous endings either below or within superficial squamous cells (Al-Aqaba et al., 2019).

Clinical presentation of diabetic corneal neuropathy

The cornea is mainly innervated by sensory nerves, which are responsible for touch, pain, and temperature sensation of the cornea, and are vital in the blink reflex, wound healing, and tear production (Shaheen et al., 2014). Patients with DCN are characterized by corneal hypoesthesia, photophobia, ocular irritation or corneal neuropathic pain. These symptoms, however, may not always correlate clinically, as a number of patients are often asymptomatic due to corneal hypoesthesia (Zhao et al., 2019).

Corneal nerves also secrete important neuromediators, including neuropeptides, neurotrophins, and neurotransmitters, to maintain ocular surface homeostasis and regulate neuronal proliferation, apoptosis, and plasticity (Liu et al., 2020b; Yang et al., 2021). The loss of these functions in DCN explains its clinical manifestations, termed collectively as diabetic neuropathic keratopathy. Around 46–64% of patients develop diabetic neuropathic keratopathy throughout the clinical course of DM (Priyadarsini et al., 2020). Neurotrophic keratopathy resulting from DCN presents as corneal epithelial damage secondary to diminished corneal sensation and trophic function (dell'Omo et al., 2018). Initial changes include irregularity of the corneal epithelium and tear film changes due to poor tear secretion (Cousen et al., 2007). The cornea therefore becomes more susceptible to trauma and recurrent erosion, which is further worsened by poor blink reflexes. Moderate cases involve a non-healing larger epithelial defect due to recurrent erosions and poor wound repair. This may progress to a neurotrophic ulcer, which may be complicated by stromal melting and corneal perforation (**Figure 3**) (Sacchetti and Lambiase, 2014). Furthermore, immunosuppressive states in DM increase the risk of secondary microbial infection of corneal ulcers, which further compounds corneal damage.

Evaluation of diabetic corneal neuropathy

Evaluation of DCN comprises clinical history taking, corneal sensitivity assessment, slit-lamp biomicroscopy evaluation, and corneal nerve imaging with *in vivo* confocal microscopy.

Clinical history, slit-lamp evaluation, and corneal sensitivity

The goal of clinical history-taking is mainly to exclude other conditions that may cause corneal neuropathy, such as herpetic keratitis, corneal surgery, or long-term use of contact lens. Pre-ganglionic causes such as intracranial space-occupying lesions or iatrogenic injury during neurosurgical procedures also need to be recorded (Sacchetti and Lambiase, 2014; dell'Omo et al., 2018).

As the tear film helps maintain ocular surface integrity, evaluating its function can prognosticate corneal health (PMID: 26439499). Patients with DM are found to have reduced tear secretion and tear film instability, attributable to lacrimal gland dysfunction (Alves Mde et al., 2008). The poor quality of tear film worsens the disease status of DCN (Zhang et al., 2016). Objective assessment tools of the tear film include Schirmer's test, tear break-up time, and tear osmolarity. Increased tear osmolarity, consistent with decreased tear secretion, was observed among patients with T2DM (Fuerst et al., 2014). Moreover, slit lamp evaluation, together with 2% w/v solution of fluorescein sodium and other vital dyes such as lissamine green or rose bengal, allows visualization of disrupted and irregular ocular surfaces, aiding disease staging and monitoring.

Findings of corneal sensitivity tests in DCN range from a diminished to a completely absent blink reflex. The inverse relationship between corneal sensitivity and severity of DM has been reported (Cousen et al., 2007). A study conducted by Tavakoli et al. (2007) found significantly reduced corneal sensitivity when assessed using the contact Cochet-Bonnet aesthesiometer among diabetic subjects compared to healthy controls (31.4 ± 19.4 mm *vs*. 52.3 ± 9.7 mm respectively; $P < 0.0001$). A similar pattern was reproduced with the non-contact, air pulsed corneal aesthesiometer, where diabetic subjects had significantly lowered corneal sensation compared to healthy controls (1.4 ± 0.9 mbar *vs*. 0.7 ± 0.1 mbar; $P < 0.0001$). Furthermore, corneal sensitivity, measured with either non-contact or contact aesthesiometer, decreased with increased duration of DM ($r = –0.22$, $P = 0.002$ and $r = 0.30$, $P < 0.001$, respectively).

