Interconnections between diabetic corneal neuropathy and diabetic retinopathy: diagnostic and therapeutic implications

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https://doi.org/10.4103/NRR.NRR-D-24-00509

Date of submission: May 6, 2024

Date of decision: June 28, 2024

Date of acceptance: July 24, 2024

Date of web publication: September 20, 2024

From the Contents

Abstract

Diabetic corneal neuropathy and diabetic retinopathy are ocular complications occurring in the context of diabetes mellitus. Diabetic corneal neuropathy refers to the progressive damage of corneal nerves. Diabetic retinopathy has traditionally been considered as damage to the retinal microvasculature. However, growing evidence suggests that diabetic retinopathy is a complex neurovascular disorder resulting from dysfunction of the neurovascular unit, which includes both the retinal vascular structures and neural tissues. Diabetic retinopathy is one of the leading causes of blindness and is frequently screened for as part of diabetic ocular screening. However, diabetic corneal neuropathy is commonly overlooked and underdiagnosed, leading to severe ocular surface impairment. Several studies have found that these two conditions tend to occur together, and they share similarities in their pathogenesis pathways, being triggered by a status of chronic hyperglycemia. This review aims to discuss the interconnection between diabetic corneal neuropathy and diabetic retinopathy, whether diabetic corneal neuropathy precedes diabetic retinopathy, as well as the relation between the stage of diabetic retinopathy and the severity of corneal neuropathy. We also endeavor to explore the relevance of a corneal screening in diabetic eyes and the possibility of using corneal nerve measurements to monitor the progression of diabetic retinopathy.

Key Words: cornea; corneal nerves; diabetes; diabetic corneal neuropathy; diabetic retinopathy; retina

Introduction

Diabetes mellitus (DM) is a dysmetabolic disorder, characterized by inappropriately high levels of glucose. It includes various subclassifications, such as type 1, type 2, gestational diabetes, neonatal diabetes, and steroid-induced diabetes (American Diabetes, 2018). Type 1 and type 2 diabetes are the main subtypes. Type 1 diabetes involves a deficiency in insulin production, whereas type 2 diabetes involves a progressive development of insulin resistance in cells. As reported by the International Diabetes Federation, the number of individuals affected by diabetes worldwide reached 537 million by 2021 (Collaborators, 2023). DM carries a heavy economic burden, with 640 million people projected to develop DM by 2040 (Markoulli et al., 2018). The economic burden of DM is projected to increase to $2.1 trillion by 2030 (Bommer et al., 2017), and this will place further stress on the economy and the public healthcare system. The causes of DM-associated mortality, diminished quality of life, and productivity are related to its macrovascular and microvascular complications. Macrovascular complications can be life-threatening, such as peripheral arterial disease, stroke, and coronary artery disease. Microvascular complications as in diabetic peripheral neuropathy, diabetic retinopathy (DR), and diabetic nephropathy, are life-disabling. Globally, 36.3% of individuals with type 2 diabetes experience DR, with one-third of these cases being vision-threatening (Zegeye et al., 2023). Diabetic corneal neuropathy (DCN) is another common complication of DM, affecting an estimated 46%–64% of diabetic patients throughout their disease course and causing a significant economic burden (Priyadarsini et al., 2020). However, DCN is often overlooked because many patients remain asymptomatic even when hyperglycemia-induced subclinical corneal changes are already present (Mansoor et al., 2020). Given the heavy economic and health burden that DM and its complications carry, there is a need for more studies looking into the development of early screening and preventative measures against DM complications.

This review discusses the relationship between DCN and DR, highlighting the potential of DCN in monitoring the progression of DR and suggesting the inclusion of corneal nerve assessment in the management of high-risk diabetic patients.

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How to cite this article: *Yu M, Ning FTE, Liu C, Liu YC (2025) Interconnections between diabetic corneal neuropathy and diabetic retinopathy: diagnostic and therapeutic implications. Neural Regen Res 20(8):2169-2180.*

Search Strategy and Selection Criteria

An extensive literature search was conducted on the electronic PubMed database to elicit the association between DCN and DR. The query performed in PubMed was a combination of keywords and MeSH terms including diabetic corneal neuropathy, diabetic cornea, diabetic keratopathy, diabetic retina, diabetic retinopathy, subbasal nerve plexus, corneal nerves, corneal sensitivity, and corneal sensation. All permutations of the keywords were used, for instance: diabetic corneal neuropathy AND diabetic retina; diabetic cornea AND diabetic retinopathy. Searches using "AND" yielded few results, hence a search eliminating the term "AND" between the keywords was conducted. Searches mostly included papers published from the years 1990–2024; however, few articles before 1990 were included if deemed relevant, and 101 records were thus identified. Secondary research articles (literature review, systemic review) were screened for relevant citations, which are also included in this review. Duplicates were eliminated and articles that require special access without sufficient information in the abstract were excluded. A total of 72 articles were included in the final manuscript.

Diabetic Corneal Neuropathy

Anatomy of corneal nerves

The human cornea is densely innervated with sensory and autonomic nerve fibers (Al-Aqaba et al., 2010). It has a central nerve density of around 7000 nociceptors per square millimeter, making it 300 to 600 times more sensitive than the skin (Muller et al., 2003; Yang et al., 2018). This ocular structure has fundamental refractive properties and consists of 5 layers: the epithelium, the Bowman's layer, the stroma, the Descemet membrane, and the endothelium. The sensory innervation of the cornea originates from the trigeminal ganglion (Lin et al., 2023). The nerve fibers emerge from the trigeminal ganglion via the ophthalmic division of the trigeminal nerve, traveling in the nasociliary nerve and its branches (Lin et al., 2023), also known as peripheral stromal nerves, penetrating the cornea. These branches divide and run parallel to the corneal superficial surface, between the basal epithelium and Bowman's layer, forming the subbasal nerve plexus which supplies the corneal epithelium. The plexus is primarily comprised of C fibers (Yang et al., 2018). Along the course of the long nerve bundles of the subbasal nerve plexus, they divide into many smaller branches that connect to form a network with a whorl-like pattern, inferonasal to corneal apex (Shaheen et al., 2014). From the trigeminal ganglion cells, there are nerve fibers which travel suprachoroidally and branch to form the limbal plexus around the corneoscleral limbus. From the limbal plexus, stromal nerve fibers arise and enter the peripheral stroma layer of the cornea before progressing anteriorly (Shah, 2019). In the stroma, nerves are organized parallel to collagen lamellae and branch into smaller fascicles as they form connections with the stroma to form the anterior stromal plexus. Some stromal nerve fibers terminate as free nerve endings, whereas others directly innervate the keratocytes (Shaheen et al., 2014).

