

Diabetic corneal neuropathy: clinical perspectives

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Abstract: Diabetic keratopathy is characterized by impaired innervation of the cornea that leads to decreased sensitivity, with resultant difficulties with epithelial wound healing. These difficulties in wound healing put patients at risk for ocular complications such as surface irregularities, corneal infections, and stromal opacification. Pathological changes in corneal innervations in diabetic patients are an important early indicator of diabetic neuropathy. The decrease in corneal sensitivity is strongly correlated with the duration of diabetes as well as the severity of the neuropathy. This review presents recent findings in assessing the ocular surface as well as the recent therapeutic strategies for optimal management of individuals with diabetes who are susceptible to developing diabetic neuropathy.

Keywords: diabetes mellitus, cornea, innervation, neuroprotective therapy

Introduction

The incidence of diabetes has risen markedly in the past four decades from 108 million in 1980 to 422 million in 2014.¹ According to the US National Diabetes Statistics Reports (2017), ~30.3 million people (9.4% of the US population) of all ages had diabetes in 2015.²

Diabetic neuropathies are characterized by the progressive loss of nerve fibers – a common complication affecting ~50% of patients with diabetes mellitus.³ These complications can occur in the cornea and can lead to diabetic neuropathy, severe reductions in visual acuity, and eventual blindness.

Diabetic retinopathy is generally considered to be a microvascular complication based on the ophthalmoscopic observations of the ocular fundus; however, growing evidence indicates that the appearance of the neuroretinal damage develops simultaneously as, or even prior to, the vascular changes.⁴⁻⁷ Evaluation of the neuronal changes at the early stages of diabetes mellitus is therefore very important.

Although increasing attention has been paid to disorders of the ocular surface in the eyes of patients with diabetes, there is a lack of review articles on the management of diabetic keratopathy. Thus, the purpose of this review is to present the findings in recent publications that discuss the clinical perspectives for ocular surface management in patients with diabetes mellitus.

Corneal surface

The corneal epithelium plays an important role as an ocular surface defense system by providing both a physical and an immunological barrier to external organic and inorganic agents.⁸ Innervation of the cornea is derived from the ophthalmic division of the trigeminal nerve; this provides the cornea with a large number of sensory receptors, such as the myelinated A- δ and unmyelinated C fibers, with ~7,000 epithelial free nerve endings per square millimeter, which is 300–600 times greater than that of the skin.⁹

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The maintenance of the corneal sensitivity, blink reflex, homeostasis of the ocular surface, and the regulation of corneal wound healing is led by corneal innervation.⁹ As a result, impairment of corneal innervation can lead to an attenuation of corneal sensitivity as well as dry eye, neurotrophic keratitis, and even blindness.¹⁰ Hyperglycemia in patients with diabetes can cause impaired corneal sensitivity, reduced nerve fiber density, and delayed epithelial wound healing.¹¹ Recent studies have demonstrated the important role of glycation in the pathogenesis of retinal diabetic neuropathy and as part of different trigger mechanisms resulting in neuronal dysfunction.^{6,7} Kim et al showed that advanced glycation end products (AGEs), 8-OHdG, and NF- κ B were expressed at higher levels in the cornea of diabetic rats than in that of healthy control rats, suggesting that these factors probably participated in apoptosis and the subsequent changes of the cornea that are related to diabetic keratopathy.¹²

Because of the reduced corneal sensitivity in patients with diabetes mellitus, there is a decrease in both reflex-induced lacrimal secretion and blink rate, and these reductions result in greater tear evaporation. These changes will then put patients with diabetes at a risk of developing dry eyes.¹³

Tear-film dysfunction and chronic tear-secretion deficiency can also be present in patients with diabetes, as their tear lipid thickness, tear quantity, and tear stability are significantly decreased.¹⁴ The recent study by Kesarwani et al on tear film dysfunction in diabetes in the Indian population demonstrated decreased tear secretion and stability, evidence of keratoepitheliopathy, abnormal results on the rose bengal staining test, squamous metaplasia, and poor goblet cell density.¹⁵