In vivo confocal microscopy to visualize corneal nerve plexuses

In vivo confocal microscopy (IVCM) is a non-invasive nerve imaging technique that has been considered a valid diagnostic and evaluation tool for nerve degeneration and regeneration process (Liu et al., 2020a; Chin et al., 2020, 2021). The confocal laser-scanning microscope is capable of providing high-resolution images at a cellular level with a magnification up to 800-fold (Liu et al., 2021). Post-imaging quantification allows reproducible and repeatable evaluation of subbasal nerve plexus parameters, including corneal nerve fiber density (CNFD), corneal total branch density, corneal nerve fiber length (CNFL), corneal nerve branch density (CNBD), corneal nerve area, corneal nerve width, nerve tortuosity, and nerve fractal dimension (Tavakoli et al., 2015; dell'Omo et al., 2018; Chin et al., 2020). These quantitative nerve metrics allow clinicians to better understand DCN in terms of pathogenesis, disease severity and progression, nerve degeneration, and regeneration patterns, as well as to evaluate the treatment efficacy objectively (Mansoor et al., 2020).

Studies have shown that decreased CNFD, CNFL and nerve beading, and increased nerve tortuosity were observed in both T1DM and T2DM patients (**Figure 4**) (Mansoor et al., 2020). Reduced nerve beading frequency reflects lower metabolic activity and translates to a higher risk of neuron damage in diabetic patients (Roszkowska et al., 2020). Among the nerve parameters, CNFL is the most consistently reduced in both types of DM (Roszkowska et al., 2021), and is the most reliable marker for early diabetic sensorimotor polyneuropathy (Hertz et al., 2011). Similarly, another study revealed that CNFD, CNBD, and CNFL were significantly reduced in patients with DPN as compared to healthy subjects (Kalteniece et al., 2020). It also found a significant inverse relationship between the severity of neuropathic symptoms with CNFD ($r = –0.20$, $P = 0.01$), CNBD ($r = –0.30$, $P = 0.007$), CNFL ($r = –0.20$, $P = 0.01$) (Kalteniece et al., 2020). Corneal nerve fractal dimension (CNFrD) is a metric to evaluate multiple nerve morphological characteristics and structural complexity. A higher CNFrD is indicative of a healthy, evenly-distributed nerve fiber network (Chen et al., 2018). Significantly lowered CNFrD has been found in diabetic patients compared to control subjects, and it was further lowered in patients with DPN compared to those without DPN (Chen et al., 2018). It was also reported that CNFrD had a similar diagnostic ability to identify patients with DPN when compared with existing metrics such as CNFL (Chen et al., 2018). Moreover, DCN may also be diagnosed more accurately and in earlier stages by analyzing subbasal inferior whorl located in the inferonasal cornea (**Figure 2B**), which shows reduced nerve fiber length and density before the nerve plexus central cornea does, making a more optimal imaging site for early detection (Petropoulos et al., 2015). The clinical utility of analyzing the inferior whorl via IVCM has been proven; Ferdousi et al. (2020) concluded that inferior whorl analysis via IVCM has comparable sensitivity and specificity to both QST and NCS in the diagnosis of diabetic neuropathy.

The correlation between corneal nerve metrics and the chronicity or severity of diabetes has also been explored. Diabetes chronicity, quantified by duration since diagnosis, was found to have a significant inverse relationship with CNFD, CNFL, and CNBD in both T1DM and T2DM (Ahmed et al., 2012; Petropoulos et al., 2013). Diabetes severity, measured by HbA1c levels, showed a similar relationship. It has also been shown that corneal nerve parameters improve as glycaemic control improves in both patients with T1DM and T2DM (Boucek, 2011; Azmi et al., 2015). Azmi et al. (2015) conducted a study in T1DM patients on continuous subcutaneous insulin and compared them to those on daily injections. The former group achieved lower HbA1c levels and showed significantly greater regeneration of the subbasal nerve plexus in terms of CNFL, CNFD, and CNBD (Azmi et al., 2015). The extent of inferior whorl corneal nerve fiber damage may also predict the severity of DPN symptoms, and was found to be more profound in patients with pain compared to painless DPN (Kalteniece et al., 2018). Other interventions relevant to T1DM such as simultaneous pancreas and kidney transplantation have also been found to help improve corneal nerve status, notably CNFL and CNFD (Petropoulos et al., 2013).

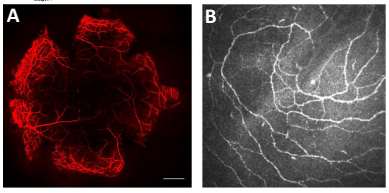

Figure 2 | **Corneal nerve plexus.**
(A) Whole mount staining of mice cornea with anti-class β III tubulin showing the nerve distribution. Scale bar: 50 μm. (B) Representative *in vivo* confocal microscopy image of inferior whorl of corneal nerve plexus. Unpublished data.

