

Influence of diabetes mellitus on anterior segment of the eye

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Abstract: Diabetes mellitus (DM) has been emerging as one of the most serious health problems worldwide. Ocular complications of DM are currently one of the major causes of blindness in developed countries, among which diabetic retinopathy is relatively well studied and understood. However, although ocular surface complications of DM are common, diabetic complications of anterior segment of the eye, such as, cornea, conjunctiva, and lacrimal glands, are often overlooked. DM is associated with progressive damage to corneal nerves and epithelial cells, which increases the risk of anterior segment disorders including dry eye disease, corneal erosion, persistent epithelial defects, and even sight-threatening corneal ulcer. In this review, the authors will discuss the association of DM with disorders of anterior segment of the eye. Studies indicating the value of corneal nerve assessment as a sensitive, noninvasive, and repeatable biomarker for diabetic neuropathy will also be introduced. In addition, treatment modalities of anterior segment disorders associated with DM is discussed. The studies introduced in this review suggest that early and periodic screening of the anterior segment of the eye, as well as the retina, is important for the optimal treatment of DM.

Keywords: anterior segment disease, corneal neuropathy, diabetes mellitus, dry eye disease, ocular surface disease, keratopathy

Introduction

Diabetes mellitus (DM), defined as “a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces”,¹ is a major global public health problem.² It is one of the most prevalent systemic diseases in the world with increasing prevalence.³ DM was reported to affect 366 million people worldwide in 2011 and estimated to affect >555 and 640 million people by 2030 and 2040, respectively.³

DM has also been increasingly prevalent in Korea, with an age-standardized prevalence among adults aged ≥ 30 years showing 8.6% in 2001, 9.6% in 2007, and 11.1% in 2013, according to the Korean National Health and Nutrition Examination Survey (KNHANES) data.⁴ Data from the National Health Insurance Service also showed a rising trend in the prevalence of type 2 DM and impaired fasting glucose from 5.6% and 21.5% in 2006, to 8.0% and 25% in 2013, respectively.⁴ As the prevalence of DM increases with age, the KNHANES data demonstrated a high prevalence of DM in age groups of ≥ 70 years old and 60–69 years of 27.6% and 25.2%, respectively, while the prevalence in age groups of 30–39 years and 40–49 years were only 2.5% and 7.3%, respectively.⁴

DM leads to complications such as neuropathy, retinopathy, nephropathy, and cardiovascular disorders, in which hyperglycemia plays a major role.³ Ophthalmologic

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complications have emerged as the leading cause of blindness in developed countries, of which retinopathy is the major manifestation that has been relatively well understood by health care providers.^{3,5}

On the contrary, anterior segment complications associated with DM, including the cornea, conjunctiva, and lacrimal glands, are not well recognized, although up to two-thirds of patients are reported to experience diabetic keratopathy during the course of DM.^{5,6} Patients with DM demonstrate progressive decrease in corneal nerve density and reduction in corneal sensitivity,^{7,8} which subsequently result in the impairment of corneal epithelial wound healing process and increased susceptibility to persistent epithelial defects and corneal infections.^{9–11} These complications can potentially lead to blindness, which underscores the importance of understanding the impact of DM on anterior segment disorders.¹²

In this review, we aimed to provide an overview of the association between DM and anterior segment diseases and discuss the underlying pathophysiologic mechanisms and treatment methods for anterior segment disorders associated with DM, as summarized in Figure 1.