Furthermore, diabetes mellitus can cause changes in the epithelial basal cells, basement membrane, and the sub-basal nerve plexus (SBN) leading to epitheliopathy and corneal adhesion disorders.¹⁶ Moreover, a loss of corneal nerves leads to a reduced supply of trophic neuropeptides, resulting in prolonged healing time.⁸

Another finding in diabetic corneas is increased corneal thickness; however, there is no significant correlation between the severity of retinopathy and the corneal thickness.¹⁷⁻¹⁹

Ultrastructural changes in the corneal stroma can be explained by the increased accumulation of AGEs which then leads to non-enzymatic cross-linking between collagen molecules and proteoglycans, thereby causing stiffening and thickening of the cornea.²⁰

A less common change in diabetic corneas is the presence of vertical lines at the level of Descemet's membrane and endothelium. These lines were initially described first by Waite and Beetham and then by Henkind and Wise.^{21,75,76}

Morphological changes have been reported in the diabetic corneal endothelium. Experimental studies have shown that there is a decrease in the corneal endothelial cell density and hexagonality, and an increase polymegathism. These changes indicate there is an increase in morphological abnormalities or pleomorphism in the corneal endothelium in individuals with diabetes.²²⁻²⁷

Corneal surface assessments

In vivo confocal microscopy (IVCM) has become the standard method of assessing the cornea at a cellular level, both in diseased and healthy eyes. Many studies have reported on the advantages of using IVCM for analysis of the sub-basal nerve plexus (eg, the central cornea and the inferior whorl) for the clinical diagnosis of early peripheral neuropathy.²⁸⁻³² Petropoulos et al reported that the nerve fiber density of the inferior region of the cornea was more sensitive to early nerve fiber damage than the central corneal region in patients with diabetes before the development of peripheral neuropathy.³³

Recent IVCM studies by Qu et al showed an increase in the densities of Langerhan cells and a decrease of density in the sub-basal nerve plexus in patients with type 2 diabetes mellitus who have corneal punctate epitheliopathy. These changes were related to a lower basal epithelial cell density leading to a delay in corneal epithelium healing.³⁴ Lagali et al went further by assessing raw images obtained by laser-scanning IVCM of 82 eyes that had been automatically processed to produce depth-corrected, wide-area mosaic images of the continuous nerve fiber paths and nerve and background intensity levels. These wide-area mosaic images produced from 82 eyes by laser-scanning IVCM showed a progressive degeneration of the sub-basal nerve plexus with increasing duration of type 2 diabetes.³⁵ They reported that comparisons of mosaics from newly diagnosed subjects (diabetes diagnosed <1 year prior to the IVCM examination) to subjects with long-term diagnosed diabetes (diagnosed >20 years prior to the IVCM examination) showed a marked degeneration of the sub-basal plexus. A predominant loss of the nerves occurred outside the whole region along with the loss of short, thin nerve branch segments.

The appearance of neuronal damage in early stages of diabetes has been demonstrated in laboratory studies,⁴⁻⁷ and the findings have been described clinically in a study by Srinivasan et al, who examined the neuronal structural integrity of the cornea and retina as markers for neuronal degeneration in non-proliferative diabetic retinopathy.³⁶ They assessed the corneal nerve fiber length (CNFL), corneal nerve branch density (CNBD), and the corneal nerve fiber tortuosity (CNFT), and reported that shorter CNFLs were significantly

associated with the severity of the nonproliferative diabetic retinopathy, CNBD, and CNFT. According to Srinivasan et al, CNFL may be a better marker, than CNBD and CNFT, for detecting corneal neuronal degeneration in patients with mild nonproliferative diabetic retinopathy, compared with controls and those with diabetes but without retinopathy.³⁶

Bitirgen et al confirmed that corneal nerve abnormalities developed before the first signs of diabetic retinopathy. They found that patients with diabetes mellitus without retinopathy and non-proliferative diabetic retinopathy had decreased basal epithelial cell density, anterior stromal keratocyte counts, and endothelial cell density. Moreover, they confirmed an inverse correlation of these parameters with the duration of diabetes mellitus.³⁷ However, the reductions of nerve fiber density, nerve branch density, and nerve fiber length were found only in patients without the usual signs of diabetic retinopathy, were progressive, and worsened with increasing severity of retinopathy.³⁷ Bitirgen et al reported a lower keratocyte density in the anterior part of the cornea in patients with proliferative diabetic retinopathy than in patients without diabetic retinopathy. In addition, they reported that the reduction in the anterior stromal keratocyte density was significantly correlated with the duration of diabetes mellitus.³⁷