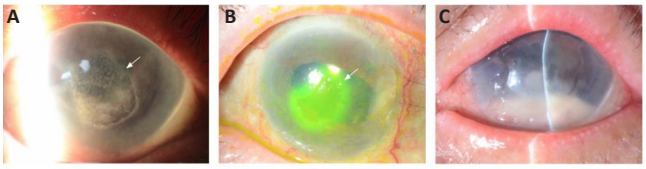

Figure 3 | **Slit lamp photos showing diabetic neurotrophic corneas.**
(A) Corneal persistent epithelial defect (arrow) with a stromal scar. (B) Fluorescein staining delineates the area of disruption of intercellular junctions and epithelial defect (arrow). (C) Hypopyon secondary to corneal epithelial defect and melting activity. Unpublished data.

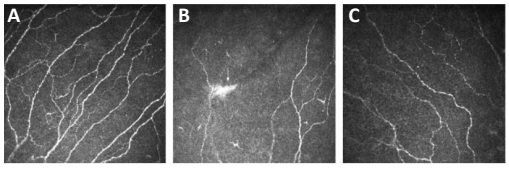

Figure 4 | **Representative *in vivo* confocal microscopy micrographs showing the subbasal nerve plexus in non-diabetes mellitus subjects (A), type 1 diabetes mellitus (B), and type 2 diabetes mellitus patients (C).**
In diabetes mellitus patients, atypical cellular-like materials secondary to inflammatory process (arrow), reduced corneal nerve fibre density, corneal nerve fiber length, and increased nerve tortuosity were observed. Unpublished data.

While the reliability of IVCM may be limited by inter or intra-observer variability, it has improved after the introduction of novel techniques such as post-imaging quantification and automated analysis (Dabbah et al., 2010). Examples of such software include NeuronJ and ACCMetrics, which enable semiautomated and fully automated quantification respectively (Dehghani et al., 2014). Studies show that automated quantification of CNFL not only offered similar capability in identifying DCN in diabetic patients accurately as compared to manual analysis, it was also more advantageous in terms of speed, objectivity, and reproducibility (Dehghani et al., 2014; Ostrovski et al., 2015). Small-fiber quantification in IVCM has also been found to have similar diagnostic efficiency with IENFD, suggesting a possible role as a surrogate marker for DPN (Chen et al., 2015).

Management of diabetic corneal neuropathy

The main principles of management for DCN include preventing the progression of corneal damage, achieving epithelial healing, and symptomatic relief (Bikbova et al., 2018). They can be split into systemic glucose control as discussed earlier, and local ocular surface management.

Local ocular surface management involves maintaining a healthy, smooth, and lubricated ocular surface to minimize symptoms of visual disturbance and discomfort (Quattrini et al., 2010; Mansoor et al., 2020). Tear film quality and consequently corneal healing can be improved with preservative-free artificial tears, ointment, or punctual occlusion, which eventually promotes corneal healing. Topical anti-inflammatory drugs, such as topical preservative-free steroids, non-steroidal anti-inflammatory drugs or ciclosporin, can be considered (Mansoor et al., 2020). In moderate cases where a persistent epithelial defect is present, it is important to prevent invasion of the underlying stroma in addition to intensive lubricant therapy mentioned above. With the increased risk of secondary infection of the eroded cornea, prophylactic antibiotic eyedrops are recommended to prevent further damage (Sacchetti and Lambiase, 2014; Mansoor et al., 2020). A trial of therapeutic corneal or scleral contact lenses can be used, to act not only as a protective barrier, but also help retain therapeutic medication and lubricants on the corneal surface (Dua et al., 2018). Surgical debridement of the thickened and stagnated edges of the ulcer may help improve healing in patients with corneal ulcers (Katzman and Jeng, 2014). During the re-epithelialization process, ulcer complications such as stromal melting can be avoided with inhibitors of matrix metalloproteinases and suppressors of neutrophil action such as topical or systemic tetracyclines and N-acetylcysteine (Hossain, 2012; Ogut et al., 2016). In refractory and severe cases, a surgical approach such as partial or total tarsorrhaphy, amniotic membrane graft transplantation, cyanoacrylate glue, conjunctival flaps or lamellar/penetrating keratoplasty may be indicated (Sacchetti and Lambiase, 2014).