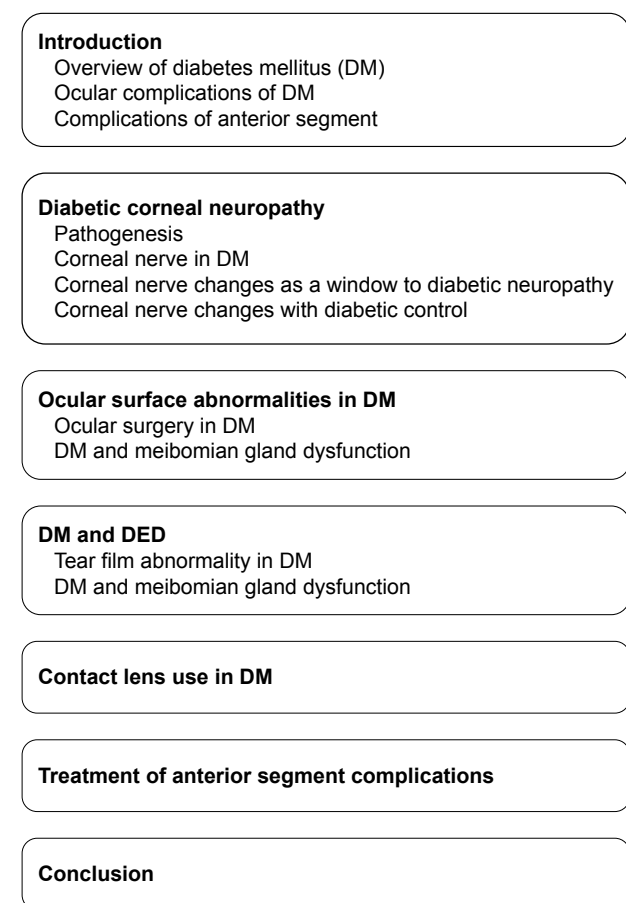


Figure 1 Graphical overview of this review.

Diabetic corneal neuropathy

Diabetic peripheral neuropathy is the most common neuropathic presentation in DM.¹³ Approximately half of the patients were reported to have diabetic peripheral neuropathy after a 25-year follow-up of DM.¹⁴

Pathogenesis

Chronic hyperglycemia is the core causative mechanism underlying the pathogenesis of diabetic neuropathy as well as other systemic complications.¹⁵ It induces pathological pathways, such as generation of reactive oxidative stress (ROS), advanced glycation end (AGE) products, sorbitol–aldose reductase pathway, and protein kinase C activation.^{16,17}

First, chronic hyperglycemia leads to excessive influx of glucose into the mitochondria, which promotes the production of ROS due to accelerated oxidative metabolism of glucose.¹⁷ These ROS induce disruption in the mitochondrial electron transport chain, which results in mitochondrial injury.¹⁷ Nerve fibers are more prone to mitochondrial damage due to their greater mitochondrial volume that subsequently leads to demyelination and conduction dysfunction.¹⁶ Mitochondrial injury is also associated with decreased neurotrophic factors including the nerve growth factor (NGF).¹⁸ An experimental study demonstrated that a marker of oxidative stress, 8-hydroxydeoxyguanosine, was increased in the diabetic rat cornea, suggesting the possible role of oxidative stress in the apoptosis of corneal cells in DM.¹⁹

Second, AGE products generated by glycation may also play an important role in the pathogenesis of peripheral neuropathy.^{20,21} Glycation is the nonenzymatic bonding of sugar molecules including glucose or fructose to a protein or lipoprotein, which leads to the formation of AGE products with altered structure and function.¹⁷ DM induces glycation of myelin proteins and deposition of AGE products in perineurial collagen and in the axoplasm of Schwann cells and neurons, which leads to microvascular dysfunction, damage to the peripheral nerves, and axonal degeneration.^{21,22} Moreover, the accumulation of AGE in the corneal epithelium promotes proapoptotic and antiproliferative local cell signaling pathways.¹⁹

Third, elevated intracellular glucose level caused by chronic hyperglycemia leads to decreased Na⁺/K⁺ ATPase activity on cell membrane, which reduces nerve conduction velocity and inhibits nerve regeneration.^{23,24} Saturation of normal glycolytic pathway caused by hyperglycemia in nerve cells results in shunting of the surplus glucose into the sorbitol–aldose reductase pathway, in which the glucose is converted to fructose and sorbitol by the enzymes sorbitol

dehydrogenase and aldose reductase.²⁵ In the shunted pathway, aldose reductase causes depletions of NADPH.²⁴ Moreover, accumulation of fructose and sorbitol results in decreased free nerve myoinositol, which causes reduced membrane Na^+/K^+ ATPase activity.^{24,26} Increased level of intracellular glucose is also associated with activation of protein kinase C pathway, which can inhibit the activity of membrane Na^+/K^+ ATPase (Figure 2).^{23,27}

An experimental study using a diabetic mouse model revealed a high concentration of antigen-presenting cells including Langerhans cells and dendritic cells in the cornea and aggregation of the cells around corneal nerve fibers.²⁸ The number of dendritic cells had a negative correlation with corneal nerve fiber density, suggesting the possible role of inflammation in the development of corneal neuropathy in DM.²⁸

