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Systemic diseases and the cornea

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Abstract

There is a number of systemic diseases affecting the cornea. These include endocrine disorders (diabetes, Graves' disease, Addison's disease, hyperparathyroidism), infections with viruses (SARS-CoV-2, herpes simplex, varicella zoster, HTLV-1, Epstein-Barr virus) and bacteria (tuberculosis, syphilis and *Pseudomonas aeruginosa*), autoimmune and inflammatory diseases (rheumatoid arthritis, Sjögren's syndrome, lupus erythematosus, gout, atopic and vernal keratoconjunctivitis, multiple sclerosis, granulomatosis with polyangiitis, sarcoidosis, Cogan's syndrome, immunobullous diseases), corneal deposit disorders (Wilson's disease, cystinosis Fabry disease, Meretoja's syndrome, mucopolysaccharidosis, hyperlipoproteinemia), and genetic disorders (aniridia, Ehlers-Danlos syndromes, Marfan syndrome). Corneal manifestations often provide an insight to underlying systemic diseases and can act as the first indicator of an undiagnosed systemic condition. Routine eye exams can bring attention to potentially life-threatening illnesses. In this review, we provide a fairly detailed overview of the pathologic changes in the cornea described in various systemic diseases and also discuss underlying molecular mechanisms, as well as current and emerging treatments.

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Keywords

diabetic cornea; Graves' disease; Addison's disease; SARS-CoV-2; herpes; zoster; tuberculosis; syphilis; *Pseudomonas Aeruginosa*; autoimmune disease; Sjögren's syndrome; inflammation; keratoconjunctivitis; genetic corneal disease; corneal deposit disorder; aniridia; Ehlers-Danlos syndrome; Marfan syndrome; immunobullous disease

1. Introduction

Cornea is an integral part of the body and reacts to various diseases or genetic abnormalities at the systemic level. These insults may be infectious agents, metabolic disorders, autoimmune diseases or heritable changes in gene expression. Clinical aspects of corneal changes in various systemic disorders have been previously discussed (Mora *et al.* 2013; Consultant360 2014; Gillan 2015; Gomes *et al.* 2015; Patel, 2017; Dua *et al.* 2018; Wilkins *et al.* 2019; Patel *et al.* 2020). In this review, the authors tried to cover whenever possible the known mechanisms, signaling pathways, and emerging treatments for corneal alterations in systemic diseases. Because of the authors' area of research and available evidence, diabetes is discussed in more detail. Attempts were made to cite newer reports. Although COVID-19 impact on the cornea is only beginning to be unraveled, pertinent literature is also covered as it is a rapidly expanding field. For certain diseases only a very limited clinical information on corneal involvement is available, mostly as case reports. Some other conditions can be cured by diet changes, e.g., vitamin deficiencies. For these reasons, such diseases were not discussed here. A summary of corneal manifestations of systemic diseases is provided in Table 1.

2. Endocrine Diseases

2.1. Diabetes Mellitus

In the last decade, diabetes mellitus (DM) has reached epidemic proportions and is the leading cause of new blindness in adults between 25 and 64 years of age (Schmidt 2018; Lee and Mesfin 2020). DM affects all parts of the body including the eyes. This is true for both insulin-dependent diabetes (type 1, T1DM; an autoimmune disease leading to destruction of insulin-producing β cells in the pancreatic islets of Langerhans) and more common non-insulin-dependent diabetes (type 2, T2DM; characterized by insulin resistance in many organs leading to hyperglycemia and gradual decline in insulin production). The most severe ocular complication of DM is diabetic retinopathy (DR) (Aiello *et al.* 1998). It is the main contributor to new blindness cases in the United States (Aiello *et al.* 1998; Negi and Vernon 2003) and is a disease of retinal microvasculature.

Although retinal changes in diabetes can become vision-threatening over time and may lead to blindness as covered in detail previously (Stitt *et al.* 2016; Cabrera *et al.* 2020; Gui *et al.* 2020; Kutlutürk Karagöz *et al.* 2020), they are outside of the scope of this review.

Ocular surface including the cornea is also affected by DM. Corneal complications are relatively frequent and are observed in 45–70% of diabetic patients (Schultz *et al.* 1981; Abdelkader *et al.* 2011; Vieira-Potter *et al.* 2016; Ljubimov 2017; Zhao *et al.* 2019;

Priyadarsini *et al.* 2020). These alterations may be symptomatically mild and are often underdiagnosed (Wylegała *et al.* 2006). For this reason, some studies have raised awareness of ophthalmologists to the necessity of assessing ocular surface changes during eye exams of diabetic patients (DeMill *et al.* 2016; Richdale *et al.* 2020). Although up to one-fourth of corneas harvested for transplantation in the United States originate from diabetic donors, convincing clinical studies have suggested that such corneas may present a risk to the graft recipients (Lass *et al.* 2019; Goldstein *et al.* 2020).

In recent years, several comprehensive reviews on clinical and experimental aspects of corneal DM have appeared (Calvo-Maroto *et al.* 2014; Misra *et al.* 2016; Vieira-Potter *et al.* 2016; Ljubimov 2017; Shih *et al.* 2017; Bikbova *et al.* 2018; Han *et al.* 2018; Zhao *et al.* 2019; Zhu *et al.* 2019; Mansoor *et al.* 2020; Priyadarsini *et al.* 2020; Roszkowska *et al.* 2020). For this reason, we will fairly briefly summarize key aspects of diabetic corneal disease, with emphasis on manifestations and mechanisms, as well as on promising approaches to treatment.

2.1.1. General Traits of Corneal Diabetes—DM leads to lasting alterations of corneal epithelium (keratopathy, DK), nerves (corneal neuropathy, DCN), stroma, endothelial cells, conjunctiva, corneal biomechanics and tear film (Ljubimov 2017; Priyadarsini *et al.* 2020; Mansoor *et al.* 2020). Symptomatically, epithelial and neural changes have been more important than others, and the bulk of the literature thus concerns these two aspects of diabetic cornea. The human diabetic cornea is also more susceptible than normal cornea to bacterial and viral infections (Wang *et al.* 2018).

2.1.1.1. Epithelial Abnormalities (Keratopathy): Diabetic epitheliopathy/keratopathy, is manifested by various epithelial defects including fragility, stem cell dysfunction, altered basement membrane (BM) composition, delayed wound healing, impaired barrier function leading to edema, recurrent erosions, and non-healing ulcers (Cavallerano 1992; Saini and Khandalavla, 1995; Gekka *et al.* 2004; Quadrado *et al.* 2006; Bikbova *et al.* 2012; Vieira-Potter *et al.* 2016; Ljubimov 2017; Shih *et al.* 2017; Alfuraih *et al.* 2020; Jan *et al.* 2020; Priyadarsini *et al.* 2020). These signs (Figure 1) seem to be exacerbated with increasing DM duration and severity.

DK is often associated with signs of DCN (Mocan *et al.* 2006; Bikbova et al. 2018) and may be developing as a consequence of DCN (Barsegian *et al.* 2018). However, some diabetic changes of the corneal epithelium do not appear to be related to DCN as shown in affected patients and animal models (Rosenberg *et al.* 2000; Saghizadeh *et al.* 2001a; 2005; 2011; Quadrado *et al.* 2006; Chikama *et al.* 2007). Additionally, animal and human cell and organ culture studies using hyperglycemic conditions showed direct and fast effects on normal corneal epithelium with diabetic-like changes in cell adhesion and impaired wound healing (Fujita *et al.* 2003; Tomomatsu *et al.* 2009; Xu *et al.* 2009; Yin and Yu 2010). Therefore, the cause-effect relationship between DK and DCN requires more in-depth studies.

2.1.1.1.1. Underlying Mechanisms of Epithelial Abnormalities: Molecular mechanisms of DK have been a subject of many recent studies. These will be discussed for both T1DM and T2DM because only few differences in corneal changes between DM types. The

epithelial cell adhesion and BM structure are altered in human *ex vivo* diabetic corneas, with reduced BM immunostaining for laminins, nidogen-1, and limbal fibronectin (Hatchell *et al.* 1983; Tabatabay *et al.* 1988; Azar *et al.* 1992; Ljubimov *et al.* 1998; Sato *et al.* 1999; Fujita *et al.* 2003; Gül *et al.* 2008; Saghizadeh *et al.* 2011). The apparently degradative BM changes could affect epithelial cell migration and result in delayed and impaired wound healing. They may be due to increased expression of proteinases, such as MMP-3, MMP-10, and cathepsin F (Saghizadeh *et al.* 2001a; 2005). This suggestion was corroborated by studies of organ-cultured human corneas that recapitulate abnormalities seen in *ex vivo* and *in vivo* corneas (Kabosova *et al.* 2003). Adenovirus-driven increase in MMP-10 and cathepsin F in normal corneas resulted in the same BM changes as observed in diabetic corneas (Saghizadeh *et al.* 2010a). Conversely, proteinase silencing in diabetic corneas normalized BM patterns and improved wound healing (Saghizadeh *et al.* 2013; 2014; Ljubimov and Saghizadeh 2015; Kramerov *et al.* 2016).

Diabetic corneal stem cells also appear to be dysfunctional as evidenced by decreased expression of putative stem cell markers in *ex vivo* and organ-cultured human diabetic corneas. Such a decrease persists in 2D cultures of human diabetic limbal epithelium enriched in progenitor cells and could contribute to slow epithelial wound healing (Saghizadeh *et al.* 2011; Kramerov *et al.* 2015). These data were later corroborated in a mouse db/db model of T2DM (Ueno *et al.* 2014). The expression of these stem cell markers and slow wound healing in human diabetic organ-cultured corneas may be largely reverted to normal by gene therapy (Ljubimov and Saghizadeh 2015; Kramerov *et al.* 2021).

Various growth factors and cytokines, as well as their signaling pathways are altered in human diabetes as well as in animal models and 3D corneal organ cultures (Ljubimov 2017). Because growth factors and cytokines play important roles in corneal epithelial cell physiology and wound healing (Klenkler and Sheardown 2004; Ljubimov and Saghizadeh 2015), their abnormal expression and function may lead to DK. They may affect cell adhesion and wound healing, contribute to epithelial fragility and subbasal nerve loss in diabetic corneas. Some better studied growth factors that are altered in diabetic corneas are discussed below.

Opioid growth factor (OGF), or [Met^5]-enkephalin, acting through its ζ receptor (OGFR) negatively regulates corneal epithelial proliferation and wound healing (Sassani *et al.* 2016). Levels of OGF are elevated in plasma of diabetic patients (McLaughlin *et al.* 2010). OGF and OGFR expression is increased in diabetic rat corneal epithelium (Zagon *et al.* 2020). Systemic or topical administration of opioid antagonist naltrexone normalized OGF blood levels as well as corneal epithelial wound healing in rats and rabbits with T1DM. Beneficial effect of naltrexone on epithelial wound healing may be due to its ability to increase cell proliferation.

Epidermal growth factor (EGF) activates through its receptor (EGFR) prosurvival signaling pathways of the phosphatidylinositol-3-kinase (PI3K) - Akt kinase axis, and extracellular regulated kinase (ERK) (Xu *et al.* 2009; Xu and Yu, 2011; Funari *et al.* 2013; Winkler *et al.* 2014). These pathways appear to be the major regulators of corneal epithelial wound healing as shown in animal models and human organ-cultured corneas (Zieske *et al.* 2000;

Nakamura *et al.* 2001; Xu *et al.* 2009; Xu and Yu 2011; Ljubimov and Saghizadeh 2015; Ljubimov 2017).

In the *in vivo* animal diabetic corneas and in human 3D organ cultures, phosphorylation/activation of EGFR and its downstream signaling mediators Akt and ERK is diminished (Xu *et al.* 2009; Saghizadeh *et al.* 2010a; Xu and Yu 2011). This reduction has functional consequences. Human *ex vivo* diabetic corneas overexpress matrix metalloproteinase-10 (MMP-10), cathepsin F and miR-146a (Saghizadeh *et al.* 2001; 2005; Funari *et al.* 2013). Using adenoviral vectors or direct transduction (miR-146a) these agents were introduced into normal organ-cultured human corneas, leading to slowing of wound healing and decreased expression of phospho-EGFR and phospho-Akt (Saghizadeh *et al.* 2010a; Funari *et al.* 2013). Conversely, inhibition of MMP-10, cathepsin F or miR-146a in diabetic organ-cultured human corneas caused an increase of phospho-EGFR and phospho-Akt with significant wound healing acceleration (Funari *et al.* 2013; Saghizadeh *et al.* 2013; 2014). Stem cell marker patterns in treated diabetic corneas were also normalized (Ljubimov, 2017; Kramerov *et al.* 2021). Reduced activity of the EGFR-Akt axis may thus be an important mechanism of abnormally slow diabetic corneal epithelial wound healing and stem cell dysfunction. Akt activation in animal diabetic corneas by SIRT1 upregulation or PTEN inhibition also accelerates epithelial wound healing (Wang *et al.* 2013; Li *et al.* 2020).

Hepatocyte growth factor (HGF) and its receptor c-Met play a role in cell migration, proliferation, and apoptosis, and are expressed in all major corneal cell types (Wilson *et al.* 1993; Kakazu *et al.* 2004; Saghizadeh *et al.* 2010b; 2011). Corneal wound healing is accompanied by HGF increase in 2D cultured animal keratocytes and epithelial cells (Li *et al.* 1996; Kakazu *et al.* 2008). In *ex vivo* human diabetic corneas, HGF expression is increased but c-Met expression is decreased, suggesting impaired HGF signaling (Saghizadeh *et al.* 2005). Adenoviral-driven c-Met upregulation in organ-cultured human diabetic corneas could normalize diabetic and stem cell marker patterns and accelerate epithelial wound healing, confirming functional significance of c-Met changes in DK. these effects were mediated by phosphorylation/activation of p38 mitogen-activated protein kinase (Saghizadeh *et al.* 2010b; 2011; Kramerov *et al.* 2016). Similar effects of c-Met on p38 kinase activation were observed in cultured rabbit and human corneal cells, and in rabbit corneal organ cultures (Sharma *et al.* 2003).

Insulin-like growth factor-1 (IGF-1) acts in corneal epithelium through receptors to both insulin and IGF. It can influence cell proliferation, migration, and survival (Lee *et al.* 2006; Stuard *et al.* 2020a). In the *ex vivo* human diabetic corneal epithelium, IGF-1 is significantly elevated (Saghizadeh *et al.* 2001b). Although in a T1DM rat model, IGF-1 was shown to stimulate diabetic epithelial wound healing synergistically with a neuropeptide substance P (Nakamura *et al.* 2003), its own action may be attenuated by its binding proteins (IGFBPs). In human diabetic tears and in 2D corneal epithelial cells cultured in high glucose, IGFBP3 levels are increased, which can block phosphorylation of IGF-1R and prevent its activation (Wu *et al.* 2012; Stuard *et al.* 2020b). Adenovirus-driven SIRT1 overexpression in mouse T1DM corneas and in 2D cultures of human corneal epithelial cells positively influenced epithelial wound healing by downregulating IGFBP3 (Wang *et al.* 2013). Thus, IGFBP3

upregulation in diabetes may interfere with normalizing effect of increased IGF-1 on the diabetic corneal epithelial wound healing.