Adjunctive treatment to promote corneal nerve recovery and function may be considered in moderate and severe cases. These include growth factor-rich therapy such as autologous serum eye drops or platelet-rich plasma to reduce neurovascular damage and promote ocular surface healing, as well as neurotrophic factor-based therapy such as nerve growth factor eye drops to promote neuronal growth and its trophic effects (Mansoor et al., 2020; Mastropasqua et al., 2020).

Relationship between Diabetic Corneal Neuropathy and Diabetic Peripheral Neuropathy

Corneal innervation and its capacity in delineating the severity of DPN has been extensively compared to the conventional means of nerve testing, such as NCS, QST as well as nerve and skin biopsies. Even though electrodiagnostic testing has always been regarded as the gold standard for the diagnosis of neuropathy, they only identify primarily large fiber changes (Petropoulos et al., 2014). Yet, the earliest nerve fibers to undergo nerve fiber damage are those of small, unmyelinated nerve fibers, significantly reducing the reliability of earlier diagnosis using these methods (Malik, 2020). Small-fiber neuropathic changes are able to be picked up by IVCM, which are otherwise undetectable in QST and electrophysiological findings (Azmi et al., 2015). Thus, attention has hence been turned towards assessing DCN as an alternative diagnostic tool for DPN.

Diabetic corneal neuropathic changes in relation to diagnosis of diabetic peripheral neuropathy

In the consideration of corneal changes as surrogate markers for DPN, it was presented that 50% of DPN patients had pathological corneal subbasal nerve plexus changes before they developed clinical signs of DPN, indicating that the onset of corneal nerve alterations precedes the progression of DPN (Bitirgen et al., 2014). In addition, changes in corneal nerve morphology, especially in the inferior whorl area, have also been observed before patients present diabetic retinopathy or microalbuminuria (Gad et al., 2020). The corneal nerve parameters, including CNFL, CNFD, and CNBD, were significantly reduced in diabetic patients with DPN compared to those without (**Figure 5**) (Misra et al., 2015; Xiong et al., 2018; Li et al., 2019). The Longitudinal Assessment of Neuropathy in Diabetes using novel ophthalmic markers (Pritchard et al., 2014) was a 4-year observational study investigating corneal nerve alterations in 396 patients categorized into three groups: T1DM patients with DPN, T1DM patients without DPN, and a control group of patients with no diabetes or neuropathy. CNFL was found to be significantly reduced in T1DM patients with DPN compared to T1DM patients without DPN (14.0 ± 6.4 mm/mm^2 *vs*. 19.1 ± 5.8 mm/mm^2, $P < 0.001$), reaffirming the association between corneal nerve parameters and DPN.

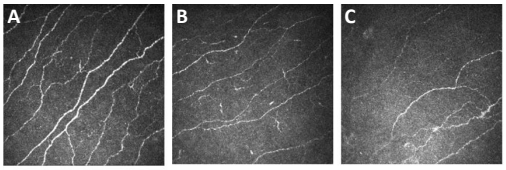

Figure 5 | **Representative *in vivo* confocal microscopy micrographs showing the subbasal nerve plexus in (A) non-DM subjects, (B) a patient with type 2 DM without DPN, and (C) a patient with type 2 DM with DPN in which marked decreased corneal nerve fiber density, corneal nerve fiber length and more tortuous nerves were observed.**
DM: Diabetes mellitus; DPN: diabetic peripheral neuropathy. Unpublished data.

Corneal nerve parameters also demonstrate diagnostic utility in DPN. CNFL and corneal total branch density have been used to differentiate patients with DPN from control subjects, as evidenced by the area under the receiver operating characteristic curve of 0.88 and area under the receiver operating characteristic curve of 0.84, respectively. CNFD also demonstrated better diagnostic ability than IENFD for patients with DPN (area under the receiver operating characteristic curve 0.81 *versus* 0.73) (Alam et al., 2017). Another study also presented that by using a CNFL cut-off of < 14.9 mm/mm^2, the development of DPN could be predicted, with the sensitivity of 0.82 and specificity of 0.69, irrespective of the results of nerve conduction and quantitative sensory testing (Lovblom et al., 2015). Similarly, a recent multi-national study concluded that CNFL demonstrated reliable predictive value for the identification of patients potentially at risk of DPN, with 6 years ahead of incidental diagnosis. An optimal CNFL cut-off at 14.1 mm/mm^2 was used for the diagnosis of new-onset DPN, with a sensitivity of 67% and specificity of 71% (Perkins et al., 2021).