The peripheral and central nerve fibers of the cornea consist of myelinated and unmyelinated nerve fibers, Aδ and C fibers respectively (Shaheen et al., 2014). Aδ fibers are mechanoreceptors, nociceptors, and thermoreceptors for cold sensation, whereas C fibers are nociceptors and thermoreceptors for heat (Zhou et al., 2022).

Physiological role of corneal nerves

Corneal nerves function to sense and transmit pain sensations, temperature, and touch, and facilitate autonomic responses such as the blink reflex. It also is vital in tear production and secretion, and wound healing, helping to sustain the health and homeostasis of the ocular surface (Shaheen et al., 2014; Yang et al., 2021). Besides sensory and autonomic function, corneal nerves also play a neurotrophic role by producing neuromediators that nourish the neurons, maintaining neuronal health and promoting corneal wound healing (Nishida, 2005). The sensory nerves produce neurotrophins and neuropeptides (Markoulli et al., 2018). Specifically, substance P and calcitonin gene–related peptide modulate corneal epithelial cell proliferation, stratification, migration, and adhesion (Wu et al., 2022). Other relevant neuropeptides include acetylcholine, cholecystokinin, noradrenaline, serotonin, neuropeptide Y, vasoactive intestinal peptide, met-enkephalin, brain natriuretic peptide, vasopressin, and neurotensin (Sacchetti and Lambiase, 2017). Furthermore, the autonomic nerves produce catecholamines and acetylcholine. Neuroimmune interactions, which involve the physical and functional interplay between nerves and immune cells, have been studied in the cornea (Wu et al., 2022). Corneal nerve damage triggers immune responses in the clearance of disrupted axons and releases neurotrophic factors, thereby initiating inflammation. However, during neurogenic inflammation and neuroinflammation, immune cell phenotypes, cytokines, and neurotrophic factors may also play protective roles in maintaining corneal innervation (Jiao et al., 2020; Liu et al., 2020).

Risk factors or associated factors of diabetic corneal neuropathy

Corneal nerve loss has been reported to be associated with total and low-density lipoprotein cholesterol, and impaired glucose tolerance (Andersen et al., 2018). Furthermore, greater corneal nerve loss was found in patients with type 1 compared to type 2 diabetes. In type 1 diabetes, loss of corneal nerves is associated with the duration of diabetes, triglycerides, and low-density lipoprotein cholesterol (Ferdousi et al., 2021). In type 2 diabetes, corneal nerve loss is associated with HbA1c, age, and weight (Andersen et al., 2018). Improvement in HbA1c (Jia et al., 2018) and weight reduction were associated with the recovery of corneal nerves (Ishibashi et al., 2019). A more recent study evaluated the associations between glucose metabolism status and various continuous measures of glycemia with corneal nerve metrics, including corneal nerve bifurcation density, corneal nerve density, corneal nerve length, and fractal dimension based on population cohort (Mokhtar et al., 2023). The findings revealed that higher levels of glycemia measures such as fasting plasma glucose, 2-hour post-load glucose, HbA1c, skin autofluorescence, and duration of diabetes were all

significantly and linearly associated with lower corneal nerve fiber metrics, suggesting that glycemia-induced corneal neurodegeneration begins well before the onset of type 2 diabetes.

Misra et al. (2015) have demonstrated a negative correlation between the total neuropathy score (which includes the symptomatic neuropathy score, clinical neuropathic assessment, quantitative sensory testing, and nerve conduction study) and corneal nerve density in patients with type 1 diabetes. Additionally, they found a negative correlation between corneal sensitivity and the expiration/inspiration component of the autonomic nerve analysis. These findings suggest that the corneal nerve damage in DCN is associated with peripheral neuropathy in diabetes. Patients with diabetic peripheral neuropathy had significantly decreased corneal nerve fiber density (CNFD) and corneal nerve branch density (CNBD) when compared to patients without DM and those with DM without peripheral neuropathy (Edwards et al., 2012).

Clinical features of diabetic corneal neuropathy

Patients with DCN are characterized by symptoms such as corneal hypoesthesia, photophobia, ocular irritation, and neuropathic corneal pain (So et al., 2022). However, this condition is substantially underdiagnosed, considering that the most of cases are initially asymptomatic, possibly as a consequence of a corneal hypoesthesia (Zhao et al., 2019). DCN manifests as decreased corneal nerve density, causing impaired corneal sensitivity, sensation, and trophic function (Teo et al., 2023). Corneal epithelium irregularity and poor tear secretion (Bikbova et al., 2018) leave the cornea more susceptible to corneal damage by trauma, erosion, and infection, exacerbated by diminished blink reflexes (So et al., 2022). Such neuropathic corneas and delayed wound healing could later develop into corneal ulcers, or even sight-threatening perforation (Shaheen et al., 2014; **Figure 1**). Moreover, patients with DM being in an immunosuppressed state, are more susceptible to bacterial or fungal infections, leading to more devastating corneal damage (Bikbova et al., 2018).

Investigations for diabetic corneal neuropathy with *in vivo* confocal microscopy

In vivo confocal microscopy (IVCM) is a rapid, non-invasive imaging technique that enables the visualization of the nerves at a cellular level with magnification up to 800-fold (Yang et al., 2021). This allows for further quantification of the subbasal nerve plexus parameters such as CNFD, corneal total branch density, corneal nerve fiber length (CNFL), CNBD, corneal nerve fiber tortuosity with several analytic software available (Liu et al., 2021; Chin et al., 2024). In DCN, there has been an observed reduction in CNFL, CNFD, and an increased nerve fiber tortuosity (Mansoor et al., 2020). The nerve fiber length and density of the subbasal inferior whorl of the corneal nerves may also decrease, manifesting earlier than central corneal nerve changes (Petropoulos et al., 2015; **Figure 1**). Furthermore, some studies have observed a significant reduction in nerve beading frequency, which indicates a reduction in neuronal metabolic activity and increases the risk of neuronal damage in DM (Ishibashi et al., 2016; Liu et al., 2023).

Pathogenesis of diabetic corneal neuropathy

In DCN, hyperglycemia damages the Aδ and C fibers in the cornea through multiple molecular pathways via accumulation of advanced glycation end products, sorbitol and fructose, reactive oxidative species as well as protein kinase C activation (non-exhaustive) (Mansoor et al., 2020).

