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Introduction

Diabetes mellitus is a major disease worldwide, and the incidence of diabetes has risen markedly in the past several decades. e complications associated with diabetes are the leading cause of blindness in the working age adults. Diabetic neuropathies characterized by a progressive loss of nerve bers are common complications a ecting about 50% of patients with diabetes [1].

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and it is believed to be also contained in corneal sensory neurons.

Nerve-derived trophic factors regulate the biochemistry of the corneal epithelium and control the normal and renewal processes of maintaining the corneal epithelial cells. us, patients with impaired corneal innervation, for example, a er herpetic keratitis, diabetes, prolonged contact lens wear, advanced age, and refractive surgery, are at increased risk of corneal damage because of diminished trophic support. Ferrari et al. reported that nerve-secreted neuropeptides in uence corneal cell proliferation in vitro, and the rate of corneal epithelial cell mitosis is altered in denervated corneas of rats. Ciliary neurotrophic factor (CNTF) has been detected in corneal endothelial cells [7]. Zhou et al. discovered that the mRNA of CNTF was more signi cantly down regulated in diabetic mice than in normal mice. A subconjunctival injection of CNTF signi cantly reduced the size of the corneal epithelial defect of 67.89 ± 12.27% to 30.10% ± 10.13% a er 48 hours. ese results suggest that impaired corneal epithelial wound healing in diabetic mice can be caused by reduced levels of CNTF, and CNTF supplementation can promote corneal epithelial wound healing by activating corneal epithelial stem/progenitor cells.

A study of the e ects of neuropathy showed that the diabetes-induced denervation of the cornea reduces the viability of the corneal epithelial cells and their ability to recover from injury. Guo et al. reported that the trigeminal ganglion neurons and the innervation of the cornea were impaired in diabetic mice. A detailed listing of the neurotrophic factors present in the cornea is shown in (Table 1).

Corneal Sensitivity in Diabetes

Patients with diabetes have decreased corneal sensitivity and thus are very vulnerable to trauma. In the study by Nielsen it was demonstrated that corneal sensitivity in 83% of diabetic patients was

Table 1: Neurotrophic factors in the cornea.

Growth factor	Healthy cornea	Injured cornea	Topical application
Nerve growth factor (NGF)	(i) Found in corneal epithelium and stromal keratocytes	Upregulated during reinnervation after nerve surgical transection, and in dry eye syndrome, in in amed conjunctiva of patients with vernal keratoconjunctivitis	(i) Augments corneal wound healing and provides recovery of corneal sensitivity and photophobia
	(ii) Critical for corneal nerve survival and maintenance, axonal branching, elongation, neuronal sprouting, and regeneration following nerve damage		(ii) Has potent antiviral properties (restrict herpes simplex virus-1)
Brain-derived neurotrophic factor (BDNF)	(i) Found in corneal epithelium and stromal keratocytes, originate from corneal sensory neurons	Expressed after experimental ap surgery in putative corneal stromal and/or in ammatory cells in a positive association with neurite extension	
	(ii) Exact role related to corneal nerves is unclear		
Glial cell-derived neurotrophic factor (GDNF)	Expressed in human corneal stromal keratocytes and may operate similarly to or synergistically with NGF by triggering gene transcription governing epithelial cell migration and wound healing	Possibly plays an important role in corneal regeneration and wound healing	Produces complete epithelial healing in a patient with a progressive neurotrophic ulcer
Neurotrophins 3, 4/5 (NT-3, NT-4/5)	(i) NT-3 transcribed in epithelial cells and stromal keratocytes	Minimal changes in NT-3 gene expression following surgical transection of corneal nerves	
	(ii) NT-4 is present in corneal epithelium and is a neurotrophic factor that may be involved in the regulation of stromal keratocytes by epithelial cells		
Ciliary neurotrophic factor (CNTF)	Promotes corneal epithelial wound healing by activating corneal epithelial stem/progenitor cells	(i) Upregulated in corneal epithelium after injury in mice	
		(ii) Down regulated in corneal epithelium of diabetic mice	
Vascular endothelial growth factor (VEGF)	Minimally present	(i) Upregulated in the injured cornea	VEGF supplementation promotes trigeminal nerve repair, and abrogation of VEGF signaling reduces corneal nerve growth
		(ii) Required for e f cient corneal nerve regeneration	
Hepatocyte growth factor (HGF)	Expressed in stromal keratocytes, stimulates corneal epithelial proliferation	Upregulated after corneal epithelial wounding and probably contributes to the epithelial wound healing process	
Keratocyte growth factor (KGF)	(i) Expressed in stromal keratocytes, broblasts	Upregulated in corneal epithelial wounding	
	(ii) Stimulates corneal epithelial proliferation, acts speci cally on cells of epithelial origin as a paracrine mediator		
Transforming growth factor-α (TGF-α), interleukin-1β (IL-1β), and platelet-derived growth factor-B (PDGF-B)	(i) Exclusively expressed in the corneal stroma		
	(ii) TGF-α and IL-1β can upregulate the transcription of neurotrophins, such as NGF in 3T3 mouse broblasts		