Accumulation of AGE products in patients with diabetes mellitus can cause protein glycation, which can explain the pathological changes of the cornea in the initial stages of diabetes.³⁸

An interesting recent study has suggested that the expression of insulin-like growth factor binding protein-3 (IGFBP-3) in basal tears of patients with type 2 diabetes mellitus can be an indicator of ocular damage.³⁹ This association was present because the concentration of IGFBP-3 in the tear fluid was increased approximately threefold in eyes with diabetic retinopathy.³⁹ The increase was not directly related to the blood sugar level because there was only a weak or modest correlation between the HbA1c level and both the nerve fiber branch density and nerve fiber length. In addition, the level of HbA1c was not significantly correlated with the concentration of IGFBP-3 in tears. These findings suggested that whereas IGFBP-3 may be a good indicator for the presence of corneal damage in patients with diabetes, it is not directly related to blood sugar control.³⁹

Di et al detected an excessive inflammatory response in diabetic corneas, which was manifested by the accumulation of polymorphonuclear cells in mice diabetic corneas. Wound healing in diabetic corneas was delayed and was accompanied by elevated levels of proinflammatory cytokines, which resulted from the excessive inflammatory response.⁴⁰

Ehmke et al used nonlinear two-photon microscopy (TPM) for in vivo imaging of the cornea of streptozotocin-diabetic Thy1-YFP mice.⁴¹ The difference between confocal and nonlinear microscopy is with their signal detection methods. In confocal microscopy, signals are generated by a linear process and are detected in the focal plane. In TPM, nonlinear signals are generated within the focal volume of the laser spot as a result of nonlinear processing.⁴¹ The authors noted that TPM was helpful in identifying early signs of diseases in animal models in vivo and can be recommended for further clinical studies.

New approaches in treatment of the ocular surface in patients with diabetes

The first treatment of corneal neuropathy should be systemic therapy for diabetes in order to attain accurate control of blood glucose level. Successful control should slow further progression of diabetic neuropathies. The successful management of neurotrophic keratopathy is generally based on achieving epithelial healing and preventing the progression of corneal damage. However, pathogenetically orientated pharmacological treatments are, so far, unavailable for neurotrophic keratopathy.

New systemic drugs have been introduced to treat diabetes, including: glutazumab, a novel long-lasting GLP-1/anti-GLP-1R antibody fusion protein;⁴² beta-carotene, reported to improve diabetes-related ultrastructural changes of the cornea in diabetic rats;⁴³ oral administration of resolvin-D1, an anti-inflammatory eicosanoid, together with fish oil, reported to reduce corneal nerve degeneration in diabetic rats;⁴⁴ and a combination of menhaden oil, α -lipoic acid, and enalapril, shown to reverse diabetic corneal and peripheral neuropathy in streptozotocin-induced diabetic rats.⁴⁵

Cell-based therapies have been reported as an option for preventing neurovascular damage and promoting regeneration of the damaged retina.⁴⁶⁻⁵⁰ The ability of mesenchymal stem cells to produce neuroprotective and neurotrophic factors, and the potential of endothelial progenitor cells to repair vasculature have been suggested to be helpful in treating early and moderately damaged retina.⁴⁶ Di et al demonstrated that a local transplantation of bone marrow-derived mesenchymal stem cells could suppress excessive inflammatory responses, activate endogenous corneal progenitor cells, promote alternative polarization of infiltrated macrophages, and enhance repair of diabetic corneal wounds.⁴⁰

Gene therapy is another approach for managing diabetic keratopathy. The goal of this method is to set one disease-associated target with high specificity and affect it through either a gain or loss of the function of the targeted gene.⁴⁰

It was reported that adenoviral gene therapy with overexpression of the c-met proto-oncogene and/or silencing of matrix metalloproteinase-10 and cathepsin F normalized epithelial wound healing and stem cell marker expression in human organ-cultured diabetic corneas.^{51,52}