Corneal nerve in DM

Changes in corneal nerve parameters, such as a reduction in corneal subbasal nerve fiber density, length, and branch

density, have been reported in both type 1 and type 2 DM,^{29,30} which show correlation with diabetic peripheral and autonomic neuropathy.^{31–34} Edwards et al³² showed that patients with diabetic peripheral neuropathy had significantly decreased corneal subbasal nerve fiber length and branch density compared with individuals without DM and those with DM but without diabetic peripheral neuropathy. Pritchard et al³⁴ demonstrated that reduction in corneal nerve fiber length measured with corneal confocal microscopy (CCM) can predict the development of diabetic peripheral neuropathy. Misra et al³¹ revealed that corneal subbasal nerve density changes assessed using CCM precede other functional changes detected by clinical and electrophysiology tests of neuropathy and that corneal sensitivity has a negative correlation with autonomic nerve analysis, suggesting that CCM and corneal sensitivity testing can be surrogate markers for the assessment of diabetic peripheral and autonomic neuropathy.³¹ Tavakoli et al³⁵ demonstrated that parameters assessed using CCM had a significant correlation with the composite autonomic symptom scale and showed a high

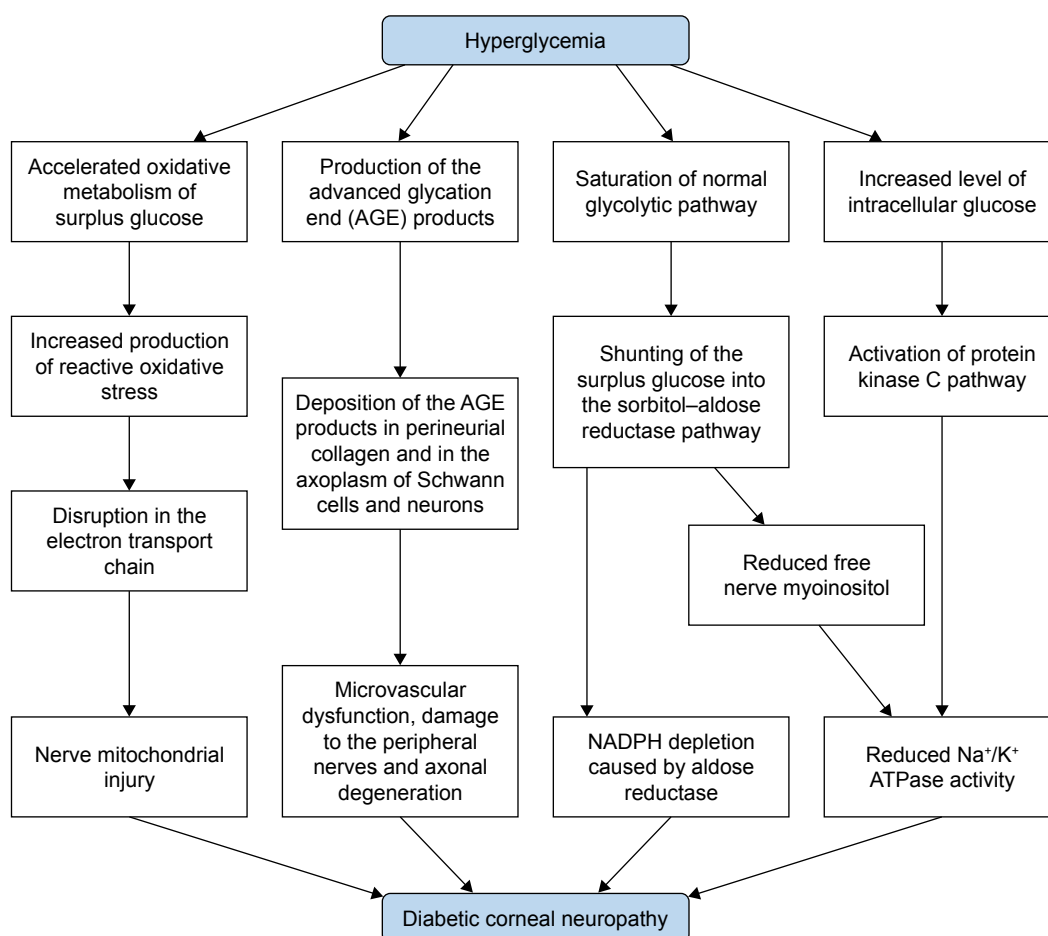


Figure 2 Pathogenesis of diabetic corneal neuropathy.