reduced below 60 mm against 38% of the controls alongside with reduced perception of vibrations (vibratory perception of the le index nger and great toe by biothesiometer). A decrease in corneal sensitivity may cause a delay in epithelial wound healing and be the cause of recurrent erosions. is is because the corneal nerves release epitheliotropic substances that promote the maintenance of the integrity of corneal surface [8]. Alterations of the corneal nerves decrease the corneal sensitivity resulting in corneal hypoesthesia that disrupts the epithelial architecture and function. ese changes would further delay the reepithelization of the cornea.

Confocal microscopy has shown promise as a noninvasive method for quantifying the damage and repair of corneal sensory nerves that can serve as markers for diabetic neuropathy. us, Rosenberg et al. using confocal microscopy found decreased corneal sensitivity together with a decreased number of long nerve ber bundles in the sub basal nerve plexus. In addition, patients with diabetes had fewer nerve ber bundles than healthy control subjects possibly due to the presence of polyneuropathy. In all patients with diabetes with neuropathy, the sub basal nerve densities were signi cantly reduced. Additionally, the authors found that even if most patients with diabetes had nerve ber bundles with a normal morphology, patients under dialysis with mild to moderate neuropathy had abnormally tortuous nerve ber bundles in the sub basal nerve plexus [9]. is con rmed the presence of an impairment of corneal sensitivity, and the duration of diabetes was signi cantly and directly correlated with the degree of polyneuropathy.

In the sub basal nerve plexus, a decrease in the nerve density, number of branches, single nerve ber length, and increased tortuosity have been found to be signi cantly correlated with established electromyography and nerve conduction parameters and with the results of the skin biopsy.

Several studies have con rmed that the cornea innervations were altered in animal models of diabetes. Davidson et al. reported a 50% loss of corneal nerve bers a er 12 weeks of high fat diet in low-dose streptozotocin-induced diabetic rats. Yin et al. described corneal changes in streptozotocininduced type 1 diabetic rats. A 50% decrease in tear secretion was found a er eight weeks of diabetes induction in SD rats [10], corneal sensitivity was decreased, and the corneal nerves had fewer branches and were thinner and shorter by 75%.

Ueno et al. found a decreased density of the corneal sub basal nerve plexus and corneal epithelial branches in leptin receptor mutant mice which are an accepted animal model of type 2 diabetes. e corneal sub basal nerves were more tortuous in these mutant mice than in normal mice. Wang et al. reported delayed corneal wound healing in the Akita diabetic mice, a model of chronic complications of type 1 DM. In a longitudinal study of corneal nerve density in a rat model of type 1 diabetes, Chen et al. found that density of nerves was initially increased in the subbasal plexus a er 8 and 16 weeks of diabetes. However, the density remained unchanged in the stromal layer. An increase could be explained by increased nerve tortuosity or collateral sprouting as reported in patients with impaired glucose tolerance.

It is di cult to translate the results from the streptozotocin-induced animals to type 1 human diabetes and that from the db/db mouse to type 2 human diabetes due to recessive homozygous mutation in the

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