Several other less well studied factors are altered in the diabetic corneas, which may underlie epithelial wound healing abnormalities. A peptide thymosin β_4 ($T\beta_4$) is an actin-sequestering protein (Dedova *et al.* 2006) but can also regulate cell migration, angiogenesis, tissue regeneration and inflammation. $T\beta_4$ can block tumor necrosis factor-α (TNF-α) induced inflammation and NF-κB activation (Sosne *et al.* 2010). It can promote corneal epithelial wound healing but is decreased in human diabetic corneas (Saghizadeh *et al.* 2005; Sosne 2018), which may contribute to slow wound closure.

Nerve growth factor (NGF) can accelerate diabetic corneal epithelial wound healing in mouse model of T2DM (Muangman *et al.* 2004) and reduce apoptosis in a rat model of T1DM (Park *et al.* 2016). However, whether its level or activity are changed in diabetic corneas, remains to be established.

Transforming growth factor (TGF)-β3 antifibrotic isoform is downregulated in healing diabetic corneal epithelium. Treatment of T1D diabetic rats with TGF-β3 improved wound healing through signaling via SMAD, PI3K-Akt and Serpine1 (Bettahi *et al.* 2014).

Changes in the levels of epithelial microRNAs (miRs), potent epigenetic regulators, have also been described in human diabetic *ex vivo* and organ-cultured corneas (Funari *et al.* 2013; Kulkarni *et al.* 2017). MiR-146a and miR-424 suppressed epithelial wound healing in 2D cultured human limbal epithelial cells and in organ-cultured corneas, and their specific inhibitors (antagomirs) expectedly accelerated healing (Funari *et al.* 2013; Winkler *et al.* 2014). This effect could be attributed to the inhibitory action of miR-146a on EGFR that was counteracted by the antagomir (Winkler *et al.* 2014). In the T1DM Akita mouse corneas and in 2D mouse limbal epithelial cell line grown in high glucose, an increase in miR-204–5p, an inhibitor of SIRT1, was observed. Concomitantly, SIRT1 was reduced in high glucose-treated cells. Subconjunctival injection of miR-204–5p antagomir in Akita mice upregulated SIRT1 and promoted wound healing (Gao *et al.* 2015). This could be due to SIRT1-induced downregulation of IGFBP3 that attenuates IGF-1 signaling (Wang *et al.* 2013). Overall, miR changes in diabetic corneas provide another important mechanism underlying epithelial abnormalities in DK.

Altered cell-cell interactions may also contribute to DK abnormalities. It was recently shown that extracellular vesicles from human normal but not diabetic 2D cultured limbal keratocytes can stimulate cultured epithelial cell migration and proliferation, as well as normal organ-cultured corneal epithelial wound healing and stem cell marker expression (Leszczynska *et al.* 2018).

Advanced glycation end products (AGEs) are formed through non-enzymatic protein glycosylation (glycation) and accumulate due to hyperglycemia in rat, monkey and human diabetic tissues including corneal cells and extracellular matrix (Zou *et al.* 2012; Madonna *et al.* 2017; del Buey *et al.* 2019). AGEs retard epithelial wound healing and cause apoptosis as shown using human 2D cultured immortalized corneal epithelial cells. This effect is dependent on AGE receptors and reactive oxygen species generated by activated NADPH

oxidase (Shi *et al.* 2013a; 2013b). AGE accumulation in the human diabetic cornea could reduce epithelial and keratocyte attachment to the extracellular matrix, such as glycated type I collagen, fibronectin, and laminin (McDermott *et al.* 2003). They may also contribute to increased stromal collagen crosslinking and rigidity of diabetic corneas (del Buey *et al.* 2019).

2.1.1.2. Corneal Nerve Abnormalities (Neuropathy): Systemic neuropathy is a hallmark of long-term DM of both types. Diabetic corneal neuropathy (DCN) was recognized over 40 years ago. Its primary clinical manifestation is reduction of corneal sensation (Bikbova *et al.* 2018; Mansoor *et al.* 2020). DCN and corneal nerve damage are observed early in human diabetes and even in pre-diabetes (Zhivov *et al.* 2013; Papanas and Ziegler, 2013; Petropoulos *et al.* 2015; Szalai *et al.* 2016; De Clerck *et al.* 2020). The severity of this pathological trait positively correlates with disease duration and DM stage, and is important for non-invasive diagnostics (Rosenberg *et al.* 2000; Saito *et al.* 2003; Cousen *et al.* 2007; Tavakoli *et al.* 2007; De Cillà *et al.* 2009; Zhivov *et al.* 2013; Cruzat *et al.* 2017; Pellegrini *et al.* 2020; Roszkowska *et al.* 2020; Salami *et al.* 2020). Loss of corneal sensation is thought to be the consequence of damage of corneal nerves, including reduced nerve fiber density and length (mostly in the inferior whorl), increased nerve tortuosity and thickness (Ljubimov 2017; Bikbova *et al.* 2018; Ferdousi *et al.* 2020). Most of the alterations concern the sub-basal (subepithelial) nerve plexus (Figure 2). This proximity and the insertion of nerve fiber terminals into the epithelial cell layer (Stepp *et al.* 2017) could explain the correlation between DK and DCN (De Cillà *et al.* 2009; He and Bazan 2012; Wang *et al.* 2012; Zhivov *et al.* 2013; Cai *et al.* 2014; Davidson *et al.* 2014; Stem *et al.* 2014). The subbasal corneal nerve reduction seen in human and animal diabetes alike correlates with alterations of dendritic cells that have neurotrophic functions (Leppin *et al.* 2014; Gao *et al.* 2016). The regeneration of subbasal nerves upon corneal epithelial wounding is significantly slower in diabetic animals (Wang *et al.* 2012; Gao *et al.* 2016). Although several factors have been implicated in the development of DCN following hyperglycemia including AGE that could reduce NGF and sphingolipids, oxidative stress, altered growth factors and signaling pathways, the mechanisms of diabetic neuropathy in general and DCN in particular still remain unclear (Markoulli *et al.* 2018; Barsegian *et al.* 2019).

2.1.1.3. Corneal Stromal Changes: Corneal stroma is also changed in DM. Deposition of abnormal collagen fibril bundles was observed in diabetic humans and monkeys (Rehany *et al.* 2000b; Zou *et al.* 2012), and keratocyte density appears to be reduced (Kalteniece *et al.* 2018). AGEs accumulate in the human diabetic corneal stroma leading to collagen crosslinking that could result in increased central corneal thickness and higher rigidity (Sady *et al.* 1995; del Buey *et al.* 2019). In diabetic rats, stromal edema was also observed (Gül *et al.* 2008). Two keratocyte MMPs, MMP-3 and MMP-10, are upregulated in the stroma of *ex vivo* human diabetic corneas and may contribute to its altered structure (Saghizadeh *et al.* 2001a). Diabetic corneal stroma also shows significant metabolic and lipidomic changes (Priyadarsini *et al.* 2016). It may be suggested that stromal alterations reflect some degenerative changes due to ECM remodeling by MMPs and collagen cross-linking due to AGE accumulation.

2.1.1.4. Corneal Endothelial Abnormalities: Endothelial signs of diabetic corneal disease comprise increased cell pleomorphism (variation of cell shape) and polymegethism (variability of the cell area/size) (Shenoy *et al.* 2009; Módis *et al.* 2010; El-Agamy and Alsubaie 2017). A number of reports indicate decreased endothelial cell density in T1DM and T2DM patients that is more pronounced in patients with DR (Shenoy *et al.* 2009; Liaboe *et al.* 2017; El-Agamy and Alsubaie 2017; Çolak *et al.* 2020; Durukan 2020; Goldstein *et al.* 2020). Descemet's membrane, the BM of corneal endothelium is also altered in DM. It contains abnormal wide-spaced collagen bundles that may result from excessive collagen glycation (Rehany *et al.* 2000a; 2000b; Akimoto *et al.* 2008). Diabetic changes in endothelial function remain unclear, although they might contribute to increased corneal thickness.

2.1.1.5. Conjunctival Involvement: Diabetic patients also present with conjunctival alterations including vascular dilation and reduction of capillaries with increased tortuosity, uneven vessel distribution, and decrease in goblet cell numbers (Cheung *et al.* 2001; Yoon *et al.* 2004; Owen *et al.* 2005; To *et al.* 2011; Gunay *et al.* 2016). Elevated proinflammatory cytokines are observed in patients with dry eye (Zhang *et al.* 2016). Conjunctival microbiome is also abnormal in diabetic patients; if treatment is needed it should involve vancomycin or other broad-spectrum antibiotics (Martins *et al.* 2004; Bilen *et al.* 2007).

2.1.1.6. Tear Film Changes: Tear film is mainly produced by the lacrimal gland. In DM, this gland suffers from inflammation, oxidative stress and AGE accumulation, resulting in reduced tear secretion with more frequent dry eye (Cousen *et al.* 2007; Manaviat *et al.* 2008; Beckman 2014). Decreased tear film stability in diabetic patients correlates with DCN, poor glycemic control, and reduced density of mucin-secreting conjunctival goblet cells (Dogru *et al.* 2001; Yoon *et al.* 2004). The severity of keratoconjunctivitis sicca correlates with the severity of diabetic retinopathy (Manaviat *et al.* 2008; Lv *et al.* 2014). Diabetic tear film alterations could also contribute to DK (Liu *et al.* 2015).

2.1.1.7. Biomechanical Abnormalities: Corneal biomechanics changes in diabetic patients have been documented. They concern corneal resistance factor (CRF) related to the tissue elasticity and corneal hysteresis (CH) as indicator of viscosity and biomechanical integrity (del Buey *et al.* 2019; Ramm *et al.* 2020; Wang *et al.* 2020). Diabetic corneas tend to have increased thickness and rigidity. Most recent studies agree that the human diabetic corneas have increased CH and CRF (Kotecha *et al.* 2010; Scheler *et al.* 2012; del Buey *et al.* 2019; Ramm *et al.* 2020; Wang *et al.* 2020). These biomechanical parameters correlate with patients' Hb1Ac levels. Further studies are needed to understand the pathophysiological role of changed biomechanics in corneal diabetic disease.

Interestingly, increased viscosity and rigidity of the human diabetic cornea may be protective against keratoconus. Most of the available data suggest an inverse association of keratoconus development with DM (Seiler *et al.* 2000, Naderan *et al.* 2014; Woodward *et al.* 2016; McKay et al. 2019; Welchel *et al.* 2019), although one study reported positive association between T2DM and the presence and severity of keratoconus (Kosker *et al.* 2014). Negative association of keratoconus with DM is attributed to AGE-related accumulating collagen

crosslinks in the diabetic corneal stroma mitigating its thinning (McKay et al. 2019; Welchel *et al.* 2019).

2.1.2. Surgical Complications with Diabetic Corneas—Structural and functional alterations in diabetic corneas pose a potential risk of complications upon eye surgery, mostly related to cataract and vitreoretinal surgery, and corneal or Descemet's transplantation. Diabetic patients account for the majority of cases of corneal surgical complications with these methods (Bikbova *et al.* 2012; Vieira-Potter *et al.* 2016; Ljubimov 2017; Goldstein *et al.* 2020; Priyadarsini *et al.* 2020). Cases of DK development after ocular surgery have also been described (Sakamoto *et al.* 2004; Chen *et al.* 2009). There are data showing that contact lens wear also bears risks of corneal epithelial damage for diabetic patients, and eye practitioners should be aware of this (Bussan and Robertson 2019). Epithelial debridement before vitrectomy or retinal photocoagulation may result in abnormally slow recovery in corneal sensation (Chen *et al.* 2009; Mahgoub and Macky 2014). Cataract surgery in diabetic patients entails increased postoperative endothelial cell loss and increased corneal thickness with edema (Hugod *et al.* 2011; Yang *et al.* 2011; Dhasmana *et al.* 2014; Tsaousis *et al.* 2015; He *et al.* 2017; Elmekawey *et al.* 2020). Refractive corneal surgery may also be riskier in diabetic patients because of various DK-associated abnormalities and increased possibility of infections (Fraunfelder and Rich 2002; Jabbur *et al.* 2004). At the same time, eye surgeries may be safe in well-controlled DM (Cobo-Soriano *et al.* 2006; Goldstein *et al.* 2020; Labetoulle *et al.* 2020), although some authors call for caution in performing refractive surgeries in all diabetics (Mohammadpour 2007).

Human studies have also found that DM of corneal tissue donor was associated with increased chances of adverse effects (lower endothelial count, and graft dislocation and survival) on Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK). Additionally, the adhesion of Descemet's membrane to the stroma is higher in diabetic corneas resulting in problems with graft preparation for DMEK (Greiner *et al.* 2014; Goldstein *et al.* 2020). It should be noted that DM donors may comprise up to one fourth of all corneal donors in the United States. This problem has been discussed in-depth in a recent review (Goldstein *et al.* 2020). Good glycemic control of the corneal donor and early DM stage appear to alleviate risks of graft rejection or further complications due to diabetic endothelial problems. However, late-stage DM may present significant risk to the recipient and such corneas should not be used (Lass *et al.* 2019; Goldstein *et al.* 2020).

2.1.3. Emerging Treatments—Diabetic complications are stable and once manifested do not usually recede with tight glucose control or available treatments. This may be due to long lasting epigenetic modifications (including DNA methylation and histone acetylation) that alter gene expression and are thought to be important in diabetic disease (Kowluru and Mohammad 2020). Currently, the treatment of DK and DCN remains symptomatic (Abdelkader *et al.* 2011; Priyadarsini *et al.* 2020). New experimental therapeutics have recently emerged, although most of them have been tested only in various *in vitro* and *in vivo* experimental models. Some of these promising treatments are discussed below.

2.1.3.1. Insulin: Insulin is a standard agent for DM treatment and has benefits for diabetic eye disease. Local insulin implants were shown to accelerate corneal wound healing in T1DM rats (Klocek *et al.* 2007). In T1DM mice, topical insulin could also prevent subbasal corneal nerve loss (Chen *et al.* 2013) and accelerate epithelial wound healing and corneal nerve repair after wounding by activating canonical Wnt signaling (Yang *et al.* 2020). Insulin eye drops significantly promoted corneal re-epithelialization after epithelial debridement for vitreoretinal surgeries in diabetic patients (Bastion and Ling 2013). Insulin in the diabetic cornea may improve cell proliferation and migration after wounding (Stuard *et al.* 2020a). However, accumulated diabetic epigenetic changes might counteract insulin action on the cornea. For instance, in human organ-cultured corneas and 2D cultured limbal epithelial cells from long-term diabetic donors, epithelial wound healing and stem cell marker expression are still impaired, although high insulin concentration is present in the medium (Kabosova *et al.* 2003; Kramerov *et al.* 2015). Overall, more human data are needed before recommending using insulin to treat DK and/or DCN.