sensitivity and specificity for the diagnosis of diabetic autonomic neuropathy, indicating that CCM can be a rapid, non-invasive, and reliable diagnostic test for subclinical diabetic autonomic neuropathy.³⁵ Maddaloni et al³⁶ also suggested that CCM could be a noninvasive tool for the evaluation of cardiac autonomic neuropathy in patients with type 1 DM. A recent study on patients with type 1 DM revealed that among seven measures of diabetic peripheral neuropathy, including CCM, peroneal nerve conduction velocity, cold, warm and vibration perception, monofilament testing, and neuropathy disability score, corneal subbasal nerve morphology evaluated using CCM demonstrated the earliest and most consistent changes in neuropathy status during a 4-year follow-up period.³⁷ A meta-analysis reported in 2016 concluded that corneal nerve fiber density, length, and branch density assessed using CCM were significantly reduced in people with diabetic peripheral neuropathy, and CCM can be useful for early detection of nerve damage in diabetic peripheral neuropathy.³⁸

Changes in corneal cells and nerve fibers were also shown to predict the development of diabetic retinopathy.^{39–41} Alterations of the corneal subbasal nerve plexus have shown to progress in parallel with diabetic retinopathy and peripheral neuropathy.³⁹ In patients with type 1 DM, CCM demonstrated corneal cellular changes including decreased epithelial and endothelial cell densities and higher keratocyte cell density, as well as small nerve fiber changes, such as lower corneal nerve fiber density and length, lower nerve branch density, and greater nerve fiber width in patients without retinopathy, which worsens with the progression of diabetic retinopathy.⁴⁰ Bitirgen et al⁴¹ revealed that changes in corneal nerve parameters including reduction of nerve fiber density, length, and branch density were observed in patients without diabetic retinopathy and aggravated with the progression of retinopathy.

Corneal nerve changes as a window to diabetic neuropathy

Although diabetic peripheral neuropathy involves both large and small nerve fibers, small nerve fibers can be more sensitive indicators of peripheral neuropathy as they are affected earlier.⁴² Vibration perception using biothesiometry has been the gold standard for the diagnosis of diabetic peripheral neuropathy.⁴³ However, the method has its limitation based on the fact that only large nerve fiber functions are measured rather than small nerve fibers.³ Visualization of small nerve fiber damage is possible using skin punch biopsy.⁴⁴ However, biopsy is invasive and nonrepeatable and is also associated with an increased risk of wound complications in patients

with DM.³ By contrast, CCM can allow noninvasive, direct visualization of subtle corneal nerve changes *in vivo*.³⁰ It can also detect diabetic nerve fiber damage earlier than vibration perception or corneal sensation testing.³⁰ Changes in corneal nerve fibers may be detected earlier compared with diabetic peripheral neuropathy in other parts of the body, ie, lower limb, due to high density of small nerve fibers in the cornea.³⁰

Alterations in the corneal subbasal nerve plexus assessed using CCM have close correlation with changes in the peripheral nerves.¹¹ These findings indicate the potential of CCM as a sensitive, noninvasive, and reliable surrogate marker for the evaluation of diabetic peripheral neuropathy,¹¹ which can enable early detection of diabetic peripheral neuropathy and prevention of serious neuropathic complications including diabetic foot (Table 1).² As retinal examination can be a window to systemic vascular changes in DM, visualization of corneal nerves using CCM can provide a window to systemic peripheral and autonomic nerve changes associated with DM.

Corneal nerve changes with diabetic control

Studies showed that diabetic neuropathy can be improved after interventions for diabetic control,⁴⁵ although it may not be completely reversed.⁴⁶ Smith et al⁴⁷ reported that significant improvements in intraepidermal nerve fiber density were detected using skin biopsy after 1 year of strict glycemic control and lifestyle modification. Improvement in risk factors for diabetic neuropathy, such as hyperglycemia, dyslipidemia, and hypertension, was associated with regeneration of corneal nerve fibers, which was confirmed using *in vivo* CCM.⁴⁵ In this study, improvement in HbA1c had significant correlation with an increase in corneal nerve fiber density.⁴⁵ *In vivo* CCM also demonstrated significant improvement in corneal nerve fiber length 1 year after simultaneous pancreas and kidney transplantation in patients with type 1 DM.⁴⁸ These results suggest that the evaluation of corneal nerve changes using CCM can be a viable option for monitoring the efficacy of therapy for diabetic control.