Advanced glycation end products pathway in diabetic corneal neuropathy

Chronic hyperglycemia causes the accumulation of advanced glycation end-products (AGE) which are end products of the advanced glycation pathway. AGE is formed from non-enzymatic reactions between proteins or lipids and sugar molecules, and leads to deposition of AGE products in perineural collagen and axoplasm of neurons and Schwann cells. This results in microvascular dysfunction, nerve fiber damage, degeneration of axons, segmental demyelination, impaired axon transport, and regenerative activity (Sugimoto et al., 2008; Han et al., 2019). Additionally, Wan et al. (2022) have demonstrated that AGEs produce reactive oxygen species (ROS), which cause the hyperactivation of the NLPR3 inflammasome in a streptozotocin-induced mouse model of type 1 diabetes. This leads to delayed healing of diabetic corneal wounds and impair corneal nerve regeneration (Wan et al., 2022), resulting in progressive corneal nerve damage and the development of diabetic keratopathy. Moreover, AGEs cross-link with structural proteins in peripheral nerves. This process induces the formation of glycated myelin proteins,

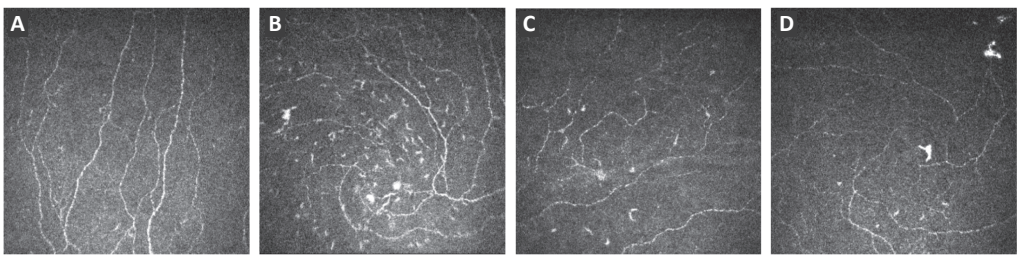

Figure 1 | **Representative *in vivo* confocal microscopy images of the central cornea and corneal inferior whorl region in a healthy subject and a patient with type 2 diabetes.**
(A) The corneal nerve morphology in the central cornea of a healthy individual. (B) The morphology of corneal inferior whorl in a healthy individual. (C) A patient with type 2 diabetes showed a decrease in nerve fiber density and nerve fiber length, and an increase in nerve tortuosity in the central cornea. (D) A patient with type 2 diabetes showed a decrease in nerve fiber density and nerve fiber length in the corneal inferior whorl. Unpublished data.

dysfunctional entities that promote demyelination, impaired regenerative activity, and axonal degeneration (Buonfiglio et al., 2024). AGEs also cross-link with collagen molecules in the corneal stroma, resulting in the glycation of laminin and fibronectin in Descemet's membrane, which may subsequently cause reduction of corneal endothelial cells and result in endothelial dysfunction and microangiopathy (Markoulli et al., 2018).

Polyol pathway in diabetic corneal neuropathy

Increased glucose levels in nerve cells shunt glucose into the polyol pathway as the normal glycation pathway is saturated. The final products of the polyol pathway are sorbitol and fructose which are impermeable to the nerve cell membrane and tend to accumulate in nerve cells. This in turn increases the osmotic stress of nerve cells and reduces free nerve myoinositol, which causes reduced membrane Na^+/K^+ ATPase activity (Oates, 2008), decreased nerve conduction velocity, and inhibited nerve regeneration (Han et al., 2019). Furthermore, aldose reductase involved in the shunted, sorbitol-aldose reductase pathway, causes nicotinamide adenine dinucleotide phosphate (NADPH) depletion which leads to diabetic corneal, making the cornea more susceptible to damage by ROS (Han et al., 2019).

Reactive oxygen species

Due to the influx of glucose, there is an accelerated metabolism of excess glucose by mitochondria, giving rise to the production of superoxide radical anion ($O_2\bullet^-$), hence increasing the production of ROS. The rise in ROS and decreased capacity of the antioxidant enzymes causes an imbalance in the electron transport chain of the mitochondria (Babizhayev et al., 2015). As nerve fibers are rich in mitochondria, they are susceptible to hyperglycemia-induced oxidative damage. Hyperglycemia-induced ROS can activate the Bax-caspase pathway, reducing the electrochemical gradient across the mitochondrial membrane, leading to cytochrome c leakage into the cytoplasm and triggering apoptosis in neuronal cells (So et al., 2022). Neuronal mitochondrial injury depletes the neurons of cellular energy, causing neuronal conduction blockade, and axonal myelination (Duby et al., 2004). Additionally, ROS activates mitogen-activated protein kinases, which serve as signal transducers in various pro-inflammatory pathways and contribute to inflammation in the pathogenesis of diabetic corneal neuropathy (Buonfiglio et al., 2024). Studies have found a possible connection between oxidative stress caused by hyperglycemia and corneal nerve fiber damage (Zhou et al., 2022; Shu et al., 2023).

Activation of protein kinase C pathway in diabetic corneal neuropathy

Increased intracellular glucose levels cause increased diacylglycerol production. Diacylglycerol activates Protein Kinase C, which inhibits the sodium/potassium ATPase activity, thereby affecting nerve conduction and regeneration (Geraldes and King, 2010). The pathogenesis of DCN is summarized in **Figure 2**.

Diabetic Retinopathy

DR is a serious complication of diabetes. Approximately one-third of patients with DM develop DR, and it is one of the leading causes of vision loss in adults aged 20–74 years globally (Lee et al., 2015). In type 1 diabetes, 71%–90% of patients develop DR in 10 years, and this incidence increases to 95% in 20–30 years. In type 2 diabetes, 67% develop DR after 10 years (Vashist et al., 2011).

DR can cause retinal ischemia, retinal neovascularization, and macular edema (Wu et al., 2013). There are two main stages of DR — non-proliferative DR (NPDR) and proliferative DR (PDR), as determined by the clinician over a fundus examination. The NPDR stage is characterized by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots. There are alterations in regional blood flow and abnormal retinal vasculature which lead to retinal ischemia. Meanwhile, in PDR, new, fragile blood vessels are formed via a process of neovascularisation which occurs in response to retinal hypoxia. These blood vessels may occur at the optic nerve and/or macula and rupture easily, possibly resulting in vitreous hemorrhage, fibrosis, and eventually retinal detachment (Aiello et al., 1998).