There has been a recent increase in interest in the dynamic role of microRNAs (miRNAs) in the modulation of tissue homeostasis. The study by Kulkarni et al, identified miRNA expression profiles in normal and diabetic human limbal cells, and a differential expression of a number of miRNAs have been found in normal corneas and those of both type 1 and type 2 diabetes mellitus. Because of the differential expression of a subset of miRNAs between type 1 and 2 diabetes mellitus, it was suggested that type 1 and type 2 diabetes are different diseases although they have the same clinical manifestations and complications.⁵³ The miR-10b miRNAs were found to control corneal epithelial homeostasis and stem cell functions. This suggested that miR-10b might be a candidate for functional studies of limbal progenitor cells in normal and disease states and potentially as new therapy for diabetic keratopathy.⁵³

There are relatively few therapeutic treatments available for regulating the functions of the corneal nerve and recovery of corneal innervations in patients with diabetic neuropathy. Some studies have reported, however, that the use of neurotrophic factors might be potential therapy for corneal nerve recovery. Neurotrophic factors are molecules that regulate the growth and survival of developing neurons, and they also participate in the maintenance of mature neurons in both the central and peripheral nervous systems. Factors such as nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), and ciliary neurotrophic factor (CNTF) have been reported to stimulate corneal epithelial cell proliferation and migration as well as to enhance their immunoprotective function through their receptors in the corneal epithelium.^{54–57}

A recent study demonstrated that the neurotrophic factors, NGF and GDNF – derived from corneal epithelial cells are involved in corneal nerve regeneration, which can be impaired by hyperglycemia.⁵⁸ Topical application of NGF reversed the apoptosis and inflammation in the cornea by promoting the formation of reactive oxygen species (ROS) in both *in vitro* and *in vivo* diabetic models.⁵⁹

Our previous review⁶⁰ presented the importance of neurotrophic factors and their potential use for restoration of corneal nerves in diabetic patients, together with a discussion of the potential of neurotrophic factors application for neuroprotective and neuroregenerative therapy, with a possibility to reverse the damage to peripheral corneal nerves.

Semaphorins belong to a class of membrane-bound proteins, and they are reported to act as axon-guidance proteins.⁶¹ *In vivo* studies have demonstrated that they can induce nerve regeneration when administered into the corneal intrastromal micropocket without inhibition of NGF.⁶¹

The aim of local treatments for diabetic keratopathy is to maintain a smooth and lubricated ocular surface with an intact epithelium and adequate blink response. This minimizes visual distortions and maximizes comfort. Agents such as topical antibiotics, bandage contact lenses, preservative-free artificial tears, amniotic membrane transplantation, tarsorrhaphy, and the conjunctival flap technique are methods that have been used to treat refractory neurotrophic corneal ulcers.⁶² An aldose reductase inhibitor, epalrestat, which is known to prevent protein glycation, was proposed by Alvarez-Rivera et al. It was suggested that it be used in silicon hydrogel contact lenses to provide a constant slow release of epalrestat in treating diabetic-related corneal damage.⁶³

Corneal epithelial defects can develop from surgical procedures on diabetic patients, and these are usually managed by an application of topical lubricants and prophylactic antibiotics. Chen et al reported that the incidence of persistent corneal epithelial defects after vitrectomy was 4.8%.⁶⁴ This is why the healing of corneal epithelial defects must be accomplished as soon as possible for the vital care of the corneas of diabetic patients.

The use of 0.5 units of topical insulin QID was demonstrated to be effective in healing corneal epithelial defects after vitrectomy in diabetic patients in a randomized control trial presented by Fai et al.⁶⁵ Thymosin beta 4 (T β 4), a naturally occurring polypeptide, has been used in diabetic patients, and its use has led to a significant reduction of non-healing epithelial defects in diabetic patients. T β 4 has been proposed to be a promising therapy for diabetic keratopathy.⁶⁶ Substance P (SP) is a neuropeptide that is released from sensory nerve fibers, and it has been demonstrated that it has an ability to promote corneal epithelial wound healing in diabetic subjects. The results of a recent study showed an improvement of mitochondrial function, recovery of corneal sensation, and decreasing levels of ROS caused by hyperglycemia.⁶⁷