Ocular surface abnormalities in DM

DM can also cause alterations in the corneal epithelial basal cells and basement membrane, leading to corneal epitheliopathy and adhesion disorders.⁴⁹ In addition, loss of corneal nerves in DM leads to reduced neurotrophic support, resulting in accelerated loss and reduced proliferation of epithelial cells.^{50,51} DM also causes production of abnormal

Table 1 Studies suggesting corneal nerve assessment can be a reliable biomarker for peripheral and autonomic nerve damage in diabetes mellitus (DM)

Study	Design	Findings
Messmer et al ³⁰ (2010)	Human cross-sectional study	Corneal confocal microscopy can detect diabetic nerve fiber injury earlier than corneal sensation testing and vibration perception.
Pritchard et al ³⁴ (2014)	Human prospective cohort study (baseline report)	Reduction in corneal nerve fiber length in type 1 DM patients without neuropathy Greater reduction in the corneal nerve fiber length in type 1 DM patients with neuropathy.
Misra et al ³¹ (2015)	Human case-control study	Corneal subbasal nerve density changes precede other clinical and electrophysiology tests of neuropathy.
Tavakoli et al ³⁵ (2015)	Human case-control study	Corneal nerve parameters had significant correlation with the composite autonomic symptom scale and had high sensitivity and specificity for the diagnosis of diabetic autonomic neuropathy.
Maddaloni et al ³⁶ (2015)	Human case-control study	Corneal nerve density was significantly lower in patients with cardiac autonomic neuropathy than in those without.
Edwards et al ³⁷ (2017)	Human prospective cohort study	Corneal nerve morphology demonstrated the earliest and most consistent changes among seven measures of diabetic peripheral neuropathy in neuropathy status during a 4-year follow-up period.

basal lamina and inadequate adhesion of epithelial cells to an abnormal basement membrane.^{6,10,52}

An experimental study demonstrated delayed corneal wound healing with decreased activation of endothelial growth factor receptor in a diabetic rat model.⁵³ Diminished expression of the tight junction proteins including β -catenin and zonula occludens-1 was also observed, indicating the disruption of cell to cell junctions in diabetic cornea.⁵³ Other animal studies showed detrimental effects of hyperglycemia on the corneal epithelium basement membrane complex and demonstrated findings suggesting compromise of corneal epithelial function, such as increase in corneal thickness, disruption of tight junctions, and loss of basal epithelial cells.^{19,54} The accumulation of AGE in the corneal epithelium basement membrane complex promotes proapoptotic and antiproliferative pathways, which results in corneal epithelial damage.¹⁹ Di et al⁵⁵ demonstrated an excessive inflammatory response manifested by the accumulation of polymorphonuclear cells in mice diabetic corneas, resulting in increased levels of proinflammatory cytokines and delayed wound healing.

DM is consequently associated with damaged epithelial barrier function and impaired epithelial healing, which increases the risk of ocular surface diseases, such as dry eye disease (DED), superficial punctate keratitis, recurrent corneal erosion, persistent epithelial defects, and neurotrophic corneal ulcer.^{6,56,57}

Ocular surgery in DM

Corneal refractive surgery induces destruction and reconstruction of corneal basal nerves, and DM might conceivably

impair the corneal epithelial wound healing process. Indeed, the Food and Drug Administration declared DM to be a relative contraindication to laser-assisted in situ keratomileusis (LASIK) in 2000.⁵⁸ Patients with DM had a substantially higher risk of corneal complications including erosions and persistent epithelial defects and worse visual outcome after LASIK compared with those without DM (47% vs 6.9%).⁵⁹