2.1.3.2. Naltrexone: Naltrexone, a potent inhibitor of the OGF-OGFR interaction, is FDA approved for clinical treatment of alcohol and opioid dependence. In T1D and T2D mice and rats, topical naltrexone can normalize corneal epithelial wound healing, tear secretion, and corneal sensitivity/nerve function (Zagon *et al.* 2014; 2020; Sassani *et al.* 2016). Unlike many other agents mediating cell migration, naltrexone acts by stimulating cell proliferation inhibited by diabetes-elevated OGF (Zagon *et al.* 2020). Clinical trials of topical naltrexone for diabetic corneal disease are currently underway (McLaughlin *et al.* 2020).

2.1.3.3. Other Pharmacological Agents: A small human study has evaluated $T\beta_4$ for facilitating corneal wound healing in diabetics with neurotrophic keratopathy. Significant improvement of epithelial defects with no side effects was observed, which makes $T\beta_4$ treatment promising for DK therapy (Sosne *et al.* 2016). Similar effects are seen with autologous serum eye drops (Schulze *et al.* 2006) that are becoming popular with eye practitioners, although it is unclear which serum components are the most effective. Antidiabetic drugs nateglinide and glibenclamide can reduce changes of the Descemet's membrane in Goto-Kakizaki T2DM rats (Akimoto *et al.* 2008). Some other agents were shown to reduce symptoms of DK and DCN in animal models. 1,5-isoquinolinediol [poly(ADP-ribose) polymerase inhibitor] could promote epithelial healing and increase corneal sensitivity in T1D diabetic rats (Byun *et al.* 2015). Topical lacritin fused with elastin-like polypeptide-based nanoparticles accelerated corneal epithelial wound healing in T1D NOD diabetic mice (Wang *et al.* 2014).

In animal T1DM and T2DM mouse and rat models, a number of treatments were recently shown to aid in restoring sensory innervation with increased corneal sensitivity and prevention of nerve fiber loss, thus alleviating DCN. Some of them could also promote epithelial wound healing. These treatments include diabetes-downregulated ciliary neurotrophic factor acting through STAT3 activation (Zhou *et al.* 2015; Guo *et al.* 2016), interleukin-1 (IL-1) receptor antagonist (Yan *et al.* 2016), substance P acting on neurokinin-1 receptor (Yang *et al.* 2014), curcumin in nanomicelles, pigment epithelium-derived factor, and resolvin D1 that can reduce reactive oxygen species (Guo *et al.* 2016;

Zhang *et al.* 2018; Liu *et al.* 2020), omega-3 fatty acids (Coppey *et al.* 2020), mesencephalic astrocyte-derived neurotrophic factor that attenuates endoplasmic reticulum stress (Wang *et al.* 2020), neuropeptide VIP that activates Sonic Hedgehog signaling (Zhang *et al.* 2020), glycyrrhizin that attenuates the expression of inflammatory mediators and oxidative stress (Somayajulu *et al.* 2021), fenofibrate that restores PPARα downregulated in diabetes (Matlock *et al.* 2020), and leucine-rich α-2-glycoprotein-1 that activates JAK/STAT, TGF-β3 and EGFR-Akt signaling axes (Li *et al.* 2020). Topical NGF provided beneficial effects in T1DM and T2DM mouse corneas (Muangman *et al.* 2004; Park *et al.* 2016). Recombinant NGF (cenegermin, Oxervate™) is approved for neurotrophic keratitis treatment in the United States and Europe (Sheha *et al.* 2019). Given the promising animal data, cenegermin could be also beneficial for diabetic corneal disease but has not been used so far for this condition. Overall, the emerging treatments for DK and DCN need more efficacy and safety studies for possible clinical translation.

2.1.3.4. Gene and MicroRNA Therapy: Gene therapy approach is a powerful method to change the expression of a specific gene altered by the disease. In many gene therapy animal studies viruses are being used as delivery vehicles (Ljubimov and Saghizadeh 2015; Mohan *et al.* 2020). We have applied adenoviral (AV) gene therapy to normalize the expression of diabetes-altered genes *c-Met, cathepsin F* and *MMP-10* in 3D organ-cultured human diabetic corneas and cultured limbal epithelial cells (Kramerov *et al.* 2016). Boosting the expression of c-Met and/or reducing cathepsin F and MMP-10 in diabetic corneas led to restoration of wound healing time and expression levels of diabetic and epithelial stem cell markers including laminins, nidogen-1 and integrin $\alpha_3\beta_1$. Gene therapy effects were mediated by activation of EGFR-Akt axis and p38 kinase (Ljubimov 2017). Combination therapy was the most effective (Saghizadeh *et al.* 2014; Kramerov *et al.* 2016). Although efficient and safe in whole corneas, AV vectors showed marked toxicity in progenitor-enriched cultures of diabetic limbal epithelial cells (Kramerov *et al.* 2016; 2021). To circumvent this unwanted effect, we recently used nanoconstructs based on natural-derived and safe polymalic acid scaffold with attached antisense inhibitors to select genes. They exerted similar beneficial effects on diabetic corneas and cultured cells as AV gene therapy but completely lacked toxicity in a range of doses (Kramerov *et al.* 2021). This approach looks promising for future translation to the clinic.

Gene expression changes can be also achieved epigenetically using miRs. A number of miRs with altered expression in the human and mouse diabetic corneas have been described (Funari *et al.* 2013; Winkler *et al.* 2014; Hu *et al.* 2019; 2020). In the human corneas, miR-146a retarded epithelial wound healing by inhibiting EGFR. MiR-146a antagomir exerted an opposite effect (Funari *et al.* 2013; Winkler *et al.* 2014). Two other miRs, miR-34c and miR-181a, were elevated in trigeminal ganglia of T1DM mice. Subconjunctival injection of its antagomir accelerated corneal epithelial wound healing and promoted corneal nerve regeneration with stimulation of autophagy (Hu *et al.* 2019; 2020). It should be noted that miRs usually have more than one target even in the same cell, necessitating a careful validation of their use for therapy. Overall, current advances in the experimental use of gene therapy for corneal diabetes warrant its further development for clinical translation.

In summary, diabetic corneal disease presents as a serious but underestimated clinical problem that is important for millions of diabetic patients. The main concerns appear to be diabetic keratopathy and neuropathy. Whereas mechanisms of DK have been studied and a number of markers and affected signaling pathways described, pertinent studies of DCN are clearly lagging behind. The same concerns alterations of corneal stroma and endothelium. Currently known molecular signatures of this disease may be used as drug targets aimed at ameliorating corneal health. Experimental studies have provided promising drug candidates of different classes for treatment, although only insulin and naltrexone have been used so far in human patients. Future investigations should be aimed at developing combined therapies directed against both DK and DCN, and unraveling corneal molecular differences between diabetes types.

2.2. Graves' Disease

Graves' disease is an autoimmune endocrine disorder marked by hyperthyroidism and goiter, resulting in an enlarged thyroid gland. It can affect an individual of any age but is mostly seen in patients between the ages of 30–50 years. Weight loss, fatigue, heat intolerance, loss of appetite, tremor, and palpitations are the most common symptoms (Smith and Hegedüs 2016). Ocular abnormalities in Graves' disease are common and often referred to as ophthalmic Graves' disease, Graves' orbitopathy, or thyroid eye disease (TED). It affects the orbit that causes eyelid retraction and proptosis (inability to close the eye), resulting in corneal exposure, which leads to redness, irritation, keratitis, dryness, and increased risk of infection (Sokol *et al.* 2010). Dry eye disease was reported in more than 66% of patients with moderate to severe TED (Kashkouli *et al.* 2018). A topographic analysis system revealed corneal changes in patients with Graves' disease undergoing strabismus surgery (Kwitko *et al.* 1992). In another study, Karabulut *et al.* (2014) showed alterations in corneal biomechanical properties in patients with TED by decreasing corneal hysteresis, indicating a difference in structural and functional properties in the eyes of TED patients compared to control eyes. However, the central corneal thickness remains unchanged (Konuk *et al.* 2008). Microbial keratitis was also reported (Naik *et al.* 2019). Treatment with prednisone is prescribed to treat ocular inflammation (Prummel *et al.* 1989; Bartalena and Tanda 2009). Other systemic immunotherapies including rituxumab (anti-CD 20), TNF-α inhibitors, tocilizumab (anti-soluble IL-6 receptor) and cyclosporine (T lymphocyte inhibitor) have shown promising results (Strianese and Rossi 2019; Shin *et al.* 2009; Eid *et al.* 2020; Perez-Moreiras *et al.* 2019). Lubricating eye drops are also recommended for treatment of dry eye associated with Graves' disease (Sokol *et al.* 2010).

2.3. Addison's Disease

Addison's disease, also known as primary adrenocortical insufficiency, is caused by infection (tuberculosis) or autoimmune reaction against the adrenal cortex. Symptoms include fatigue, nausea, weight loss, dizziness, and hyperpigmentation of the skin (Hellesen *et al.* 2018). Ocular manifestations are rare and include photophobia, ptosis, blepharitis and loss of eyelashes, keratoconjunctivitis, episcleritis, corneal ulcers, cataract, and papilloedema (Chopra *et al.* 2012). In two siblings with Addison's disease, bilateral progressive vision loss and photophobia secondary to limbal stem cell deficiency (LSCD) were reported with diffuse corneal vascularization and delayed punctate fluorescein staining

of corneal epithelium (Mohammadpour and Javadi 2006; Mohammadpour *et al.* 2006). Treatments involve hormone replacement therapy to restore the patient's hormone levels, and corticosteroids to reduce inflammation (Hellesen *et al.* 2018).

2.4. Hyperparathyroidism

Hyperparathyroidism is caused by the abnormal secretion of the parathyroid hormone, resulting in hypercalcemia. It mainly affects postmenopausal women, but in 10–20% of the patients, it may be caused by an inherited parathyroid gland hyperfunction (Taniegra 2004). There are two forms of hyperparathyroidism, primary and secondary. Primary hyperparathyroidism develops from enlarged parathyroid glands, leading to hypercalcemia, whereas secondary hyperparathyroidism results from an underlying condition that causes hypocalcemia (Cordellat *et al.* 2012). Patients can present with skeletal, renal, gastrointestinal, ocular, cardiovascular, and neuromuscular manifestations associated with increased calcium and parathyroid hormone serum levels (Blackburn and Diamond 2007; Cordellat *et al.* 2012). A common cause of secondary hyperparathyroidism is chronic renal failure (Yuen *et al.* 2016).

In the cornea, hypercalcemia results in calcium deposition in the Bowman's layer causing band keratopathy (Porter and Crombie 1973a; Golan *et al.* 1975; Petrohelos *et al.* 1977; Eom *et al.* 2013). The same manifestation occurs in chronic renal failure (Caldeira *et al.* 1970; Easterbrook and Mortimer 1970; Porter and Crombie 1973b; Klaassen-Broekema and van Bijsterveld 1993; Aktaş *et al.* 2007; Mullaem and Rosner 2012). Abeysiri and Sinha (2006) have reported in hyperparathyroidism an unusual pattern of Vogt white limbal girdle with adjacent flakelike subepithelial deposits of the conjunctiva, and peripheral white corneal deposits in the anterior stroma in a patient. Corneal endothelial changes in chronic renal failure, such as polymegethism and pleomorphism were also noted (Ohguro *et al.* 1999). Additionally, in an ovariectomized rat model, hypercalcemia significantly delayed corneal epithelial wound healing (Nagai *et al.* 2015). Primary hyperparathyroidism patients also show increased central corneal thickness and intraocular pressure (Baser *et al.* 2016; Sati *et al.* 2016). Treatments for hyperparathyroidism aim to control parathyroid hormone levels and consequently calcium levels, that can reduce corneal symptoms. When appropriate, surgery is recommended to remove the hyperfunctioning parathyroid tissue (Silva *et al.* 2018). Pharmacological options such as cinacalcet, a calcimimetic agent that binds to the calcium-sensing receptor to reduce serum calcium levels, has also been successfully used (Peacock *et al.* 2005).

3. Infectious Diseases

3.1. Viral Infections

3.1.1. Coronavirus Disease 2019 (COVID-19)—The severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2), a highly contagious new coronavirus, is responsible for coronavirus disease 2019 (COVID-19) pandemic which poses unprecedent challenges to the modern global health care system. Significant efforts were focused in most countries on lowering the community spread of SARS-CoV-2, which includes social distancing and the use of face masks. Besides the inhalation of aerosols from asymptomatic

or COVID-19 patients, SARS-CoV-2 can gain entry via the mucosal surfaces present in the eye (Arora *et al.* 2020; Li *et al.* 2020) suggesting that the eye may be an important portal for SARS-CoV-2 entry and the manifestation of COVID-19. Therefore, eye protection (e.g., goggles or face shields) is strongly recommended for health care workers to reduce the risk of contracting COVID-19 (Chu *et al.* 2020). Importantly, better understanding of viral transmission and its pathogenesis at the ocular surface could help in the development of preventative and therapeutic measures to combat COVID-19.

The involvement of the eye in the transmission of infectious diseases has been documented since the 19th century (Maxcy 1919). Some recent studies have reported the presence of SARS-CoV-2 RNA in tears and conjunctiva of COVID-19 patients, as well as the expression of viral entry receptors, angiotensin-converting-enzyme-2 (ACE2) and TMPRSS2, in the cornea and conjunctiva (Zhou *et al.* 2020a; Sirakaya *et al.* 2020; Aiello *et al.* 2020; Roehrich *et al.* 2020; Guemes-Villahoz *et al.* 2020). However, the ocular surface involvement in SARS-CoV-2 transmission, either as a reservoir or as a target organ, is still unclear. Whereas anatomical and physiological characteristics render the eye a gateway for virus transmission to extraocular sites such as lungs (Belser *et al.* 2020), current evidence suggesting that the ocular surface is a possible entry route for the virus to cause COVID-19 remains scarce.

One report on various routes of SARS-CoV-2 entry in *Rhesus* monkey showed the presence of virus in the nasolacrimal and respiratory systems upon conjunctival inoculation (Makovoz *et al.* 2020). SARS-CoV-2 can also infect human ocular cells and eye organoids (Deng *et al.* 2020). Whereas these studies imply that SARS-CoV-2 can gain access to lungs and other tissues via ocular route, more studies are required to prove it unequivocally.