Risk factors of diabetic retinopathy

The risk factors that are most strongly predictive of DR development are the duration of DM, glycemic control, and higher HbA1C levels (Zhang et al., 2001). There are other less predictive risk factors, such as Indian ethnicity, systolic blood pressure (Tan et al., 2018), dyslipidemia, and the presence of other microvascular complications such as diabetic nephropathy and peripheral neuropathy. Pregnancy is also found to be associated with worsening retinopathy (Viswanath and McGavin, 2003).

Clinical features of diabetic retinopathy

Early stages of DR can be asymptomatic (Roy et al., 2020). With chronic hyperglycemia damages the retinal microvasculature in NPDR, features of ischemia, vascular leakage, and central vision loss due to diabetic macular edema will be observed (Vujosevic et al., 2020). As the condition progresses to PDR, vision loss occurs due to neovascularization, hemorrhage, and retinal detachment (Wang and Lo, 2018). Without appropriate intervention, approximately half of all patients with high-risk PDR will experience visual impairments within 5 years of diagnosis (Moshfeghi et al., 2020).

Pathogenesis of diabetic retinopathy

DR is predominantly regarded as a microangiopathic disease, as small blood vessels are vulnerable to damage from hyperglycemia. However, recent studies suggest that DR is a complex neurovascular complication. The disruption of interactions among neurons, vascular cells, glia, and local immune cells, which together form the neurovascular unit, is associated with impairments in the structure and function of microvasculature and neurons, contributing to the progression of DR (Gardner and Davila, 2017; Liu et al., 2019). The pathophysiology of DR is strictly correlated with the hyperglycemia-induced molecular cascades that

activate alternative metabolic pathways, which ultimately are responsible for inflammation, oxidative stress, and vascular dysfunction (Chalke and Kale, 2021). These pathways result in the production of cytokines and growth factors, causing vascular endothelial dysfunction and increased vascular permeability. Eventually, microvascular occlusion occurs, resulting in retinal ischemia. Retinal ischemia promotes angiogenesis and neovascularization, which is seen in PDR (Neelam et al., 2023). The pathogenesis of DR is summarized in **Figure 3**.

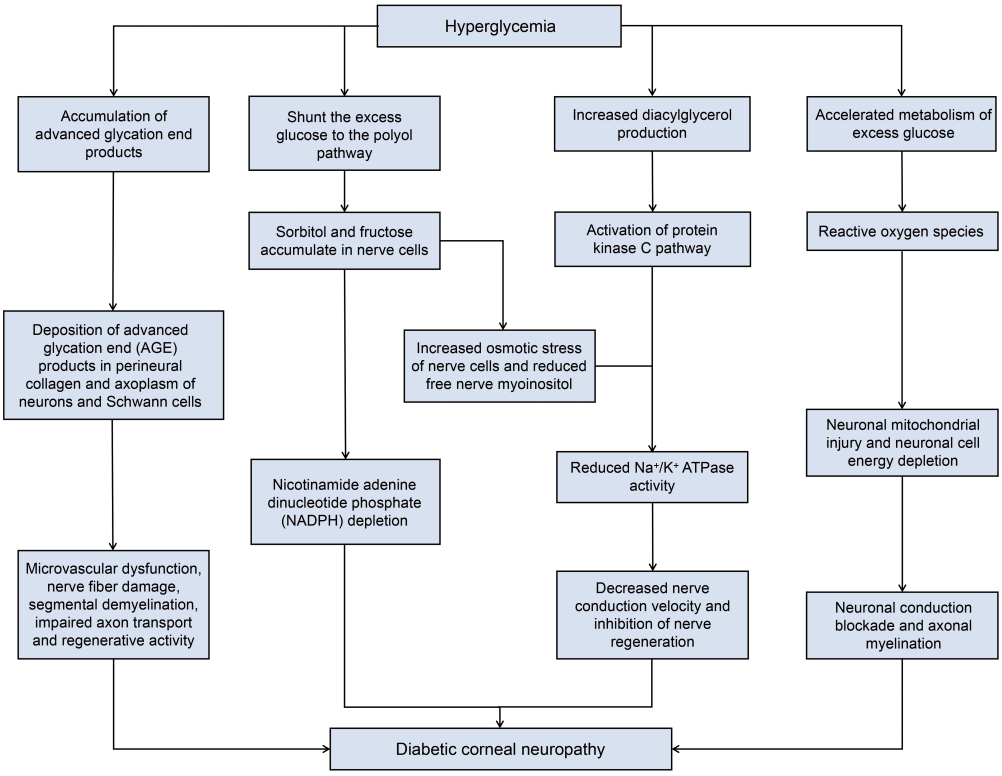

Figure 2 | Summary of the pathogenesis of diabetic corneal neuropathy.

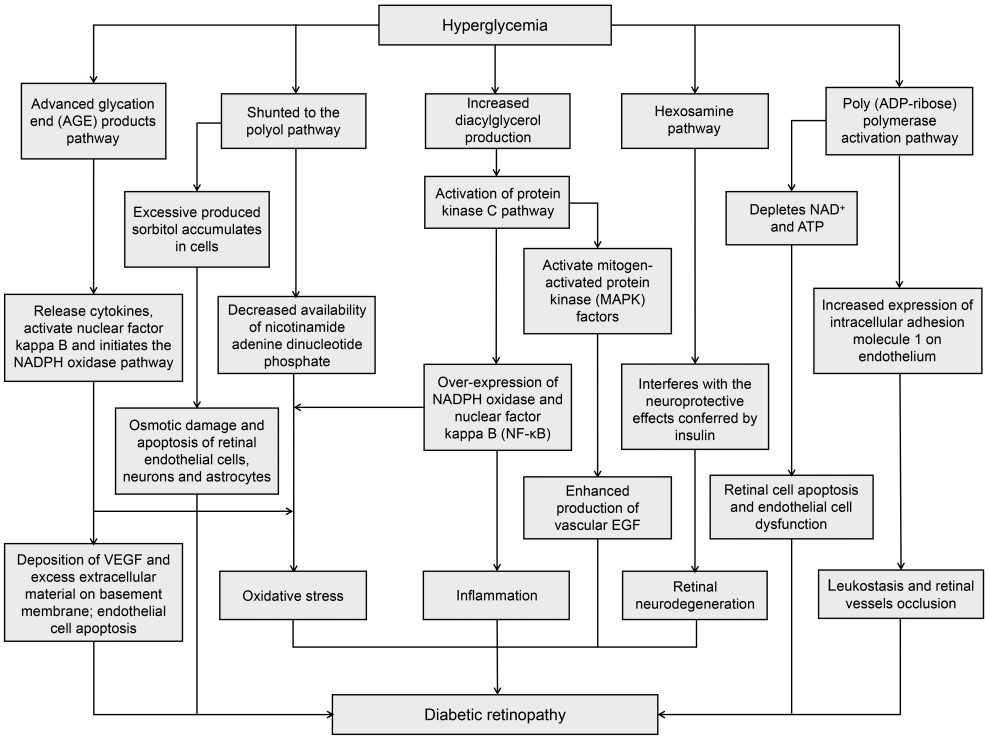

Figure 3 | Summary of the pathogenesis of diabetic retinopathy.