Relationship between DCN and the severity of DPN

In addition to diagnostic value, measures that quantify functional and structural severity of DCN also correlate to the severity of DPN. Functionally, when diabetic subjects were stratified by the severity of DPN with NDS, significantly worse corneal sensitivity was noted in patients with moderate and severe DPN (Tavakoli et al., 2007). Studies further demonstrated significant correlation between decreased corneal sensitivity and NDS (r = 0.441, $P < 0.001$) (Tavakoli et al., 2010). Pritchard et al. (2012) also found that corneal sensitivity thresholds correlated significantly with cold sensation thresholds (r = –0.32, $P < 0.001$), vibration threshold (r = 0.29, $P < 0.001$), and warm sensation threshold (r = 0.27, $P < 0.001$) among diabetic patients with DPN. Interestingly, the Multidimensional Scaling analysis plot comparing

similarities between corneal sensation and function scores of DPN yielded mixed results: while corneal sensitivity thresholds were largely similar to NDS and diabetic neuropathy symptom score, they were dissimilar to more objective metrics such as conduction velocities and quantitative sensory testing variables (Pritchard et al., 2012).

Structurally, IVCM quantifies small fiber damage rapidly, noninvasively, and detects earlier stages of nerve damage compared to IEFND pathology (Quattrini et al., 2007). Corneal nerve metrics have been shown to worsen as DPN progresses, helping to determine the course and severity of DPN. CNFD showed a progressive decrease with increasing neuropathic severity measured by NDS, diabetic neuropathy symptom score, and QST (all $P < 0.001$). The correlation was consistent when the diabetic subjects were further stratified into mild, moderate, and severe neuropathy (Quattrini et al., 2007). Similarly, Petropoulos et al. (2013) found that CNFD, CNBD, and CNFL were significantly lowered between controls and diabetic patients with worsening severity of neuropathy assessed via the NDS, vibration perception threshold, and nerve conduction studies ($P < 0.001$). In addition, a cross-sectional study reported a significant correlation between CNFD and total neuropathy score ($r = -0.78$, $P < 0.01$), as well as between CNFD and motor nerve axonal hyperexcitability measurements ($r = 0.44$, $P < 0.01$) (Tummanapalli et al., 2020). Coupled with the recent development of an artificial intelligence-driven deep-learning algorithm for IVCM imaging in evaluating DPN, assessment of corneal nerve status can be a promising alternative to the conventional diagnostic and monitoring methods for DPN (Salahouddin et al., 2021).

The role of DCN in the stratification of complications of DPN

IVCM not only detects subclinical and clinical DPN, but is also able to monitor the declines in corneal nerve parameters in time to identify the development of gross diabetic complications (Dehghani et al., 2016). It was reported that CNFD yielded 84% specificity for early stage small fiber neuropathy, 86% sensitivity for severe small fiber neuropathy, 75% specificity for the diagnosis of DPN, and 72% specificity for the diagnosis of foot ulceration (Quattrini et al., 2010). In patients who developed diabetic neuroosteoarthropathy, CNFL, CNFD, CNBD, and corneal nerve connecting points were significantly reduced compared to non-DM controls (Herlyn et al., 2018). Corneal nerve changes also correlated with the severity of neuropathic pain from foot ulcerations (Kalteniece et al., 2020). Assessment of the corneal nerve plexus is hence capable of not only detecting initial and significant changes across the course of DPN, but also can risk-stratify and determine the optimal time for intervention directed towards the mitigation of complications.

Conclusions

DCN and DPN affect 46–64% and 50% of diabetic patients, respectively, during the clinical course, resulting in a significant economic burden. Early detection of DPN is paramount to halt the progression of debilitating symptoms, such as pain and sensory deficits, and late limb-threatening sequelae. At present, the gold standard for the diagnosis of DPN remains clinical assessment via careful history and sensory testing. However, neuronal damage occurs before clinical functionality changes, and DPN is often advanced and irreversible by the time it is symptomatic or clinically detectable. Many studies have validated the use of the assessment of DCN as a surrogate marker for DPN. Corneal nerve parameters such as CNFL, CNFD, and CNBD are not only significantly associated with the severity of DPN, but also observed to be altered prior to the development of clinical manifestations of DPN. In comparison with existing diagnostic tools for early DPN such as IEFND, IVCM showed higher sensitivity in diagnosing DPN. Future studies may extend to the use of artificial intelligence-based evaluation of DCN in relation to natural progression and treatment efficacy of DPN.

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Conflicts of interest: *There are no conflicts of interest.*

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