COVID-19 has increased severity and mortality in patients with some comorbidities, including type 2 diabetes, which is commonly associated with obesity (Belančić *et al.* 2020; Noor and Islam 2020; Wang and Meng 2020). The diabetic cornea presents with abnormalities that could facilitate viral infection including the breakdown of barrier function and tear film, as well as impaired wound healing and stem cell functions (Lee *et al.* 2019; Ljubimov 2017; Saghizadeh *et al.* 2017). Diabetic patients have significantly higher incidence of viral conjunctivitis (Ansari *et al.* 2017). Therefore, the abnormal diabetic ocular surface may present an easier entry site for SARS-CoV-2 than a non-diabetic one. Also, ocular transmission of SARS-CoV-2 can occur due its ability to infect and proliferate in ocular surface cells while DM may increase this response, in part, by modulating innate antiviral signaling (Graham *et al.* 2008; Lokugamage *et al.* 2020).

Studies have shown that SARS-CoV-2 may cause conjunctivitis and viral RNA has been detected in tears of COVID-19 patients (Wu *et al.* 2020; Xia *et al.* 2020; Colavita *et al.* 2020; Guan *et al.* 2020; Chen *et al.* 2020; Zhou *et al.* 2020b; Seah *et al.* 2020). Recent study by Sawant *et al.* (2020) showed a notable (13%) prevalence of SARS-CoV-2 in corneal and conjunctival tissues from COVID-19 donors (Figure 3).

Although these studies indicate the possibility that ocular surface cells can be infected by SARS-CoV-2, the presence of viral RNA does not equate live viral infection, and to prove that, one needs to show viral antigens in the ocular tissue of COVID-19 patients (Sawant *et*

al. 2020; Figure 3). Recently, the nucleocapsid protein antigen of SARS-CoV-2 was detected on the cells of the conjunctiva, trabecular, and iris of the patient infected with COVID-19 but not in the control participant (Yan *et al.* 2020).

Although published studies (Wang and Meng 2020; Makovoz *et al.* 2020; Wu *et al.* 2020; Xia *et al.* 2020; Colavita *et al.* 2020; Guan *et al.* 2020; Chen *et al.* 2020; Zhou *et al.* 2020b; Seah *et al.* 2020) indicate the possibility that SARS-CoV-2 could infect and replicate in corneal epithelial cells, some important aspects of virus-corneal cell interactions require thorough examination. These may include cytopathic effects of SARS-Cov-2 in corneal cells, or innate signaling pathways activated in infected cornea as compared to lung. Further studies would allow to examine specific interactions of SARS-CoV-2 with corneal epithelial cells, and induction of corneal innate antiviral mechanisms in COVID-19.

There is mounting evidence of the virus presence in ocular secretions and corneal cells of affected patients (Amesty *et al.* 2020; Ho *et al.* 2020; Sawant *et al.* 2020). The ocular surface tropism of SARS-CoV-2 and its potential to cause localized ocular disease should be considered as an opportunity for early diagnostics but also as a problem for corneal transplantation. The precise pathophysiological mechanisms of SARS-Cov-2 ocular infection and transmission remain to be elucidated.

3.1.2. Herpes Simplex Keratitis—Corneal herpetic keratitis results from viral infection most often caused by herpes simplex virus 1 (HSV-1). Although HSV-2 can also infect the eye, more than 90% of HSV ocular infections are caused by HSV-1. HSV-1 is known to be the leading infectious cause of corneal blindness and ulcers worldwide due to its facilitated acquisition *via* airborne droplet transmission (Liesegang 2001). Approximately 30,000 people in the United States suffer from recurrent ocular HSV infections annually, and, although medications exist to treat these infections, severe recurrent cases may require corneal transplants (Hill 1987; Liesegang 1999; 2001; Rajasagi and Rouse 2018). The most common contributing factor of HSV-1 ocular infection is inflammation of the ocular surface including the cornea (Figure 4), sclera, and conjunctiva (Chang *et al.* 2000). Additionally, immune system compromise as seen in HIV-infected people can significantly increase the risk of developing ocular HSV symptoms (Sobol *et al.* 2016). HSV-1-induced corneal scarring, also known as herpes stromal keratitis (HSK), can lead to blindness.

Although a strong immune response is elicited following HSV-1 ocular infection, the virus has acquired several mechanisms to evade immune clearance (Kurt-Jones *et al.* 2017; Matundan *et al.* 2019; Tormanen *et al.* 2020). As a consequence, after an initial eye infection, HSV-1 travels to the sensory nerve ganglia, where it establishes a latent state and from where it can periodically reactivate and cause recurrent infections (Rock *et al.* 1987; Wechsler *et al.* 1988; Nicoll *et al.* 2012). The probability of recurrence increases after each reactivation event. These recurrent infections and prolonged inflammatory response after viral clearance lead to corneal scarring, opacification, neovascularization and loss of visual acuity (Lobo *et al.* 2020; Farooq and Shukla, 2012).

It is well established that corneal scarring is the result of inflammatory response to the pathogen (Brandt 2005; Koelle and Ghiasi 2005; Matundan *et al.* 2019; Lobo *et al.* 2020;

Tormanen *et al.* 2020). Several attempts have been made to treat corneal HSV-1 using immune pathway to regulate the affect of stromal keratitis. Both lymphotoxin-α and -β are proinflammatory cytokines detectable up to 48 hours post viral infection *in vitro* and play a role in the induction of chemokines related to cornea-infiltrating proinflammatory cells. By using anti-lymphotoxins, stromal keratitis may be mitigated (Veiga-Parga *et al.* 2013). However, lymphotoxin-α knockout mice had increased corneal scarring, latency and mortality in response to HSV-1 ocular infection (Wang *et al.* 2019). Increased corneal opacity is mediated by IL-17, which is produced by CD4+ T-cells. Using anti-IL-17 in recurrent HSV-1 mouse models, downregulation of TNF-α expression in recurrent corneas with decreased herpetic stromal keratitis has been reported (Xia *et al.* 2012).

Typical treatment for HSV-1 ocular infections includes antiviral acyclovir and topical corticosteroids to suppress inflammation (Koelle and Ghiasi 2005). Most recently, topical treatments such as 2% cyclosporine-A and 1% prednisolone acetate eye drops have been found to improve corneal opacity from herpetic stromal keratitis (Peyman *et al.* 2018). Oral antivirals, e.g., acyclovir, are beneficial as prophylactic treatment reducing ocular recurrences (Young *et al.* 2010). Kim *et al.* (2018) described a novel treatment in which administration of prophylactic oral acyclovir and ascorbic acid has shown to reduce and prevent the recurrence of corneal epithelial herpetic keratitis. As many of these treatments are still being investigated, more work is needed in order to develop effective ways to treat and especially prevent ocular manifestations of HSV-1.

3.1.3. Shingles Caused by Varicella Zoster—A DNA virus Varicella zoster (chickenpox, herpesvirus type 3, VZV) causes shingles, or Herpes zoster, an inflammatory viral disease presenting as maculopapular or vesicular rash as a result of reactivation of latent virus acquired in childhood in the sensory nerve ganglia (Kalogeropoulos *et al.* 2015; Minor and Payne 2020). T-cell mediated responses are crucial for maintaining VZV in a latent state. Stress factors such a malignant disease, immunosuppressive treatments, HIV infection or even chemical or physical stressors may act as triggers for VZV reactivation (Kalogeropoulos *et al.* 2015; Depledge *et al.* 2018). When the latent virus becomes reactivated in ophthalmic region of trigeminal cranial nerve (V), it causes herpes zoster ophthalmicus (HZO). HZO represents 10–20% of all VZV cases. Ocular manifestations include common keratitis, uveitis, iritis, conjunctivitis, episcleritis, as well as rare retinal necrosis (Kalogeropoulos *et al.* 2015; Vrcek *et al.* 2017; Minor and Payne, 2020). The most severe eye-threatening complications of HZO are pan-uveitis and retinal necrosis (although it is rare). Studies have found that the amount of viral load in the aqueous humor of VZV patients is correlated to the manifestation and severity of anterior uveitis (Kido *et al.* 2008; Kalogeropoulos *et al.* 2015). Intravenous antiviral treatments, like acyclovir, may be recommended for 48 to 72 hours to reduce complications and decrease pain in severe cases, and oral antivirals may be taken if there are no complications (Kedar *et al.* 2019). Two vaccines Shingrix® (recombinant glycoprotein E; for adults over 50) and Zostavax® (live attenuated VZV) are in use in the United States. Centers for Disease Control guidelines state that Shingrix® is preferred because of higher efficacy (Lal *et al.* 2015; Warren-Gash *et al.* 2017; Kedar *et al.* 2019; Sullivan *et al.* 2019).

3.1.4. Human T-Cell Leukemia Virus HTLV-1—Human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus that propagates using its encoded reverse transcriptase to generate provirus DNA from viral RNA, which then is integrated into the host genome and primarily affects CD4+ T-cells (Terada *et al.* 2017). Aside from being known to cause adult T-cell leukemia, a neurological disorder tropical spastic paraparesis (TSP) and HTLV-1-associated myelopathy, HTLV-1-associated uveitis has been known to promote ocular complications, such as keratoconjunctivitis sicca, and interstitial keratitis. Patients with HTLV-1 present corneal abnormalities, such as corneal haze and opacities, thinning and scarring of the peripheral cornea, keratopathy, and neovascularization (Buggage *et al.* 2001). Treatments for HTLV-1-assocaited uveitis may include intraocular corticosteroids (Kamoi and Mochizuki 2012).

3.1.5. Epstein-Barr Virus—Epstein-Barr virus (EBV) is a ubiquitous human herpes virus type 4 infecting more than 90% of the adult population involving B lymphocytes and epithelial abnormalities (Nowalk and Green 2016). It is a common cause of infectious mononucleosis. Several ocular symptoms such as keratitis, uveitis, granulomatous conjunctivitis, choroiditis, retinitis, and papillitis are linked to EBV infections (Slobod *et al.* 2000). In the cornea, stromal keratitis related to EBV infection with granular, ring-shaped opacities has been reported (Matoba 1990). Mononucleosis can also cause delayed onset bilateral peripheral interstitial keratitis (Iovieno et al. 2020). *In vivo* confocal microscopy revealed corneal endotheliitis in eyes infected with EBV; this is also observed in cases of cytomegalovirus (CMV) infection (Alfawaz *et al.* 2013; Peng *et al.* 2020). EBV infection in human corneal epithelial cell cultures caused epithelial-mesenchymal transition (EMT) *via* PI-3K/Akt/ERK activation induced by TGF-β1-dependent Syk and Src phosphorylation, which could lead to corneal fibrosis. Targeting these pathways may have therapeutic potential in treating EBV-induced EMT (Park *et al.* 2014). Due to its self-limiting nature, EBV treatment is mainly supportive. Antiviral drugs such as acyclovir, ganciclovir, cidofovir, and foscarnet, among others have been used to treat EBV and also CMV infection (Alfawaz *et al.* 2013; Yaro 2013). Acyclovir has shown significant reduction in EBV infected B lymphocytes, and systemic treatment has alleviated ocular symptoms (Rafailidis *et al.* 2010; Keorochana 2016). EBV-related inflammation can be treated with a corticosteroid regimen (Matoba 1990).

3.2. Bacterial Infections

3.2.1. Tuberculosis—Tuberculosis (TB), a communicable disease caused by *Mycobacterium tuberculosis* (Mtb), most commonly affects lungs. Nearly one-third of the world's population is latently infected with TB, and more than nine million new cases are diagnosed each year, with 95% of infections in developing countries. When the airborne particles containing Mtb are inhaled, the bacteria reach the alveoli and are taken up by alveolar macrophages. Mtb can subvert antimicrobial macrophage machinery and avoid being degraded by phagolysosomes by blocking their maturation (Upadhyay *et al.* 2018). They also interfere with cellular trafficking and escape immune recognition (Zhai *et al.* 2019) allowing them to enter the lymphatic and circulatory system where they will travel systemically and affect multiple organs including the anterior and posterior segments of the eye. Corneal or anterior ocular manifestations of TB include lid vulgaris, conjunctivitis,

scleritis, episcleritis, corneal phlycten, interstitial keratitis, and granulomatous uveitis (Oluleye 2013). Absence of Mtb in the lungs does not mean it cannot be found in the eye, as 60% of patients with extra-pulmonary manifestations of tuberculosis will not have the infection in their lungs (Alvarez and McCabe 1984).

Clinical case studies reported that chronic conjunctivitis caused by Mtb may present with approximately 2 × 2 mm gelatinous conjunctival lesions along the limbus, granulomas, nodule ulcerative lesions, or even subconjunctival nodular masses (Solmaz *et al.* 2018; Balyan *et al.* 2019; Chaurasia *et al.* 2019). Interstitial keratitis with corneal perforations has also been noted as a sign of systemic TB (Yangzes *et al.* 2019). Phlyctenular keratoconjunctivitis is a nodular inflammation of the limbus as an allergic response. According to a case study of 112 persons with this condition, in 86 patients (76.7%) it was associated with TB (Rohatgi and Dhaliwal 2000). These ocular manifestations of TB may lead to mild to pronounced vision loss depending on the severity. When anterior ocular manifestations of TB are diagnosed, treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for a 6–9 months is recommended as a standard procedure (Figueira *et al.* 2017). In addition, corticosteroids are used along with anti-TB therapy to treat ocular complications. In severe cases, excision of nodule, granular, conjunctival, or lid masses may be necessary to prevent further ocular damage to avoid vision loss (Kee *et al.* 2016).

3.2.2. Syphilis—Syphilis is caused by *Treponema pallidum*, a spirochaete bacterium, and is commonly contracted *via* sexual interactions or congenitally from mother to child at birth, initially presenting itself in the form of painless sores and mild rashes. When left untreated for longer than 10 weeks, the bacterium will affect internal organs such as the eyes, brain, heart, nerves, bones, joints, and liver (Tudor *et al.* 2020). Syphilis can manifest on the ocular surface at any stage of the infection, anterior, intermediate, and posterior, with uveitis and syphilitic keratitis being the most common ocular manifestations. It may also cause interstitial keratitis, as well as chorioretinitis, retinitis, retinal vasculitis and cranial nerve and optic neuropathies (Barrow *et al.* 2020). Patients that are diagnosed with ocular syphilis are advised to get tested for human immunodeficiency virus (HIV) and neurosyphilis due to their similar risk factors and symptoms. Treatment for syphilis usually requires administration of antibiotics, most commonly parenteral penicillin G at any of the stages of bacterial infection (Kiss *et al.* 2005).