Advanced glycation end products pathway in diabetic retinopathy

The first pathway involves the production of AGEs. AGEs are formed from a non-enzymatic reaction between intracellular glucose-derived precursors and amino acids. AGEs bind to AGE receptors expressed on inflammatory cells, vascular smooth muscle cells, and endothelium. This results in the release of cytokines such as transforming growth factor-β, which in turn leads to a deposition of vascular endothelial growth factor (VEGF) and excess extracellular material and basement membrane, as implicated in DR (Valle et al., 2021). In addition, the accumulation of AGEs leads to the overactivation of nuclear factor kappa B (NF-κB), resulting in altered gene expression of VEGF, platelet-derived growth factor, and endothelin-1, and the release of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6. These changes ultimately cause endothelial apoptosis and angiogenesis (Sahajpal et al., 2019). Furthermore, the interaction between AGEs and RAGE initiates the NADPH oxidase pathway (Chen et al., 2018), leading to the generation of ROS, which act as second messengers regulating endothelial cell injury (Koulis et al., 2015).

Polyol pathway in diabetic retinopathy

Due to chronic hyperglycemia, excess glucose is shunted to the polyol pathway, and there is enhanced aldose reductase activity, which increases glucose metabolism through the polyol pathway, and this causes excessive production of sorbitol and fructose (Szwergold et al., 1990). Sorbitol is impermeable and remains in the cells, causing osmotic damage and apoptosis of retinal endothelial cells, neurons, and astrocytes (Szwergold et al., 1990). Additionally, glucose can be metabolized to fructose-3-phosphate and deoxyglucosone, which are strong glycolysing agents, resulting in AGE deposition (Gabbay, 1975). Furthermore, upregulation of the polyol pathway leads to a decreased availability of NADPH, an antioxidant, causing increased sensitivity of cells to oxidative stress (Barnett et al., 1986).

Protein kinase C activation pathway in diabetic retinopathy

Another pathway involved is the activation of protein kinase C (PKC). Intracellular glucose increases the synthesis of diacylglycerol, which is the second messenger of the PKC signaling pathway. This results in the activation of the PKC signaling pathway, which activates the mitogen-activated protein kinase factors, resulting in enhanced production of the pro-angiogenic molecule VEGF (Li et al., 2023). Additionally, PKC activation stimulates the over-expression of NADPH oxidase and NF-κB in vascular cells, causing oxidative stress and inflammation (Koya and King, 1998).

Hexosamine pathway Flux pathway

The hexosamine pathway activates in response to intracellular glucose excess beyond glycolytic capacity. Elevated glucose levels prompt conversion to glucose-6-phosphate, subsequently metabolized to fructose-6-phosphate (Nagy et al., 2019). Under conditions of hyperglycemia, fructose-6-phosphate is converted to N-acetylglucosamine-6-phosphate by the enzyme glutamine fructose-6-phosphate amidotransferase (Lehmann et al., 2018). This results in the formation of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), which appears to induce alterations in protein function and gene expression that may compromise cellular protection (Lehmann et al., 2018). It has been reported that the hexosamine pathway can mediate ROS-induced toxic influence in hyperglycemia (Lund et al., 2019). Moreover, Safi et al. (2014) have demonstrated that the increased glucose metabolism via the hexosamine pathway alters the glycosylation of proteins and interferes with the neuroprotective effects conferred by insulin, mediated by protein kinase B, leading to retinal neurodegeneration.

Poly(ADP-Ribose) polymerase activation pathway

Hyperglycemia-induced oxidative stress also activates the poly(ADP-Ribose) (PARP) pathway. Overactivation of the PARP pathway depletes NAD^+ and ATP, causing retinal cell death. Furthermore, PARP causes endothelial cell dysfunction. PARP increases the DNA binding affinity of NF-κB by binding to its subunits. NF-κB-mediated transcription then results in an increased expression of intracellular adhesion molecule-1) on endothelial cells which induces leukostasis and possible occlusion of retinal vessels (Zheng et al., 2004).

Connections Between Diabetic Corneal Neuropathy and Diabetic Retinopathy

Although DCN and DR affect different ocular structures, recent evidence suggests that there is a complex relationship between these two conditions. DCN and DR share common underlying pathophysiological pathways, including the AGE pathway, the protein kinase C pathway, and the polyol pathway as previously mentioned. Furthermore, DCN and DR show similar risk factors such as dyslipidemia, elevated HbA1c levels, and prolonged duration of diabetes. However, the precise relationship between these two diabetic microvascular complications remains an ongoing subject of investigation. Elucidating the relationship between DCN and DR may contribute to the development of novel strategies for early detection and prevention of visually threatening stages, ultimately improving visual outcomes and enhancing the quality of life for diabetic individuals. **Table 1** summaries findings on the relationship between DCN and DR

Exacerbation of diabetic corneal neuropathy and progression of diabetic retinopathy

Progressive corneal nerve damage in DCN can manifest as decreased corneal sensitivity functionally and abnormalities in corneal nerve morphology structurally. Multiple studies have demonstrated a correlation between DR severity and corneal sensitivity, as assessed using the Cochet-Bonnet esthesiometer. Salami et al. (2020) observed a significant reduction in corneal sensitivity among DR patients compared to those without DR. Furthermore, Saito et al. (2003) reported that diabetic patients with varying stages of retinopathy, including simple DR (defined by the presence of microaneurysms, dot or blot hemorrhages, and either hard or limited soft exudates in the retina), pre-PDR, and PDR, exhibited a notable decline in corneal sensitivity compared to those without DR. Eyes with PDR or a history of PDR exhibited a 1.79-fold increased