However, other studies revealed that LASIK did not increase the risk of corneal complications in individuals with well-controlled DM,⁶⁰ and there was no significant difference in anatomic and visual outcomes between the patients with DM and those without.⁶¹ Although data regarding the safety and efficacy of LASIK in DM patients are limited, there are only few reports of significant corneal complications despite the large number of refractive surgery performed annually.⁶² These findings indicate that LASIK can be performed effectively and safely at least in selected patients with well-controlled DM.^{61,62}

Therefore, in 2005, the American Academy of Ophthalmology recommended that LASIK can be safely performed in a selected group of DM patients despite the risk of delayed corneal wound healing, although informed consent and close postoperative monitoring are mandatory.⁶² The candidates eligible for LASIK should have stable and well-controlled fasting glucose with HbA1c <9 and no evidence of systemic DM complications including nephropathy or peripheral neuropathy.⁶² Although those with mild DM retinopathy can be considered for LASIK on a case-by-case basis, individuals with significant DM retinopathy or a history of diabetic ocular complications should be excluded.⁶²

Because DM is associated with an increased risk of cataract even in the population younger than 65 years, increasing number of cataract surgery has been performed in patients with DM.³ In addition to a higher risk of postoperative complications of the retina including cystoid macular edema and exacerbation of diabetic retinopathy, DM is also associated with an increased risk of corneal complications, such as persistent corneal edema, corneal abrasion, and delayed epithelial wound healing.⁶³ Cataract surgery can worsen the subbasal nerve damage in patients with reduced tear production or an impaired corneal epithelial integrity associated with DM.⁶⁴

DM is a significant risk factor for corneal complications following other procedures, such as trabeculectomy, vitrectomy, and laser photocoagulation.^{65–67} Dogru et al⁶⁵ demonstrated that patients with DM had increased corneal staining score, decreased corneal sensitivity, and decreased tear film breakup time after argon laser photocoagulation using coupling fluid and retinal laser lens compared with those without DM.⁶⁵ DM is also a risk factor for developing DED after intraocular surgery.⁶⁸

These findings indicate that special attention should be paid for corneal complications in patients with DM after any kind of ocular surgery, including even minor procedures.⁶⁹

DM and DED

Diabetic peripheral neuropathy can theoretically increase the risk of DED,⁷⁰ and half of patients with DM experience dry eye symptoms.⁷¹ Misra et al⁷² reported impairment of lipid layer quality and tear film stability in DM patients. Hyperglycemia can lead to microvascular damage to the lacrimal gland, and diabetic autonomic neuropathy is associated with impairment of lacrimal innervation, which both contribute to diminished tear production.⁸ Diabetic peripheral neuropathy leads to decreased corneal nerve fiber density, which results in impaired corneal sensitivity and diminished reflex tearing.^{71,73} Corneal hypoesthesia can cause decreased mucin production by goblet cells, which leads to reduced tear film stability.⁸ A higher tear osmolarity probably caused by reduced tear production or increased tear evaporation was also observed in patients with DM.³³

The severity of dry eye signs has close correlation with the degree of peripheral neuropathy and severity of diabetic retinopathy.^{10,71,74} However, with prolonged disease duration, patients are often asymptomatic even in the presence of serious ocular surface damage due to reduced corneal sensitivity, which reflects the progression of diabetic peripheral neuropathy.⁷⁵

The presence of DED in DM patients further increases the risk of damage to the corneal epithelium.⁵¹ Therefore, periodic screening of ocular surface damage and dry eye symptoms in addition to retinal examination would be necessary for patients with DM.^{70,75}

Tear film abnormality in DM

Substance P plays a role in the maintenance of healthy ocular surface by providing neurotrophic support and promoting proliferation and migration of corneal epithelial cells.⁷⁶ Reduction in substance P level may result in impairment of corneal epithelial homeostasis, potentially leading to exacerbation of corneal complications associated with DM.⁷⁷ The concentration of substance P in the tear film is correlated with corneal nerve fiber density,⁷⁸ and corneal hypoesthesia is associated with diminished substance P level.⁷⁹ The tear substance P level was also shown to be related to the duration of DM and severity of diabetic retinopathy.⁷⁷