3.2.3. Pseudomonas Aeruginosa—Pseudomonas infection is caused by *Pseudomonas aeruginosa*, a Gram-negative aerobic rod-shaped bacterium, that is commonly found in water, soil, and plants (Norina and Raihan 2008). The bacterium generally does not cause infections in uncompromised individuals (Evans and Fleiszig 2013). In the healthy cornea, there are a number of defense mechanisms precluding infection that include antimicrobials such as β-defensins, cathelicidin LL-37, cytokeratin-derived antimicrobial peptides, and RNase7, and immunomodulators such as SP-D and ST2 Innate defenses of the cornea depend in part on MyD88, a key adaptor protein of toll-like receptors, and interpeukin-1R signaling (Evans and Fleiszig 2013). Severe infections with *P. aeruginosa* are typically seen in people who are immunocompromised or have preexisting conditions, such as cystic fibrosis and diabetes (Mulcahy *et al.* 2014). This bacterium is an important cause of

hospital infections. *P. aeruginosa* is one of the most common cause of pneumonia in cystic fibrosis patients in their second and third decade of life (Burns *et al.* 2001) and wound infections in burn victims (Mayhall 2003). Infection can also lead to sepsis, ecthyma gangrenosum, osteomyelitis, otitis externa, urinary tract infections, and skin infections.

In the cornea, *P. aeruginosa* may cause contact lens-related ulcers and keratitis (Pinna *et al.* 2008). The bacteria produce reactive oxygen species, toxins and proteases, and can alter host immune responses (Duran and Refojo 1987; Kandasamy *et al.* 2010; Hilliam *et al.* 2020). Secreted proteases can cause corneal liquefactive necrosis leading to corneal damage and ulcer formation (Kreger and Gray 1978). The bacteria's ability to form a biofilm allows irreversible surface adhesion. They adhere to contact lens surfaces more easily than many other pathogens (Marshall 1976). Treatment consists of antibiotics, most commonly fluoroquinolones and aminoglycosides. Emerging experimental therapies include cathelicidin peptides as adjuvants to vancomycin, topical flagellin (a ligand for toll-like receptor 5), and immunotherapeutics including monoclonal antibodies (Kumar *et al.* 2010; Mohammed *et al.* 2019; Hebert *et al.* 2020).

4. Autoimmune and Inflammatory Diseases

4.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease resulting in a chronic and painful inflammatory response, primarily in the joints. Manifestations of RA that are non-articular are present in 10–20% of diagnosed patients. Systemic chronic inflammation in this disease may also cause inflammatory ocular diseases, leading to scleritis and episcleritis (Zlatanović *et al.* 2010; Sainz de la Maza *et al.* 2012). In a clinical correlational study, over 80% of RA participants with inflammatory ocular disease had scleritis, episcleritis, and peripheral ulcerative keratitis, and 62% had uveitis (Caimmi *et al.* 2018). RA may also result in secondary Sjögren's syndrome, a severe ocular surface dryness due to desiccation or insufficient production of fluid or mucus in secretory glands as a result of the immune cell infiltration, which will negatively impact the eyes and ocular surface.

Therapy is still a major field of study as some mechanisms that cause RA are not fully understood. Rainsford *et al.* (2015) reviewed different treatments and pharmacological properties of hydroxychloroquine and chloroquine to aid in alleviating RA and related diseases. It was suggested that hydroxychloroquine and chloroquine are affecting MHC Class II expression and antigen presentation, and the production of pro-inflammatory cytokines like IL-1 and TNF-α, as well as controlling the generation of leucocyte reactive oxygen species. There are conclusive data supporting the efficacy and benefit of using systemic treatments in autoimmune disease to also resolve the ocular manifestations. Available treatments for RA include non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs (DMARD) including methotrexate, and various biologicals, such as TNF-α inhibitors, immunosuppressive drugs/antibodies inhibiting immune cell activity and pro-inflammatory interleukins (abatacept, rituximab, tocilizumab, sarilumab, cyclosporine A) and targeted synthetic DMARDs like Janus kinase inhibitors (Kaçmaz *et al.* 2009; Smolen *et al.* 2020). All of these treatments alleviate joint-related

symptoms and consequentially may treat some ocular manifestations such as conjunctivitis, scleritis, episcleritis, keratitis and more (Burmester and Pope 2017).

4.2. Sjögren's Syndrome

Sjögren's syndrome is a rheumatoid autoimmune disease in which the salivary and lacrimal glands are compromised due to infiltration of immune cells including CD4+ helper T cells, CD8+ cytotoxic T cells, B cells, plasma cells, macrophages, dendritic and mast cells resulting in an immune-mediated secretory dysfunction (Rischmueller *et al.* 2016; Srivastava and Makarenkova 2020). This is a reaction of immune system to autoantigens and cytokines released by the epithelium of affected glands (Srivastava and Makarenkova 2020). This disease may be classified as primary if it occurs without any pre-existing rheumatoid disease, or secondary if the disease arises as a result of another rheumatoid disease such as RA, systemic lupus erythematosus, or scleroderma (Hernández-Molina *et al.* 2010). In Sjögren's syndrome, the production of salivary, tear, and mucus secretions is inhibited, which detrimentally affects the ocular surface, because the dryness not only causes discomfort, but can also lead to corneal melt/perforation (Figure 5), uveitis, scleritis and more, due to the insufficient lubrication on the ocular surface promoting ulcers or inflammation, in addition to the internal ocular inflammatory response (Akpek *et al.* 2019).

Evaluations to diagnose Sjögren's syndrome based on ocular manifestations include Schirmer's test which measures the amount of tear production in a period of time, serological testing for SS-A/Ro antibodies, and histological exam of a labial salivary gland biopsy (Stefanski *et al.* 2017). Despite many therapies available, there is yet to be a cure found for this syndrome, possibly due to the heterogeneity of the disease pathology (Srivastava and Makarenkova 2020). A number of treatments symptomatically address the dry eye disease including topical tear substitutes (e.g., amino acid enriched sodium hyaluronate, cyclosporine A, serum tear drops), corticosteroids, hydroxychloroquine, secretagogues, fatty acids, immunosuppressive agents, scleral contact lenses, occlusion of lacrimal puncta surgery, and tarsorrhaphy (Aragona *et al.* 2013; Valim *et al.* 2015; De Paiva *et al.* 2019; Ramos-Casals *et al.* 2020). More recently, emphasis was put on biological therapies that suppress T and B cell activation (e.g., lifitegrast, rituximab, abatacept and belimumab) and are also used to treat RA and lupus (Perez *et al.* 2016; Ramos-Casals *et al.* 2020). Life expectancy is not reduced by Sjögren's syndrome; however, quality of life rapidly diminishes in patients who experience blurred vision, eye fatigue, and difficulty reading, in addition to all the other symptoms, regardless of having perfect visual acuity.

This autoimmune disease can also cause LSCD. Samoila and Gocan (2020) reviewed the clinical outcomes of transplanting cultivated allogeneic stem cells *vs.* oral mucosa epithelial cells in the total bilateral stem cells deficiency. Results suggest that autologous oral mucosa epithelial cells have some advantages over cultivated allogeneic limbal stem cells due to low or no risk of immune activation and no need to use immunosuppression. However, oral mucosa epithelial cells may entail a risk of persistent epithelial defects and graft failure, as compared to cultivated allogeneic limbal stem cells. Stem cell transplantation may be recommended in cases of severe disease with LSCD.

4.3. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that causes inflammation of the joints, produces sensitive skin rashes and may even cause severe organ failure involving the kidneys, lungs, or damage to the central nervous system (Oates *et al.* 2003). SLE is a multi-factorial disease, which may develop from both endogenous genetic or immunoregulatory causes and exogenous acquired factors such as epigenetics, environmental and infectious diseases (Esen *et al.* 2012). Patients with SLE also have the risk of ocular manifestations such as disrupted mucocutaneous membranes and tissues, and of secondary diseases such as RA and Sjögren's syndrome that lead to severe dry eye and can also cause retinal vascular and neuroophthalmic disease (Sivaraj *et al.* 2007). Ocular manifestations as a result of inflammatory responses include cataracts, keratoconjunctivitis sicca, glaucoma, discoid lesions of eyelids, episcleritis, scleritis, keratitis, and uveitis. Such ocular involvements were observed in 29 out of 98 SLE-diagnosed participants of a clinical study, and 20 out of those 29 had more than one ocular involvement (Dammacco *et al.* 2018).

Proinflammatory cytokines such as IL-17 and IL-23 are found in abundance in tear samples of patients with autoimmune diseases (Oh *et al.* 2011). This makes such genes a target for gene therapy since expression studies and clinical trials suggest that inhibition of IL-17 be a promising therapeutic approach for SLE (Koga *et al.* 2019). Research regarding significantly higher IFN-α activity in SLE-patients suggests that it is a heritable factor and may play a role in the development of the disease (Niewold *et al.* 2007; Lyn-Cook *et al.* 2014) Immunosuppressive treatments that target inflammation, which is the main cause of other manifestations at the ocular surface, include non-steroidal anti-inflammatory agents, anti-malarial drugs such as hydroxychloroquine, immunosuppressants like commonly used methotrexate and azathioprine, and biological drugs like belimumab and rituximab (Prados-Moreno *et al.* 2017; Felten *et al.* 2018; Plantone and Koudriavtseva 2018). These systemic SLE treatments will often have a beneficial effect on ocular manifestations of inflammation and secondary complications, but more investigations are needed to target the root causes of SLE.

4.4. Gout

Gout is a type of inflammatory arthritis that affects over nine million people in the United States, mostly middle-aged men and postmenopausal women (Singh *et al.* 2019). It is due to increased level of uric acid in the body that results in the accumulation of monosodium urate (MSU) crystals mainly in the joints. Subsequently, MSU crystals trigger an inflammatory cascade releasing pro-inflammatory cytokines, IL-1β, IL-6, and TNF-α (Dalbeth and Haskard 2005). Symptoms include pain, redness, warmth, swelling, and reduced range of motion in the affected joints. Gout is often associated with metabolic diseases such as obesity, hypertension, diabetes, and cardiovascular disease (Singh *et al.* 2011). Ocular abnormalities include gout keratitis in the cornea, scleritis, optic neuritis, glaucoma, and retinal hemorrhages and thrombosis (Sharon and Schlesinger 2016). Deposition of MSU crystals (tophi) have been reported in the cornea and conjunctiva in rare cases (Sarma *et al.* 2010; Lin *et al.* 2013; Lo, Broocker, and Grossniklaus 2015). Kösekahya *et al.* (2019) found that corneal endothelial function was impaired in gout patients, which was directly corelated

to the duration of disease and uncontrolled uric acid levels. This may affect endothelial stability and increase corneal thickness by reducing Na,K-ATPase pump activity. Symptoms associated with gout can be treated with nonsteroidal anti-inflammatory drugs, oral and intravenous corticosteroids, colchicine, and diet modification by decreasing the consumption of foods high in purines (Hainer *et al.* 2014).

4.5. Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is a non-infectious allergic inflammatory disease associated with atopic dermatitis. Environmental allergens contribute to immune system dysregulation with the involvement of mast cells, T-cells, eosinophils and basophils to cause atopic dermatitis, and subsequently, AKC. Typically, AKC starts in the early teens and can continue until the late 50s. It is marked by itching, redness, and burning of the eyes, eczema of the eyelids, blepharitis along the lid margin, conjunctival inflammation, excessive tear production, and corneal complications (Bielory and Bielory 2010; Chen *et al.* 2014). Both pro- and anti-inflammatory cytokines such as IFN-γ, TNF-α, IL-2, IL-4, and IL-10 have been reported to be elevated in the tears of AKC patients (Calder *et al.* 1999). Corneal complications arise from the exposure to inflammatory factors and lead to punctate keratitis and corneal erosions. More severe cases present with corneal ulcerations, edema, epithelial defects, neovascularization, and scarring that will eventually lead to blindness (Power *et al.* 1998; Messmer *et al.* 2002; Tanaka *et al.* 2004; Chen *et al.* 2013; Zemba *et al.* 2016; Jan *et al.* 2020). AKC patients show significantly lower basal epithelial cell density as compared to control eyes (Hu *et al.* 2008). Histopathologic investigations also revealed the presence of major basic protein, a cytotoxic eosinophil granule protein that impairs epithelial cell migration and proliferation, resulting in corneal erosions (Messmer *et al.* 2002; Utine *et al.* 2018).

Therapies for AKC are aimed at reducing eyelid, conjunctival, and corneal inflammation. Mast cell stabilizers, antihistamines, corticosteroids, and calcineurin inhibitors are the most commonly prescribed drugs for AKC. Mast cell stabilizers such as topical nedocromil sodium and sodium cromoglycate prevent the release of inflammatory mediators from mast cells and efficiently decrease inflammation but need re-application (Castillo *et al.* 2015). Antihistamines that block either or both H1 and H2 receptors are topically applied to reduce itching, redness, and eyelid swelling (Castillo *et al.* 2015; Ridolo *et al.* 2019). In severe cases of AKC with unsuccessful treatment with mast cell stabilizers and antihistamines, systemic and topical corticosteroids are recommended, but patients may develop serious side effects with long-term use such as increased risk of developing diabetes, glaucoma, and cataract (Jones and Rhee 2006; Penfornis and Kury-Paulin 2006; Pilkey *et al.* 2012; Rice *et al.* 2017; Kačmař and Cholevík 2019). To prevent such adverse lasting effects, immunosuppressive calcineurin inhibitors are considered. Ophthalmic suspension of 0.1% tacrolimus has been effective for the treatment of AKC in patients that do not respond to standard care (Yazu *et al.* 2019; Benaim *et al.* 2019). Studies have also demonstrated the effective use of topical 0.05% cyclosporin to reduce AKC-associated inflammation (Akpek *et al.* 2004).

4.6. Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a bilateral, chronic allergic inflammatory condition that affects the conjunctiva and the cornea during the warm seasons. Unlike AKC, disease onset is typically earlier in life between the ages of 8–12 years. Symptoms include palpebral and limbal conjunctivitis, itching, redness, photophobia, mucosal discharge along the palpebral conjunctiva, blurred vision, and foreign body sensation (Wong 1999). As with AKC, VKC is also caused by T cell-mediated hypersensitivity reaction resulting in hyperproduction of IgE and activation of eosinophils and mast cells (Leonardi 2013). Although conjunctival inflammation is the hallmark of VKC, visual loss occurs due to corneal complications often seen in the perennial form of the disease. Eosinophil secretions such as major basic protein and eosinophilic cationic protein (ECP), as well as other inflammatory cell secreted factors such as MMP-2, MMP-9, TGF-β1, FGF, and EGF cause corneal epithelial, BM, and stromal damage (Kumagai *et al.* 2006; Leonardi 2013; Feizi *et al.* 2020). 3–20% of VKC patients develop shield ulcers as a result of continuous untreated epithelial erosions and keratopathy that can further lead to plaque formation from protein and mucin secretions on the stroma (Cameron 1995; Arif *et al.* 2017). Other corneal manifestations include the more common keratoconus with corneal ectasia, corneal hydrops, and decreased corneal thickness observed in several VKC patients (Cameron *et al.* 1989; Totan *et al.* 2001; Feizi *et al.* 2020), and rare LSCD observed in 1.2% of cases (Sangwan *et al.* 2011). Patients with VKC showing a clinical evidence of LSCD revealed a presence of goblet cells in the cornea (Saboo *et al.* 2013).