Table 1 | Studies investigating the relationship between DCN and DR

Authors	Study subjects	DCN/DR-related parameters	Study findings
Salami et al., 2020	Diabetic patients with and without DR	Corneal sensitivity	Significant reduction in corneal sensitivity among DR patients compared to those without DR; At a cut-off value of 0.58 mm^2/g, the sensitivity and specificity of corneal sensitivity for PDR screening are 100% and 58%, respectively.
Saito et al., 2003	Diabetic patients with simple DR, pre-PDR, PDR, and non-DR	Corneal sensitivity	Diabetic patients with simple DR, pre-PDR, and PDR exhibited a notable decline in corneal sensitivity compared to those without DR.
Singer et al., 2024	Eyes with PDR or a history of PDR, eyes with NPDR	Corneal sensitivity	Eyes with PDR or a history of PDR exhibited a 1.79-fold increased likelihood of corneal sensitivity impairment across all four regions of the cornea compared to eyes with NPDR; No significant difference between corneal sensitivity in eyes that regressed from PDR to NPDR with anti-VEGF treatment and in newly diagnosed PDR eyes without any treatment.
Nitoda et al., 2012	Diabetic patients with NPDR, PDR, and non-DR and healthy subjects	CNFD, CNBD, CNFL	Significant reduction in CNFD in both NPDR and PDR compared to non-DR diabetic patients; Significant reductions in CNFD, CNBD, and CNFL in non-DR diabetic patients than in healthy subjects.
Mocan et al., 2006	PDR and non-DR diabetic patients.	Subbasal long nerve fiber density, CNBD	Significant lower subbasal long nerve fiber density among PDR patients compared to non-DR patients; Lower CNBD in PDR patients than in NPDR patients but not statistically significant.
Bitirgen et al., 2014	Non-DR diabetic patients, PDR patients with or without argon laser photocoagulation treatment, healthy subjects	CNFD, CNBD, CNFL	Significant decrease in CNFD, CNBD, and CNFL in type 2 diabetic patients without DR compared to healthy subjects; PDR patients with argon laser photocoagulation treatment have significantly lower CNFL than untreated PDR patients.
Saini et al., 1996	Non-DR diabetic patients, DR patients, healthy subjects	Corneal sensitivity	Significant lower corneal sensitivity in non-DR diabetic patients than in healthy subjects; At a cut-off value of 1.49 gm/mm^2, the sensitivity and specificity of corneal sensitivity for PDR screening are 89% and 80%, respectively
Gao et al., 2015	Non-DR diabetic patients and healthy subjects	Tear secretion volume	Schirmer I test showed significantly lower tear secretion volume in non-DR diabetic patients than in healthy individuals, suggesting that nerve fiber damage can occur in the absence of observable signs of the development of DR.
Hafner et al., 2019	Type 2 diabetic patients without DR	CNFD, CNBD, CNFL, parafoveal vessel density in the retinal capillary plexus, inner retinal layers thickness, total retinal thickness	Significant positive correlation between the parafoveal deep vessel density and the inner retinal layers thickness, including peripapillary retinal nerve fiber layer, macular ganglion cell layer, inner plexiform layer, and the total retinal thickness.
Frydkjaer-Olsen et al., 2016	Type 2 diabetic patients with early DR or without DR	Peripapillary retinal nerve fiber layer thickness, central retinal vein equivalent	Significant positive correlation between the peripapillary RNFL thickness and central retinal vein equivalent.
Mitamura et al., 2023	Non-DR diabetic patients	Radial peripapillary capillary perfusion density,	Significant positive correlation between radial peripapillary capillary perfusion density and the retinal nerve fiber layer thickness within the corresponding capillary areas.
Alvarenga et al., 2003	PDR patients	Corneal sensitivity	At a cut-off value of 0.58 mm^2/g, the sensitivity and specificity of corneal sensitivity for PDR screening are 72% and 57%, respectively.
De Cilla et al., 2009	PDR patients with or without argon laser photocoagulation treatment	Subbasal nerves number	PDR patients with argon laser photocoagulation treatment had a significantly reduced number of subbasal nerves than untreated PDR patients.
Polat et al., 2022	Patients with diabetic macular edema or neovascular age-related macular degeneration receiving anti-VEGF treatment; healthy subjects	CNFD, CNBD, CNFL, CDFractal dimension, corneal sensitivity	Significant decrease in CNFD, CNBD, CNFL, CNFractal dimension, and lower corneal sensitivity in patients receiving anti-VEGF treatment for diabetic macular edema or neovascular age-related macular degeneration, compared to healthy subjects.

anti-VEGF: Anti-vascular endothelial growth factor; CDFractal: corneal nerve fiber fractal; CNBD: corneal nerve branch density; CNFD: corneal nerve fiber density; CNFL: corneal nerve fiber length; DCN: diabetic corneal neuropathy; DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; RNFL: retinal nerve fiber layer.

likelihood of corneal sensitivity impairment (≤ 4 cm by Cochet-Bonnet esthesiometer) across all four regions of the cornea compared to eyes with NPDR (Singer et al., 2024). In terms of corneal nerve alterations, Nitoda et al. (2012) assessed the corneal nerve fiber parameters between diabetic patients with various status of retinopathy using IVCM. Compared with non-DR patients, a significant and consistent reduction in CNFD was observed in both NPDR and PDR patients. A similar declining trend was evident in CNBD, with significant reductions observed in NPDR and PDR patients. Similarly, CNFL showed markable reductions in both NPDR and PDR patients. Furthermore, Mocan et al. (2006) found a significant decrease in subbasal long nerve fiber density among PDR patients compared to non-DR patients. The authors also observed a lower CNBD in PDR compared to NPDR patients, although it was not statistically significant. Taken together, these findings suggest that the corneal nerve fiber impairment progresses in parallel with DR.