Insulin is found in the tear film, and insulin receptors are identified on the ocular surface.⁸⁰ Insulin is thought to provide neurotrophic support to the ocular surface and promote the metabolism and growth of the lacrimal gland⁸¹; thus, decrease in insulin activity is postulated to be associated with damage to the corneal nerves in DM.⁸² Upregulation of insulin-like growth factor binding protein 3 and activation of insulin-like growth factor receptor are observed in type 2 DM, which may cause corneal epithelial damage by the disruption of corneal epithelial cell–basement membrane complex.⁸³ Experimental studies showed that topical insulin can facilitate improvement of corneal epithelial integrity and sensitivity in animal models of diabetic keratopathy.^{84–86}

DM and meibomian gland dysfunction

An experimental study revealed that insulin stimulated the proliferation of immortalized human meibomian gland epithelial cells in a dose-dependent manner, while excess glucose resulted in progressive cell loss, suggesting that insulin deficiency and hyperglycemia may be toxic for the meibomian gland epithelial cells and increase the risk of meibomian gland disorders.⁸¹

Contact lens (CL) use in DM

CL wear is associated with theoretical risks as follows¹⁰: 1) exacerbated corneal epithelial fragility increases the risk of corneal damage; 2) tear film instability could deteriorate DED; 3) impairment of corneal hydration control could lead to corneal edema; and 4) CL-induced endothelial polymegathism can cause corneal endothelial

decompensation after intraocular surgery. These factors, together with reduced corneal sensitivity and the vulnerability to infection in DM, may increase the risk of corneal complications including infectious keratitis in the diabetic CL wearer.¹⁰ Reports of ocular complications in diabetic CL wears do exist, mostly occurred in patients with advanced diabetic ocular complications or those using extended wear CL.⁸⁷

However, prospective studies suggest that CL wear might not be contraindicated in patients with DM.^{88,89} O'Donnell et al⁸⁹ demonstrated that there was no significant difference in conjunctival injection, corneal staining score, corneal thickness, or sensitivity after 1 year of CL wear between patients with DM and those without.⁸⁹ Another prospective study revealed that DM had no significant influence on corneal hydration and recovery, indicating that CL wear can be recommended in DM patients.⁸⁸ However, given the adverse impact of DM on the ocular surface, detailed advice to the patients and close monitoring for corneal complications are mandatory.³

Based on the findings that tear glucose concentrations correlate with blood glucose levels,³ tear glucose sensing devices for noninvasive monitoring of glycemic control using CL has been developed and may be widely used in the near future.

Treatment of anterior segment complications

As in other diabetic complications, strict glycemic control is essential for the treatment and prevention of anterior segment disorders associated with DM.² Topical artificial tears can be helpful for the maintenance of healthy ocular surface and clear visual axis. Topical anti-inflammatory medications, such as NSAIDs, steroids, and cyclosporine A, are also useful for alleviating ocular surface inflammation and encouraging re-epithelialization.⁹⁰ Bandage CL can be helpful for an irregular ocular surface, recurrent corneal erosion, and persistent epithelial defects.²

Autologous serum is theoretically beneficial for facilitating corneal wound healing and nerve regeneration as it contains high amounts of growth factors.^{2,91} Topical autologous serum was shown to accelerate corneal epithelial healing after vitrectomy in DM patients.⁹² Topical application of umbilical cord serum and platelet-derived plasma was also suggested to be effective in facilitating corneal nerve regeneration and epithelial healing.⁹¹

Substance P can attenuate apoptosis of corneal epithelial cells induced by hyperglycemia and accelerate the epithelial healing process via the neurokinin-1 receptor signaling pathway.^{37,93} Insulin-like growth factor 1 (IGF-1) was also

shown to promote regeneration of corneal nerves and ocular surface homeostasis.⁹⁴ Topical application of substance P and IGF-1 derivatives promote proliferation and migration of corneal epithelial cells in neurotrophic keratopathy including diabetic corneal neuropathy.^{5,76} A prospective clinical study demonstrated that topical administration of substance P and IGF-1 combination eye drops was effective in the prevention of postoperative superficial punctate keratopathy.⁹⁵

NGF can stimulate regeneration of damaged neurons and mucin production by goblet cells.⁹⁶ Topical NGF was shown to improve ocular surface integrity and corneal sensitivity in corneal neuropathy.⁹⁷ Park et al⁹⁸ reported that topical NGF can alleviate inflammation and hyperglycemia-induced apoptosis of epithelial cells in diabetic corneas. Kim et al⁹⁹ revealed that oral nicergoline promoted corneal wound healing in diabetic rat corneas, which was conceivably related to increased NGF in the cornea and lacrimal gland.⁹⁹