Like in AKC, antihistamines such as H1 receptor blockers, and mast cell stabilizers are the first line of treatment for VKC (Leonardi 2013). In severe cases unresponsive to antihistamines, corticosteroids may be cautiously prescribed due to severe adverse effects including diabetes and infectious keratitis. Calcineurin inhibitors such as cyclosporine A and tacrolimus that block Th2 lymphocyte proliferation and IL-2 and IL-5 production have been used for the treatment of VKC with no serious side effects (Pucci *et al.* 2002; Keklikci *et al.* 2008; Leonardi 2013). Topical cyclosporine (0.05%) has been effectively used for the resolution of shield ulcers (Westland *et al.* 2018). In severe cases of vernal shield ulcers, surgical interventions have been considered. Complete debridement of shield ulcer and plaque with multilayered amniotic membrane transplantation have been successfully performed (Sharma *et al.* 2018). Cameron *et al.* (1995) reported the removal of central corneal lesions and inflammatory plaques by excimer laser phototherapeutic keratectomy (PTK), with rapid re-epithelialization. For VKC associated keratoconus, corneal cross-linking is effective (Abozaid *et al.* 2019; Alrobaian *et al.* 2019). Management and treatment of VKC was previously reviewed in more details (Leonardi 2013; Feizi *et al.* 2020).

4.7. Multiple Sclerosis

Multiple Sclerosis (MS) affects between 300,000 and 400,000 in The United States (Wallin *et al.* 2019). It is a demyelinating central nervous system disease and thought to be an autoimmune disorder (Graves and Balcer 2010). Alterations of vision are common in the affected individuals; about 50% of patients develop optic neuritis (Graves and Balcer 2010). This disorder mainly affects the retina and optic nerve but recently, corneal abnormalities have also been documented. Using *in vivo* corneal confocal microscopy, it was shown that

MS results in significant reduction of corneal nerve fiber density, as well as branch density and length with axonal loss (Bitirgen *et al.* 2017; Mikolajczak *et al.* 2017; Petropoulos *et al.* 2017). There is also conflicting evidence about the changes in epithelial dendritic cell density (Bitirgen *et al.* 2017; Testa *et al.* 2020). These changes suggest corneal neuropathy development in MS, reminiscent of DCN. The mechanisms of these alterations as well as possible changes in corneal nerve myelination in MS remain to be established.

4.8. Granulomatosis with polyangiitis

Granulomatosis with polyangiitis is a rare, idiopathic, multisystem inflammatory disease characterized by necrotizing granulomatous inflammation and vasculitis. It mainly affects the upper and lower respiratory tract, lungs, and the kidney, but also the central nervous system, skin, joints, and the eye (Weeda and Coffey 2008). Ocular involvement is seen in 20–66% of patients with symptoms that include proptosis (it can provoke exposure keratopathy), conjunctivitis, scleritis, keratitis, dacryoadenitis, uveitis, optic nerve vasculitis, and retinal artery occlusion (Leavitt and Butrus 1991; Weeda and Coffey 2008; Almouhawis *et al.* 2013; Keorochana *et al.* 2017; Sfiniadaki *et al.* 2019). In the cornea, peripheral ulcerative keratitis (PUK) is a common feature of the disease. It is due to the presence of autoantibodies and inflammatory cells from limbal blood vessels (Messmer and Foster 1999; Ebrahimiadib *et al.* 2016; Lu *et al.* 2016; Cao *et al.* 2017). PUK is commonly unilateral but in up to 40% of patients may be bilateral and often associated with scleritis. Other corneal problems include peripheral keratitis without ulceration, peripheral corneal thinning, and more rarely, interstitial keratitis (Sfiniadaki *et al.* 2019). Reynolds *et al.* (1999) have shown that cytokeratin 3, a corneal epithelial-specific keratin, is an autoantigen associated with PUK in patients with this condition. Limbal edema and corneal defects with thinning have also been observed in some cases (Hood and Lowder 2010; Reddy *et al.* 2011). Similar to other systemic inflammatory diseases, corticosteroids (topical for eye problems) and immunosuppressive drugs are the main form of treatment that have increased patient survival to 95% at 5 years and 80% at 10 years. More recently, monoclonal antibodies to TNF-α and CD20 have also shown efficacy against scleritis and PUK (Weeda and Coffey 2008; Sfiniadaki *et al.* 2019).

4.9. Sarcoidosis

Sarcoidosis is an inflammatory granulomatous disease that affects the lung, mediastinal lymphatic system, skin, and the eye. It is characterized by the formation of non-caseating, giant cell granulomas with T lymphocyte and macrophage involvement (Salah *et a*l. 2018). Ocular manifestations are presented in 20–50% of the cases and include scleritis, keratitis, uveitis, retinitis, dry eye, and conjunctival nodules (Heiligenhaus *et al.* 2011; Pasadhika and Rosenbaum 2015). In the cornea, there is small nerve fiber loss and damage due to decreased nerve fiber density (Dahan *et al.* 2013). One case report documented interstitial keratitis with posterior uveitis and optic nerve edema (Lennarson and Barney 1995), whereas another study reported peripheral ulcerative keratitis that progressed to corneal perforation (Siracuse-Lee and Saffra 2006). In some cases, patients show band keratopathy caused by calcium deposits in the Bowman's layer (Crick *et al.* 1961). A multilobular, nodular, perilimbal mass has also been reported in a 16-year girl as a manifestation of sarcoidosis (Hegab *et al.* 1998). Treatment for ocular sarcoidosis includes topical and systemic

corticosteroids to manage inflammation. In patients that are intolerant to corticosteroids, immunosuppressive anti-metabolites and calcineurin inhibitors have been considered (Pasadhika and Rosenbaum 2015).

4.10. Cogan's Syndrome

Cogan's syndrome is a rare autoimmune disorder that is characterized by systemic vasculitis of unknown etiology, and inflammation in the eye and the inner ear. Autoantibodies to a corneal antigen can be isolated from patients (Iliescu *et al.* 2015). Ocular symptoms include redness, irritation, photophobia, excessive tear production, and diminished visual acuity (Iliescu *et al.* 2015). Bilateral interstitial keratitis is the most common manifestation of the disease (Belhoucha *et al.* 2014). Other corneal findings involve bilateral peripheral subepithelial keratitis with faint, nummular lesions and deep stromal keratitis in some cases (Cobo and Haynes 1984). In other cases, irregular, granular corneal infiltration in the posterior cornea near the limbus was described (Grasland *et al.* 2004). Corticosteroids are usually the first line of treatment, followed by immunosuppressive agents if needed (Iliescu *et al.* 2015).

4.11. Immunobullous Diseases

Immunobullous diseases, also known as autoimmune blistering diseases, are a group of conditions caused by specific autoantibodies that bind to epithelial cells, resulting in blistering lesions on the skin, mucous membrane, and oral cavity by affecting the cell-cell and cell-matrix adhesion (Otten *et al.* 2014; Witte *et al.* 2018). They mainly include pemphigus, mucous membrane pemphigoid, epidermolysis bullosa acquisita, and linear IgA disease, among others.

Pemphigus is characterized by the presence of autoantibodies on skin keratinocytes that react to desmosomal component desmoglein. It comprises three forms, pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus (Buonavoglia *et al.* 2019). Ocular involvement is rare, and mainly includes non-cicatrizing bilateral conjunctivitis, blepharitis, dry eye, photophobia, redness, and tearing (Tan *et al.* 2015; Buonavoglia *et al.* 2019). Corneal abnormalities are observed only in paraneoplastic pemphigus with punctate epithelial erosions, bilateral corneal perforations, and corneal melting (Beele *et al.* 2001; Tam *et al.* 2009; Venkateswaran *et al.* 2020). Mucous membrane pemphigoid is triggered by autoantibodies to bullous pemphigoid (BP) 180, BP230, laminin-332, and the β4 subunit of α6β4 integrin on the epithelial BM. It causes blistering skin lesions and scarring along with conjunctivitis (Carey and Setterfield 2019). *In vivo* confocal microscopy revealed decreased corneal nerve density and elevated inflammatory dendritic cell density along with metaplasia of the corneal epithelial layers, intraepithelial defects, anterior stromal fibrosis, and hyperreflective endothelial deposits in patients with non-end-stage disease, whereas end-stage disease patients showed corneal neovascularization and scarring (Tepelus *et al.* 2017).

Epidermolysis bullosa acquisita (EBA) is mediated by autoantibodies to collagen type VII causing vesicle and bullae formation on the skin and mucous membrane erosions. Ocular features include severe cicatrizing conjunctivitis and scarring, symblephara formation, and abnormal positioning of the eyelashes (Kridin *et al.* 2019). In some cases, corneal

involvement resulting in blindness has been reported with lesions, peripheral perforation, and advanced thinning (Dantas *et al.* 2001; Rousseau *et al.* 2020).

Linear IgA disease is a sub-epidermal blistering disease marked by linear deposits of BM IgA antibodies (Venning 2011). Like EBA, linear IgA disease also causes lesions associated with bullae or vesicles and presents with similar symptoms as other immunobullous diseases, such as dry eye, conjunctivitis and scarring, photophobia, foreign body sensation, and abnormal positioning of the eyelashes. For this reason, diagnosis must be confirmed with a skin biopsy showing linear IgA deposits between the dermis and epidermis (Aultbrinker *et al.* 1988; Ramos-Castellón *et al.* 2010). Cicatrizing conjunctivitis can lead to corneal perforation with epithelial defects, opacification, and superficial vascularization (Smith *et al.* 1999; Ramos-Castellón *et al.* 2010).

Topical and systemic therapies for treating immunobullous diseases have been reviewed in detail (Buonavoglia *et al.* 2019; Kridin *et al.* 2019). Corticosteroids as well as immunosuppressive drugs such as azathioprine, mycophenolate mofetil, and methotrexate are routinely used. Neutrophil targeting drugs like colchicine and dapsone have been prescribed to EBA patients, alone or in combination with immunosuppressants or corticosteroids (Hughes and Callen 2001; Kim *et al.* 2011; Adachi *et al.* 2016). Anti-CD20 antibody rituximab has also been tested (Kim et al. 2012; Herbert and Joly 2018; Lamberts *et al.* 2018). However, patients with linear IgA disease have been less responsive to rituximab, possibly due to continuous IgA-secreting B-cell population that is resistant to anti-CD20 therapy (Pinard *et al.* 2019; He *et al.* 2015).

5. Genetic Corneal Deposit Disorders

5.1. Wilson’s Disease

Wilson’s disease, also known as hepatolenticular degeneration is a rare autosomal recessive disease that results in excessive copper accumulation due to impaired copper metabolism (Ala *et al.* 2007). It is due to a mutation in the copper transporting gene encoding Wilson disease protein, or *ATP7B* on chromosome 13, and primarily affects the liver, but also the brain, cornea, and kidney (Bull *et al.* 1993; Petrukhin *et al.* 1993). In the cornea, this disease presents in the form of sunflower cataracts and Kayser-Fleischer ring (Figure 6) caused by the deposition of copper in the anterior capsule and Descemet’s membrane, respectively (Goel *et al.* 2019). Kayser-Fleischer ring appears as a reddish/greenish band of 1–3 mm in width, starting with an arc in the superior pole, followed by an arc in the inferior pole, and eventually forms a ring around the cornea (Ellis 1969; Suvarna 2008). These rings are detected by a slit lamp examination but can also be visible to the naked eye. Recently, anterior segment optical coherence tomography has been suggested for early detection as angle view is obscured by the corneal limbus during the early stages of the disease (Sridhar *et al.* 2017; Broniek-Kowalik *et al.* 2019). Apart from the Kayser-Fleischer ring, individuals with Wilson’s disease also show low blood ceruloplasmin levels (< 10 mg/dl) and other neurological symptoms, mainly affecting motor functions (Bandmann *et al.* 2015). Wilson’s disease can be managed with a low-copper diet and treated with chelating agents such as D-penicillamine (Van Caillie-Bertrand *et al.* 1985; Hedera 2019).

5.2. Cystinosis

Cystinosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *CTNS* gene that encodes the protein cystinosin, resulting in intracellular accumulation of cysteine crystals in several organs, including the kidney, liver, spleen, eye, bone marrow, pancreas, thyroid, muscle, and brain (Nesterova and Gahl 2012). It is diagnosed by measuring leucocyte cysteine levels (de Graaf-Hess, Trijbels, and Blom 1999; Levtchenko *et al.* 2004). There are three forms of cystinosis; infantile, adolescent, and adult, with the infantile form being the most severe (David *et al.* 2019). In the infantile form, cystinosis is the most common cause of Fanconi syndrome with impaired reabsorption in the proximal renal tubule. Polyuria, growth retardation, rickets, and progressive renal failure are other manifestations of infantile cystinosis that can be managed by dialysis and kidney transplantation (Nesterova and Gahl 2008; David *et al.* 2019). The adolescent form is less severe, whereas the adult form is benign and asymptomatic.

Ocular indicators include corneal cysteine crystals and photophobia, which is seen in all three forms of cystinosis (Biswas *et al.* 2018). Corneal crystals appear at the periphery and progress centripetally over time. They do not affect visual acuity until the crystals reach the central cornea. Foreign body sensation and inflammatory symptoms of recurrent corneal erosions are also reported when cysteine crystals enter the Bowman's layer (Anikster *et al.* 2000; Fung *et al.* 2007; Tsilou *et al.* 2007). Beside the corneal involvement, deposition of cysteine crystals was also observed in the conjunctiva, iris, ciliary body, choroid, fundus, and optic nerve (Tsilou *et al.* 2007). A large cross-sectional study has reported that 75% patients aged 20–29 and 87% of patients over the age of 30 years with cystinosis showed anterior segment involvement separate from the corneal and conjunctival crystal deposits (Tsilou *et al.* 2002). Treatment mainly consists of oral cysteamine, however, topical administration of 0.5% cysteamine is required to effectively dissolve corneal crystals and reduce symptoms of photophobia (Iwata *et al.* 1998; Sham *et al.* 2014).

5.3. Fabry Disease

Fabry disease is an X-linked disorder caused by a deficiency of α-galactosidase enzyme due to mutations of the *GLA* gene, resulting in lysosomal accumulation of glycosphingolipids, mainly globotriaosylceramide over time (Schiffmann 2015). It affects both males and heterozygotic females but to a lesser extent (El-Abassi *et al.* 2014). Although the disease manifests at an early age, it usually remains undiagnosed until adulthood (Mastropasqua *et al.* 2006). Symptoms range from pain in arms and legs, reddish-purplish blemishes on the skin, and decreased sweating to myocardial infraction, stroke, and renal failure (El-Abassi *et al.* 2014).