Occurrence of diabetic corneal neuropathy may precede the onset of diabetic retinopathy

Previous research has shown that diabetic patients experience corneal nerve damage before the onset of DR. Bitirgen et al. (2014) observed a significant decrease in CNFD, CNBD, and CNFL in type 2 diabetic patients without DR compared to healthy subjects, analyzed using ACCMetrics software. Nitoda et al. (2012) reported similar findings using a customized MATLAB routine for analyzing, with significant reductions in CNFD, CNBD, and CNFL in type 2 diabetic patients without DR compared to healthy subjects. In addition, corneal sensitivity in diabetic patients without DR was significantly worse compared to healthy subjects, as measured by a Cochet Bonnet aesthesiometer (Saini and Mittal, 1996). Moreover, the Schirmer I test revealed a tear secretion volume of 20 ± 5 mm in healthy individuals, which significantly decreased to 12 ± 6 mm in diabetic patients without DR, showing a significant difference (Gao et al., 2015). Hence, these data may indicate that nerve fiber damage occurs even in the absence of observable signs of the development of DR, therefore challenging the conventional understanding that the vascular pathomechanism of diabetes is primarily responsible for the neurogenic aspect of the disease. Instead, neuropathy may precede retinopathy, with initial diabetic neuropathy-induced innervation loss leading to retinal vessel impairment (Singer et al., 2024).

It is important to note that the fundamental difference in the vascular supply of the cornea and retina may elucidate why DCN tends to occur earlier than DR in individuals with diabetes.

DCN mainly affects the avascular cornea and is driven by hyperglycemia-induced nerve dysfunction without direct vascular involvement. Chronic hyperglycemia leads to metabolic changes, including AGE accumulation, increased polyol pathway flux, ROS production, and activation of the PKC pathway as the abovementioned. These interconnected metabolic alterations collectively result in direct damage to the trigeminal nerve and branches, leading to a reduction or even loss of corneal nerve fibers, particularly affecting Aδ and C nerve fibers (Iqbal et al., 2018). Additionally, prolonged diabetes lowers the concentration of neuromediators, such as nerve growth factors (Tummanapalli et al., 2020). As a result, the impaired neurotrophic support exacerbates the reduced corneal nerve fiber metrics, attenuated corneal sensitivity, dry eyes, and delayed wound healing, subsequently developing into corneal ulcers, perforations, and even blindness (Markoulli et al., 2018).

In contrast, the highly vascularized structure of the retina suggests that microvascular damage contributes significantly to diabetic retinopathy pathogenesis. The imbalance between the synthesis and degradation of the extracellular matrix causes the thickening of the retinal vascular basement membrane and leads to vascular leakage (Roy et al., 2015). Moreover, hyperglycemia-induced pericyte apoptosis and dropout from retinal vessels lead to a lack of structural support for retinal capillaries and increased permeability of the selective inner blood–retinal barrier (Park et al., 2017). This results in the formation of microaneurysms, one of the first lesions detectable during ophthalmoscopic examination in individuals with NPDR (Sohn et al., 2016). Pericyte dropout also causes endothelial cell damage, a key pathological feature of DR (Arboleda-Velasquez et al., 2015). In response to retinal non-perfusion, ischemic retinal neurons secrete a broad range of angiogenic factors and cytokines, most notably vascular endothelial growth factor, to promote the formation of abnormal new blood vessels (Sohn et al., 2016). This neovascularization is the central microvascular characteristic of PDR and can cause extensive bleeding from the fragile neovessels into the vitreous (Nawaz et al., 2019). Overall, the fundamental difference in vascular supply indicates that corneal nerves are directly affected by diabetes-related metabolic disruptions, while DR primarily arises from the progressive deterioration of retinal blood vessels.

Another explanation is that the initial loss of innervation due to retinal neuropathy may lead to the development of small vessel disease, capillary nonperfusion, and subsequent proliferative changes (Singer et al., 2024).

Pathophysiological interconnection between diabetic corneal neuropathy and diabetic retinopathy

It is widely known that during diabetes, neuronal and microvascular dysfunction are known to be interdependent, leading to a vicious cycle of neurodegeneration and vascular damage that contributes to the development of DR (Abcouwer and Gardner, 2014; Simo et al., 2018). As DCN shares risk factors with microvascular dysfunction in DR and the impairment of corneal nerve and corneal sensitivity precede DR and worsens as DR progresses, DCN may have a predictive role in the progression of DR. However, the correlation between early diabetic neurodegenerative signs in the cornea and retina, and the respective associations with markers of microvascular pathology in DR remains a topic of debate.

Hafner et al. (2019) detected the association between corneal nerve fiber parameters by IVCM and parafoveal microvascular perfusion using optical coherence tomography angiography imaging systems in type 2 diabetic patients without DR. The parafoveal vessel density was used to represent retinal microvascular integrity in the study, and no significant association was found between CNFD, CNBD, or CNFL and the parafoveal superficial and deep vessel density in the retinal capillary plexus. However, it was worth noting that the study did not investigate the correlation between corneal nerve morphology and microvascular damage in the peripheral retina due to the limitations of optical coherence tomography angiography in angiographic imaging. Therefore, further research is required to elucidate this aspect.

Furthermore, Hafner et al. (2019) demonstrated a significant positive correlation between the parafoveal deep vessel density and the inner retinal layers thickness, including peripapillary retinal nerve fiber layer, macular ganglion cell layer, inner plexiform layer, and the total retinal thickness. This finding was similar to that of the study of the European Consortium for the Early Treatment of DR, identifying a significant positive correlation between the peripapillary RNFL thickness and central retinal vein equivalent (Frydkjaer-Olsen et al., 2016), and that of the study of Mitamura et al. (2023),

reporting a significant positive correlation between the radial peripapillary capillary perfusion density and RNFL thickness within the corresponding capillary areas in non-DR diabetic patients.

It is currently unclear why there is a poor connection between IVCM parameters and retinal microvascular changes. One possible explanation is that initial retinal neurodegeneration, manifested as inner retinal layers thinning, may contribute to the onset of microvascular dysfunction, capillary nonperfusion, and subsequent proliferation changes, while corneal neurodegeneration occurs as an independent pathological process (Dodo et al., 2015). Furthermore, there is a lack of research on the correlation between corneal sensitivity and retinal microvascular damage in DR. Consequently, these hypotheses require validation through future studies.