Sodium hyaluronate (HA) has the potential to bind water due to the sponge-like structure of the polysaccharide chains, and it can slowly release the water molecules, thereby acting as a reservoir. It was reported to be effective in promoting corneal epithelial regeneration, improving corneal sensitivity, and increasing the density of corneal nerve fibers and conjunctival goblet cells in diabetic mice.⁶⁸ The effective concentration of HA was 0.3%.⁶⁸ Topical application of the

synergy peptide PHSRN – a fibronectin-derived peptide – significantly facilitated the healing of corneal epithelial wounds in diabetic rats.⁶⁹ Topical application of pigment epithelium-derived factor (PEDF) in combination with docosahexaenoic acid (DHA) has been reported to lead to significant increases in corneal epithelial nerve regeneration and substance P–positive nerve density in both injured and intact corneas of diabetic mice. Additionally, an elevation of the corneal sensitivity and tear production was noted in the treated corneas.⁷⁰ The intranasal delivery of a nanomicelle curcumin solution promoted corneal epithelial/nerve healing in diabetic mice by delivering the pharmaceutically active ingredients to the trigeminal neurons, thus helping to heal diabetic corneal epithelial cells and nerve wounds.⁷¹ An extract of aloe vera has been reported to promote corneal wound healing in diabetic rats,⁷² and topical lacritin delivered by elastin-like polypeptide based nanoparticle improved the regeneration of corneal epithelium in non-obese diabetic mice.⁷³ However, most of the suggested therapies have been determined by experiments on animal models, and further clinical studies are needed to provide an effective care routine for patients with diabetes. A summary of the advances in the treatment of diabetic keratopathy is presented in Table 1.

Table 1 Advances in the treatment of diabetic corneal disease

Therapy	Administration	References
Glutazumab (long-acting GLP-1/anti-GLP-1R antibody fusion protein)	Systematic	Li et al ⁴²
Beta-carotene	Systematic	Abdul-Hamid and Moustafa ⁴³
Resolvin-D1	Systematic	Shevalye et al ⁴⁴
Combination therapy of menhaden oil, α -lipoic acid, and enalapril	Systematic	Davidson et al ⁴⁵
Gene therapy of limbal cells		Saghizadeh et al ⁵¹
Stem cell therapy		Di et al ⁴⁰
Substance P	Eye drops	Yang et al ⁶⁷
Insulin	Eye drops	Fai et al ⁶⁵
Thymosin beta-4	Eye drops	Sosne et al ⁶⁶
PEDF in combination with DHA		He et al ⁷⁰
CNTF	Subconjunctival injection	Zhou et al ⁷⁴
NGF	Eye drops	Park et al ⁵⁹
Nanomicelle curcumin	Intranasal administration	Guo et al ⁷¹
Semaphorins	Injection to intrastromal micropocket	Zhang et al ⁶¹
Extract of aloe vera	Eye drops	Atiba et al ⁷²
Epalrestat, in silicon hydrogel contact lenses	Silicon hydrogel contact lenses	Alvarez-Rivera et al ⁶³
HA	Eye drops	Di et al ⁶⁸
Fibronectin-derived peptide PHSRN	Eye drops	Morishige et al ⁶⁹

Abbreviations: GLP-1, glucagon-like peptide-1; PEDF, pigment epithelium-derived factor; DHA, docosahexaenoic acid; CNTF, ciliary neurotrophic factor; NGF, nerve growth factor; HA, sodium hyaluronate.

Conclusion

Evaluations of the diabetic ocular surface are very important for all physicians, and not just for ophthalmologists. Assessments of the corneal nerve parameters can detect early indicators for the development of diabetic neuropathy and can also be used to monitor the course of diabetes. Using different imaging techniques such as IVCN and nonlinear two-photon microscopy should be very helpful methods for in vivo examination of the corneal structure at the cellular level. Although there is still no unified routine care available for the management of the cornea in diabetic individuals, recently published therapeutic agents including targeted molecular therapies (eg, gene and stem cell therapies) appear promising. Further investigations to establish pathogenetically orientated therapy for diabetic neuropathy bringing animal models to clinical trials should be one of the main focuses of future research.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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