Cornea verticillata (vortex keratopathy) is the most common ocular finding of this disease, which shows white or golden-brown whorl-like pattern of epithelial and subepithelial deposits in the cornea (Figure 7). It is reported to be more pronounced in affected females, although it is observed in both male (74%) and female carriers (66%) (Samiy 2008). Pitz *et al.* (2015) also demonstrated that ocular signs correlated well with disease severity, and patients with cornea verticillata appeared to have more severe disease than those without it. The group further reported that the prevalence of cornea verticillata was significantly higher

in patients with null (male, 76.9%; female, 64.5%) and missense (male, 79.2%; female, 67.4%) mutations as compared to patients with mild missense (male, 17.1%; female, 23.1%) and the p.N215S (male, 15.0%; female, 15.6%) mutations (Pitz *et al.* 2015). Apart from cornea verticillata, patients also show conjunctival vessel tortuosity, corneal haze, lens opacity, retinal vessel tortuosity, anterior and posterior cataracts (Kalkum *et al.* 2016; Michaud 2019). Treatment for Fabry disease involves enzyme replacement therapy (ERT) with agalsidase α/Replagal and agalsidase β/Fabrazyme (Sirrs *et al.* 2014; Spada *et al.* 2019). ERT resulted in a decrease in globotriaosylceramide levels in the blood and reduced pain and the risk of other adverse effects such as renal failure and cardiac death (Schiffmann *et al.* 2003; Banikazemi *et al.* 2008; Rombach *et al.* 2014). ERT is also supplemented with other supportive medications such as angiotensin-converting enzyme (ACE) inhibitors, statins, and aspirin (Sirrs *et al.* 2014).

5.4. Meretoja's Syndrome

Meretoja's syndrome, also known as familial amyloidosis Finnish type, or lattice corneal dystrophy type II, is a rare inherited autosomal dominant disease caused by mutations in the gelsolin gene (*GSN*) at chromosome 9q32–34. This mutation results in the substitution of asparagine by aspartate at residue 187 leading to extracellular amyloid deposition in several tissues such as cornea, skin, vascular walls, and perineurium (Casal *et al.* 2017; Friedhofer *et al.* 2017). Clinical manifestations have late onset, often appearing only between the third and fifth decades of life (Kiuru 1992). Corneal lattice dystrophy is often the first sign of the disease in most cases, although it is not considered a dystrophy anymore as it is caused by systemic amyloidosis (Nikoskinen *et al.* 2015; Friedhofer *et al.* 2017). Lattice formation is due to amyloid deposits under the Bowman's layer, mainly in the anterior stroma resulting in subepithelial opacities (Kivelä *et al.* 1993; Huerva *et al.* 2007). Systemic features include facial paralysis, polyneuropathy, skin fragility, and hair loss (Casal *et al.* 2017; Carrwik and Stenevi 2009; Cabral-Macias *et al.* 2020). Facial paralysis and polyneuropathy lead to corneal ulcers, recurrent corneal erosions, and dry eye due to impaired eyelid closing and cranial nerve involvement. Patients with Meretoja syndrome also suffer from photophobia, dysfunction of the meibomian glands, early development of cataract, and higher risk of open-angle glaucoma (Kiuru, 1992; 1998; Carrwik and Stenevi, 2009; Starck *et al.* 1991). However, the mutated *GSN* gene in the trabecular muscle cells, but not the amyloid deposition appears to be responsible for increased intraocular pressure (IOP) in these patients (Kiuru, 1998).

Currently, there is no cure for Meretoja's syndrome, and the treatment is mostly symptomatic. As most complications are ocular, ophthalmologists play an important role in the management and treatment of the symptoms. Eye examination, eyelid function test, and IOP measurements are highly recommended at regular intervals. In some cases, plastic surgery is considered for facial paralysis and impaired eyelid closure, which in turn also helps alleviate corneal abnormalities (Pihlamaa *et al.* 2011; Friedhofer *et al.* 2017). Pressure reducing topical treatments and lubricating eyedrops are prescribed to control the IOP and dry eye syndrome, respectively; however, care must be taken that they do not contain preservatives, as patients show low tolerance to preservatives. Keratoplasty is required for patients with vision loss due to amyloid deposits, although this will only prolong the natural

process of the disease (Carrwik and Stenevi 2009). Phototherapeutic keratectomy (PTK) is performed to treat corneal opacities; however, it has been reported to cause delayed epithelial healing, and requires close monitoring until the epithelium is fully healed, to avoid ulceration, scarring, and infection (Das *et al.* 2005; Lee *et al.* 2018). Moreover, recurrence of the disease after PTK is a possibility, and may need retreatment (Dinh *et al.* 1999).

5.5. Mucopolysaccharidosis

Mucopolysaccharidosis (MPS) is a group of lysosomal storage disorders characterized by the accumulation of glycosaminoglycans (GAG) in bone, cartilage, tendons, cornea, skin, and connective tissue. It is due to inborn errors of GAG metabolism (Wraith *et al.* 1995). Seven different subtypes of the disease have been identified based on the enzyme defect with varying symptoms and severity (Ashworth *et al.* 2006; Khan *et al.* 2017). Ocular manifestations include corneal clouding, retinopathy, glaucoma, and optic nerve abnormalities (Del Longo *et al.* 2018). Corneal clouding is caused by increasing keratocyte size, the displacement of collagen fibrils, and progressive accumulation of GAG that appears as yellowish-grey granules deposited in all layers of the cornea, but mainly in the stroma (Fahnehjelm *et al.* 2012). Severity of corneal clouding has been reported to correlate with an increase in age and it subsequently results in loss of visual acuity (Couprie *et al.* 2010).

Evaluation of corneal transparency and corneal thickness by slit-lamp examination and optical coherence tomography (OCT), respectively, can be useful in the diagnosis of MPS. Several therapeutic approaches have been tested in different MPS subtypes including ERT, hematopoietic stem cell transplantation (HSCT), and gene therapy to replace or restore normal functional enzyme. In ERT, the enzymes are delivered to the lysosome by binding to the mannose-6-phosphate (M6P) receptors on the cell surface. Intravenous ERT has been effectively used for treating MPS I, MPS II, MPS IV, and MPS VI in visceral organs (Muenzer *et al.* 2002; Tomatsu *et al.* 2015; Brunelli *et al.* 2016; da Silva *et al.* 2016; Jameson *et al.* 2019). However, due to short half-life of the enzyme and its inability to cross the blood-brain barrier, there is limited penetration in the cornea, brain, bone, and heart, and hence, which renders it ineffective in alleviating symptoms in these tissues (Chen *et al.* 2019). Furthermore, patients require weekly and bi-weekly treatment that makes it considerably more expensive. Patients may also develop antibodies to the infused enzyme, resulting in an immune response that can block its effect (Ponder 2008). HSCT has been used for the treatment of MPS types I, II, IVA, VI, and VII and comprises transplantation of healthy donor cells. Unlike ERT, where only the deficient enzyme is infused that circulates with a short half-life, HSCT involves the circulation of the donor stem cells in the bloodstream (Taylor *et al.* 2019). HSCT is a one-time procedure, but finding an acceptable donor makes it a lengthy process (Noh and Lee, 2014) and has not shown any success in the treatment of corneal clouding (Guffon *et al.* 1998).

Gene therapy has shown promising results in restoring normal enzyme function in the cornea. Kamata *et al.* (2001) have reported that adenoviral injection of gene expressing human β-glucuronidase into the anterior chamber or intrastromal region of the cornea successfully treated corneal clouding of MPS VII in mice. Corneal clouding was also reduced in a model of canine MPS VII (Serratrice *et al.* 2014). Transduction of the gene

encoding α-L-iduronidase (IUDA) *via* recombinant adeno-associated virus restored IUDA function in the cornea (Vance *et al.* 2016).

5.6. Hyperlipoproteinemia

Hyperlipoproteinemia is characterized by elevated levels of lipids and lipoproteins in the blood, mainly cholesterol (hypercholesterolemia). Diabetes, atherosclerosis, hypertension, and cardiovascular disease are comorbidities associated with hyperlipoproteinemia. Ocular manifestation is often the first sign of the disease involving the deposition of lipids in the cornea and limbus, known as corneal arcus or arcus senilis (Crispin, 1989; 2003; Hayasaka *et al.* 1989). It is a white, yellowish-grey ring in the corneal periphery caused by lipid infiltration of the stroma that does affect vision. Corneal arcus can also be a sign of familial hypercholesterolemia in children (Lock *et al.* 2019). Clinically, corneal arcus is asymptomatic and does not require specific therapy but can be improved by treating the underlying hyperlipidemia (Munjal and Kaufman 2020).

6. Other Genetic Disorders Presenting Corneal Manifestations

6.1. Aniridia

Aniridia is characterized by the absence of iris and may be an isolated ocular complication or associated with a syndrome. Usually, both eyes will have no iris, and the abnormality is mostly a result of a haploinsufficiency truncating mutation in the *PAX6* gene, congenitally, and by ocular injury (Wawrocka and Krawczynski 2018). Aniridia is co-related with WAGRO syndrome, which stands for Wilms tumor, aniridia, genitourinary anomalies, mental retardation, and obesity. As mentioned, WAGRO syndrome is caused by a deletion on chromosome 11(11p) where the *PAX6* gene is located. A proportion of deletion will often include several other genes, some of which include Wilms tumor gene (*WT1*) at location 11(13p) that mediates nephroblastoma development especially in children, and brain-derived neurotrophic factor gene (*BDNF*) at location 11(14.1p), which is the known candidate gene for obesity (Van Heyningen *et al.* 2007; Han *et al.* 2008; Ferreira *et al.* 2019).

Aniridia-associated keratopathy (AAK) causes damage to the cornea as a result of genetic factors described above, and may be also associated with dry eye due to meibomian gland dysfunction. It is linked to alterations of the epithelial phenotype with progressive conjunctivalization due to LSCD, decreased subbasal nerves, and invasion of immune cells (Lagali *et al.* 2018). In a recent study where 275 eyes were characterized based on corneal abnormalities from congenital aniridia, 13% of participants had central corneal opacity at birth, whereas 25% developed AAK with age (Lee *et al.* 2018). Most corneal damage associated with aniridia is related to the mutation of *PAX6* gene as it is correlated to corneal blindness via LSCD and secondary glaucoma (Käsmann-Kellner *et al.* 2018). Change or damage of limbal epithelial palisades of Vogt in AAK causes ocular surface defects at different stages (Voskresenskaya *et al.* 2017). Latta *et al.* (2018) identified proteins that may be regulated by *PAX6* and showed that *SPINK7* mRNA, coding for a serine peptidase inhibitor, is downregulated in patients as well as in primary aniridia cell model. The results suggest that *PAX6* gene controls corneal epithelial differentiation of retinoic acid signaling processes through ADH7 and ALDH1A1. Additionally, altered regulation in miR and

mRNA levels supports that the conjunctiva in aniridia is maintained in pro-angiogenic and proliferative state, which mediates *PAX6* mutation-related neovascularization (Latta *et al.* 2020). Downstream signaling in AAK is also altered, with suppression of Notch1 pathway but activation of Wnt pathways, both canonical and non-canonical, and Sonic hedgehog pathway (Vicente *et al.* 2018).

There is currently no cure for aniridia as it is mostly caused by LSCD, but in some cases limbal stem cell transplantation (LSCT) and Boston keratoprosthetics (KPro) done on patients at severe stages (III-Va) of AAK and LSCD resulted in significant improvement of visual acuity (Yazdanpanah *et al.* 2020). Management for aniridia may also include iris reconstruction by implanting an iris prosthesis (Mostafa *et al.* 2018). Although this is typically done for patients who have aniridia as a result of cataract, it may be a step towards AAK management. Gene therapy tools such as the CRISPR/Cas 9 system may be able to supply recombinant PAX6 protein as an efficient therapeutic approach for treating AAK (Roux *et al.* 2018). Anterior segment optical coherence tomography and *in vivo* confocal microscopy may be good diagnostic tools to monitor limbal stem cell progenitors and corneal epithelial changes in AAK (Voskresenskaya *et al.* 2017).

6.2. Ehlers-Danlos Syndromes

Ehlers-Danlos syndrome (EDS) is a group of genetic disorders caused by mutations in genes encoding fibrillar collagens. It comprises thirteen subtypes based on the affected gene with a wide range of musculoskeletal defects (Malfait *et al.* 2017). Corneal manifestations are seen mainly in brittle cornea syndrome (BCS), an autosomal recessive disorder caused by mutations in the genes *ZNF469* or *PRDM5* that play a role in corneal and extracellular matrix development, respectively (Walkden *et al.* 2019). Corneal problems involve thinning with central corneal thickness measuring often < 400 μm, which can subsequently cause keratoconus, keratoglobus, and high myopia. Loss of structural integrity can result in spontaneous rupture of these corneas that leads to vision loss (Burkitt Wright *et al.* 2013; Wan *et al.* 2018). There is also an increased risk for retinal detachment in these patients (Christensen *et al.* 2010). Non-ocular features of BCS include hyper-elasticity in skin and hearing impairment (Walkden *et al.* 2019). Significantly thinner and steeper corneas compared to the controls are also observed in some cases of classic EDS with mutated type V collagen genes, either *COL5A1* or *COL5A2* (Villani *et al.* 2013). Early diagnosis of BCS is important to prevent ocular rupture. However, due to its rarity and non-specific systemic symptoms BCS is often underdiagnosed, which may hamper proper disease management. Protective glasses have been prescribed to protect the corneas from thinning and perforation (Walkden *et al.* 2019). In some cases of progressive BCS, surgery is recommended including epikeratoplasty (host corneal epithelium is replaced with donor corneal disc) and penetrating keratoplasty (Kanellopoulos and Pe 2005). Collagen cross-linking was also tested to treat keratoconus with varying results (Caporossi *et al.* 2010; Caporossi *et al.* 2012; Kaufmann *et al.* 2015).

6.3. Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant connective tissue disease caused by mutations in the fibrillin-1 gene (*FBN-1*) located on chromosome 15q15–21 (Yuan and Jing

2010). Fibrillin is the major component of 10 to 12 nm microfibrils. It plays a critical role in maintaining elasticity and contributes to the force-bearing capacity of ocular connective tissue (Robinson and Godfrey 2000). MFS is characterized by skeletal, cardiovascular, and ocular manifestations. Displacement of the crystalline lens from its normal location, known as ectopia lentis, is the main ocular feature of MFS (Bitterman and Sponseller 2017). Other abnormalities include flattened cornea, astigmatism, increased axial length, iris and ciliary body hypoplasia, and retinal detachment (Esfandiari *et al.* 2019). In a prospective case series, Sultan *et al.* (2002) reported decreased keratometry and pachymetry scores indicating flattening of the cornea and corneal thinning, respectively, in MFS patients as compared to control subjects. *In vivo* confocal microscopy also confirmed corneal thinning and showed opaque stromal matrix with an increased light backscattering in the stroma. Moreover, MFS patients also show increased corneal astigmatism associated with lens dislocation (Konradsen *et al.* 2012; Chen *et al.* 2018) and significant corneal deformation (Beene *et al.* 2016; Scheibenberger *et al.* 2018; Vanhonsebrouck *et al.* 2020).