Corneal esthesiometry as a screening tool for diabetic retinopathy

Corneal sensitivity esthesiometry may offer a simple and efficient means of screening for DR. Several validation studies have investigated the efficacy of the use of corneal sensitivity as a screening tool for DR. A study conducted in Brazil used the Cochet-Bonnet esthesiometer to screen for PDR (Alvarenga et al., 2003). At a cut-off value of 0.58 mm^2/g, patients with PDR were detected with a sensitivity of 72.2% and a specificity of 57.4%. This study also noted reduced corneal sensitivity in older patients with brown eyes, particularly in the presence of arcus senilis (Alvarenga et al., 2003). Additionally, a study in India reported sensitivity and specificity for PDR screening to be 89% and 80%, respectively, at a cut-off value of 1.49 gm/mm^2 (Saini and Mittal, 1996). While in Nigeria, a study found sensitivity and specificity for screening PDR at the 50 mm cut-off point were 100% and 58%, respectively (Salami et al., 2020). Introducing the assessment of corneal sensitivity as a standard component of the evaluation of diabetic patients, and incorporating corneal sensitivity esthesiometry into the management protocols for DR may enhance the identification of individuals at risk and enable prompt intervention. This method is particularly useful in primary care settings or large health screening programs, where access to specialists is limited. Moreover, it is a cost-effective option for countries with limited healthcare resources, especially in regions with a growing prevalence of diabetes, and where traditional methods such as dilated examinations and tele-imaging are not feasible.

Impact of diabetic retinopathy treatment on corneal metrics

Various therapeutic interventions for DR, such as laser photocoagulation, intravitreal injections, and vitrectomy, aim to prevent vision loss and preserve the function of the retina. These treatments were also reported to have an impact on the structure and function of the corneal nerves.

Argon laser photocoagulation is a procedure that focuses laser energy on specific areas of the retina to prevent or shrink abnormal blood vessels. It is the standard treatment for patients with PDR and severe NPDR due to its effectiveness in reducing the risk of severe vision loss (Flaxel et al., 2020). However, argon laser photocoagulation may cause corneal hypoesthesia associated with damage to the short ciliary nerves (Schiodte, 1984). Among patients with PDR, those who received argon laser photocoagulation treatment exhibited a significantly lower CNFL compared to untreated patients (Bitirgen et al., 2014). This finding is consistent with the results from a study by De Cilla et al. (2009), which demonstrated that PDR patients treated with argon laser photocoagulation had a significantly reduced number of corneal subbasal nerves compared to those who did not receive treatment.

Polat et al. (2022) observed a significant decrease in CNFD, CNBD, CNFL, CDFractal dimension, and lower corneal sensitivity in patients receiving anti-VEGF treatment for diabetic macular edema or neovascular age-related macular degeneration, compared to healthy subjects. These findings raised the concern that anti-VEGF treatment may have an impact on corneal nerves. However, their study design does not clearly elucidate the specific contributions of anti-VEGF therapy versus the underlying disease states to the observed corneal nerve impairment. In contrast, another study investigated whether the improvements in the DR severity with anti-VEGF therapy were associated with changes in corneal sensitivity (Singer et al., 2024). The authors found that the mean corneal sensitivity in eyes that regressed from PDR to NPDR with anti-VEGF therapy was not significantly different from that in newly diagnosed PDR eyes without any treatment. Similarly, Qi et al. (2023) observed that repeated (three times) intravitreal anti-VEGF injections led to a reduction in CNFD and CNFL compared to pre-treatment levels, and these reductions were not statistically significant.

Pars plana vitrectomy is another promising intervention for DR, particularly in advanced cases such as vitreous hemorrhage, tractional retinal detachment, or macular edema, where therapies of laser photocoagulation or intravitreal anti-VEGF injections have proven ineffective or insufficient (Stitt et al., 2016). At present, there are few studies investigating changes in corneal nerves before and after vitrectomy in patients with PDR. Tosi et al. (2018) demonstrated a significant reduction in CNFD 6 months after pars plana vitrectomy compared to preoperatively for treatment of rhegmatogenous retinal detachment. They also observed a significant decrease in corneal sensitivity of 6 months postoperatively compared to preoperatively.

Altogether, current findings do not confirm that the treatment to manage DR will significantly negatively impact the morphology or function of corneal nerves. Although the exact mechanisms of corneal nerve changes after treatment for DR are not yet fully understood, current research findings indicate that clinicians should not limit their focus to treating retinopathy, but should pay attention to the condition of the ocular surface health. Such attention will help prevent severe damage to the cornea, which may have already been affected by diabetic neuropathy.

Future Direction

Future research should aim to clarify the common pathways between DCN and DR to help detect potential biomarkers, genetic predispositions, and new therapeutic targets. The

application of wide-field or large-area IVCM scanning systems has the potential of detecting and monitoring alterations of corneal nerve plexus over a larger area (Stewart et al., 2021), allowing a more accurate evaluation of the relationship between DCN and DR. Furthermore, the integration of artificial intelligence technology and multimodal data (for example, clinical and imaging data) can substantially improve the DR risk prediction models (Liu et al., 2021). As DCN and DR are interconnected manifestations of systemic metabolic dysfunction, the diagnostic process in the clinical practice critically requires a multidisciplinary collaboration, which extends beyond corneal and retinal specialists to include ophthalmologists, neurologists, endocrinologists, and technicians from relevant fields. This will enable the development of personalized and effective management strategies to provide timely intervention, reduce the burden of sight-threatening complications of diabetes, and ultimately improve the quality of life of those affected.

Conclusions

In conclusion, our review has illuminated the interconnection between DCN and DR based on the existing literature, offering an updated overview of the main pathophysiological events shared between the two conditions. DCN and DR are both prevalent complications of diabetes and share similar pathogenetic pathways. IVCM and corneal sensation testing are rapid and non-invasive tools to evaluate DCN, providing a comprehensive assessment of both the structure and function of the corneal nerves. However, the interconnection between DCN and DR is far from being fully understood. DCN typically precedes the onset of DR and its severity tends to increase in parallel with the progression of DR. Corneal sensitivity esthesiometry is an effective tool in the monitoring of the progression of DR. Currently, there is little evidence to suggest that treating DR can significantly affect the management of DCN. However, clinicians should monitor potential adverse effects on corneal nerves when treating DR. Summarizing, the existing findings underscored that ophthalmologists may carefully monitor cases of DR and incorporate the management of corneal neuropathy into their treatment protocols.

Author contributions: *MY and FTEN contributed to the literature search and manuscript writing. CL contributed to image acquisition. YCL reviewed the manuscript and provided the overall supervision of this review. All authors contributed to the conceptualization, design, definition of intellectual content, critical appraisal, editing, and review of the manuscript, and approved the final version of this manuscript.*

Conflicts of interest: *The authors declare no conflicts of interest.*

Data availability statement: *Not applicable.*

Open peer reviewers: *Sara B A Mokhtar, Maastricht University, Netherlands; Francesco Buonfiglio, Mainz University, Germany.*

Additional file: *Open peer review reports 1 and 2.*

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P-Reviewers: Mokhtar SBA, Buonfiglio F; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y