Aldose reductase inhibitor can theoretically reduce nerve damage and promote corneal epithelial regeneration by attenuating activation of the sorbitol–aldose reductase pathway.³ Oral aldose reductase inhibitor was effective in improving corneal epithelial damage and corneal sensitivity after cataract surgery in DM patients.⁶⁹ Topical aldose reductase inhibitor has also shown to promote corneal epithelial wound healing in DM.¹⁰⁰

Naltrexone, an opioid antagonist, is useful for corneal wound healing by accelerating DNA synthesis.¹⁰¹ DM is associated with the production of excessive opioid growth factors, which leads to inhibition of cell proliferation. Naltrexone is expected to promote wound healing in diabetic corneas as it blocks the opioid growth factor and its receptor pathway. Its topical application was shown to improve corneal regeneration and tear production in a type 1 diabetic rat model.¹⁰² Topical naltrexone also promoted corneal epithelial repair in a type 2 diabetic mouse model.¹⁰³

Resolvin D, a docosahexaenoic acid-derived anti-inflammatory mediator, is also expected to be effective for the treatment of diabetic anterior segment disorders.¹⁰⁴ An *in vitro* study revealed that resolvin D attenuated the synthesis of inflammatory cytokines in the corneal epithelium.¹⁰⁵ An experimental study using a diabetic rat model also reported that oral administration of resolvin D alleviated corneal and peripheral nerve degeneration.¹⁰⁶

Antioxidants, such as carnosine and β -carotene, were also suggested to be beneficial for the prevention of DM-related corneal changes.^{106,107} Experimental treatment modalities including gene therapy, molecular, and stem cell therapies have been developed.^{12,55} Di et al⁵⁵ recently showed that bone

Table 2 Effects of the medications for anterior segment disorders associated with diabetes mellitus

Medications	Effects
Artificial tears	Maintenance of healthy ocular surface and clear visual axis
Topical anti-inflammatory medications (NSAIDs, steroids, and cyclosporine A)	Reduction of ocular surface inflammation Encouragement of re-epithelialization
Substance P and insulin-like growth factor I	Facilitation of corneal nerve regeneration Promotion of corneal epithelial cell proliferation and migration
Autologous serum	Promotion of corneal wound healing and nerve regeneration
Nerve growth factor	Facilitation of corneal wound healing Stimulation of damaged neuron regeneration
Aldose reductase inhibitor	Attenuation of the sorbitol–aldose reductase pathway activation Reduction of the nerve damage Promotion of corneal epithelial regeneration
Naltrexone (opioid antagonist)	Promotion of corneal wound healing via inhibition of the opioid growth factor and its receptor pathway
Resolvin D (a docosahexaenoic acid derivative)	Inhibition of inflammatory cytokine synthesis in corneal epithelium Attenuation of corneal and peripheral nerve degeneration

marrow-derived mesenchymal stem cells could attenuate excessive inflammatory responses, activate corneal progenitor cells, and enhance wound healing of diabetic cornea. However, these experimental methods still have to overcome myriad of barriers to be translated into clinical practice.² The effects of medications for anterior segment complications associated with DM are summarized in Table 2.

Conclusion

DM has an adverse impact on ocular surface integrity, corneal sensitivity, corneal epithelial regeneration, and tear production.³ Diabetic keratopathy is common, and its severity can vary from mild DED to sight-threatening corneal ulcer. The severity of diabetic corneal neuropathy correlates with diabetic peripheral and autonomic neuropathy of other organs. Subtle diabetic neuropathy in the cornea often precedes retinopathy and neuropathy of other parts of the body. Therefore, examination of the corneal nerve plexus using CCM can be a viable biomarker for the assessment of diabetic neuropathies. Although several medications were introduced to be effective for the treatment and prevention of anterior segment disorders associated with DM, further researches are still necessary for the development of better treatment methods.

The studies introduced in this review highlight the need for periodic screening of anterior segment diseases as well as retinal examination for patients with DM. Guidelines for screening ocular surface pathologies should also be established. An enhanced understanding in both patients and medical practitioners of the impact of DM on the anterior segment of the eye would be important for the optimal management of DM.²

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Disclosure

The authors report no conflicts of interest in this work.

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