Eye examinations with keratometry and pachymetry tests can be used for diagnosing the disease in addition to ectopia lentis, which does not present in all cases of MFS (Heur *et al.* 2008; Luebke *et al.* 2017). Blurred vision due to ectopia lentis can be corrected with eyeglasses that will also correct for corneal astigmatism (Esfandiari *et al.* 2019).

7. Conclusions

Cornea offers a unique window into a number of life-threatening systemic diseases. Although many of the corneal abnormalities associated with systemic pathology are not exclusive to a specific disorder, along with other symptoms they can reveal many systemic diseases. Therefore, it is important for eye health practitioners to recognize these manifestations for timely diagnosis, management, and treatment to prevent or retard the development of corneal blindness. It should also be noted that management and therapies for corneal complications of systemic diseases especially the emerging ones may be local and specific to the ocular surface (Antunes-Foschini *et al.* 2020). Future studies should also elucidate mechanisms of corneal alterations in systemic diseases, as this research area is currently underdeveloped.

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- Corneal involvement has been observed in a number of systemic diseases
- Systemic diseases may affect the entire ocular surface
- Corneal problems are seen in genetic, infectious, immune and endocrine diseases
- Underlying mechanisms and emerging treatments are discussed

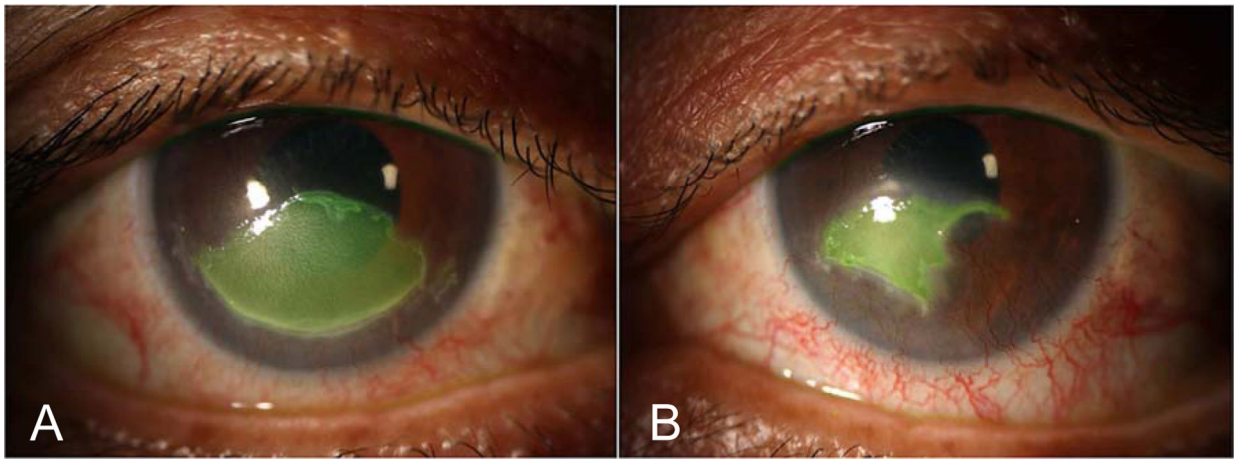

Figure 1.

Neurotrophic corneal ulcers in the right eye (A) and left eye (B) of a diabetic patient unresponsive to conventional treatments before starting topical insulin (25 IU/mL), with large persistent epithelial defects.

Reproduced with permission from: Tong, C.M., Iovieno, A., Yeung, S.N., 2020. Topical insulin for neurotrophic corneal ulcers. Can. J. Ophthalmol. 55, e170–e172.

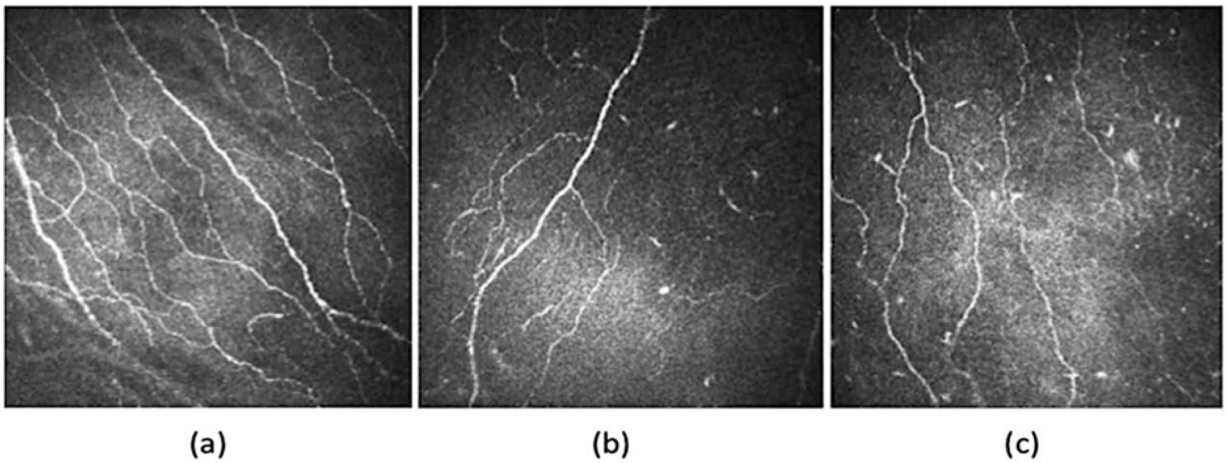

Figure 2.

In-vivo confocal images of the subbasal nerve plexus of the (a) non-diabetic, (b) Type 1 diabetic and (c) Type 2 diabetic individuals. In both Type 1 and Type 2 diabetic patients, the corneal nerve fiber density, nerve fiber length, and total branch density are decreased compared to non-diabetic subjects. The nerves are more tortuous in patients with DM compared to controls.

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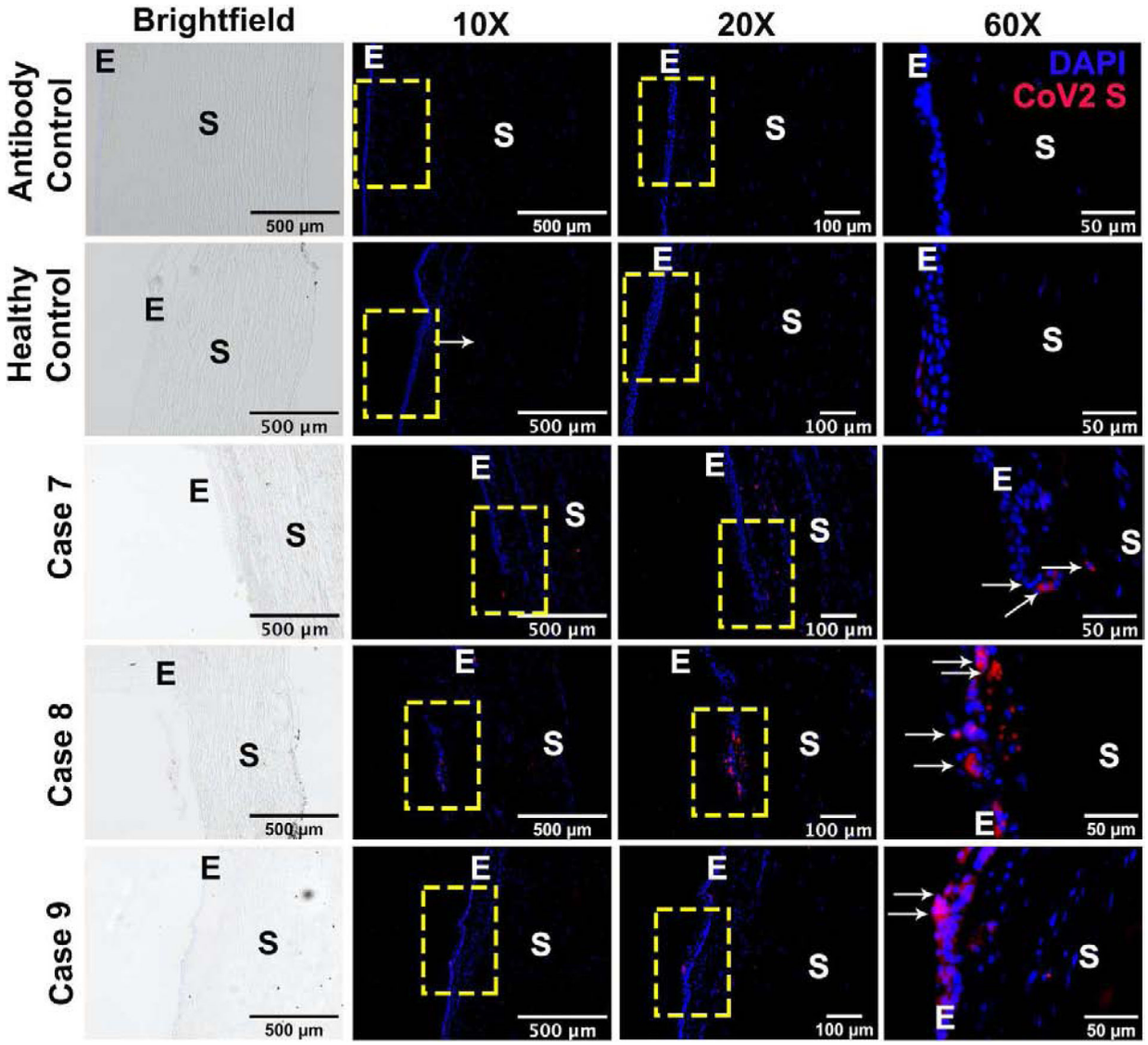

Figure 3.

SARS-CoV-2 Spike (S) protein was detected in the corneal epithelium of the COVID-19 donors that were procured without any PVP-I disinfection treatment. OD (right) corneas from healthy and COVID-19 donors were fixed in formaldehyde and 10 µm thin sections were stained for IHC using antibody against SARS-CoV-2 Spike (S) protein (red color) while DAPI was used for nuclear staining (blue color). The image was captured at different magnifications (10X, 20X, and 60X) to visualize cellular location of the viral proteins. The region of interest has been highlighted using a yellow box and white arrows. E, corneal epithelium; S, corneal stroma. Sections stained with secondary antibody (anti-mouse Alexa Fluor 594) was used to assess the antibody specificity.

Reproduced with permission from: Sawant, O.B., Singh, S., Wright, R.E., Jones, K.M., Titus, M.S., Dennis, E., Hicks, E., Majmudar, P.A., Kumar, A., Mian, S.I., 2020. Prevalence of SARS-CoV-2 in human post-mortem ocular tissues. Ocul. Surf. S1542-0124(20)30168-3. doi: 10.1016/j.jtos.2020.11.002.

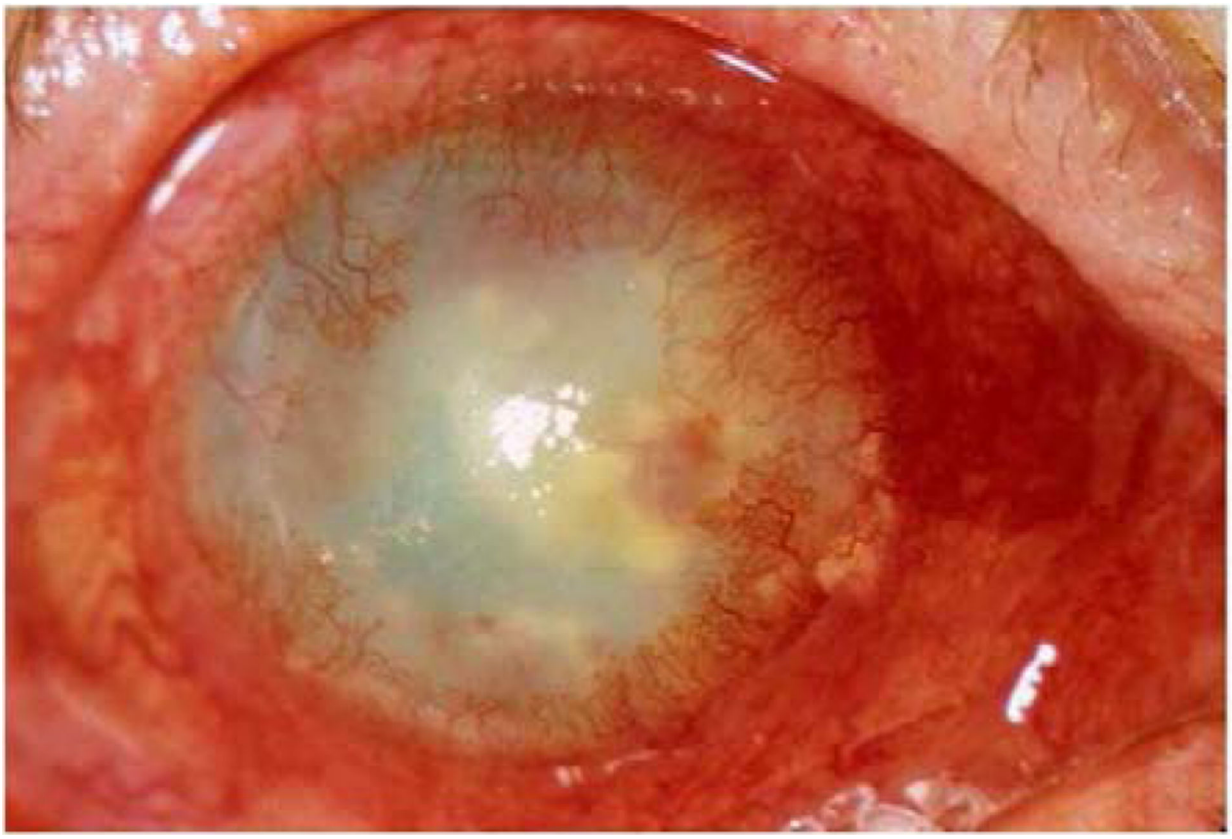

Figure 4.

Depiction of advanced herpetic stromal keratitis that has caused significant corneal opacity and neovascularization.

Reproduced with permission from: Rowe, A.M., St Leger, A.J., Jeon, S., Dhaliwal, D.K., Knickelbein, J.E., Hendricks, R.L., 2013. Herpes keratitis. Prog. Retin. Eye. Res. 32, 88–101.

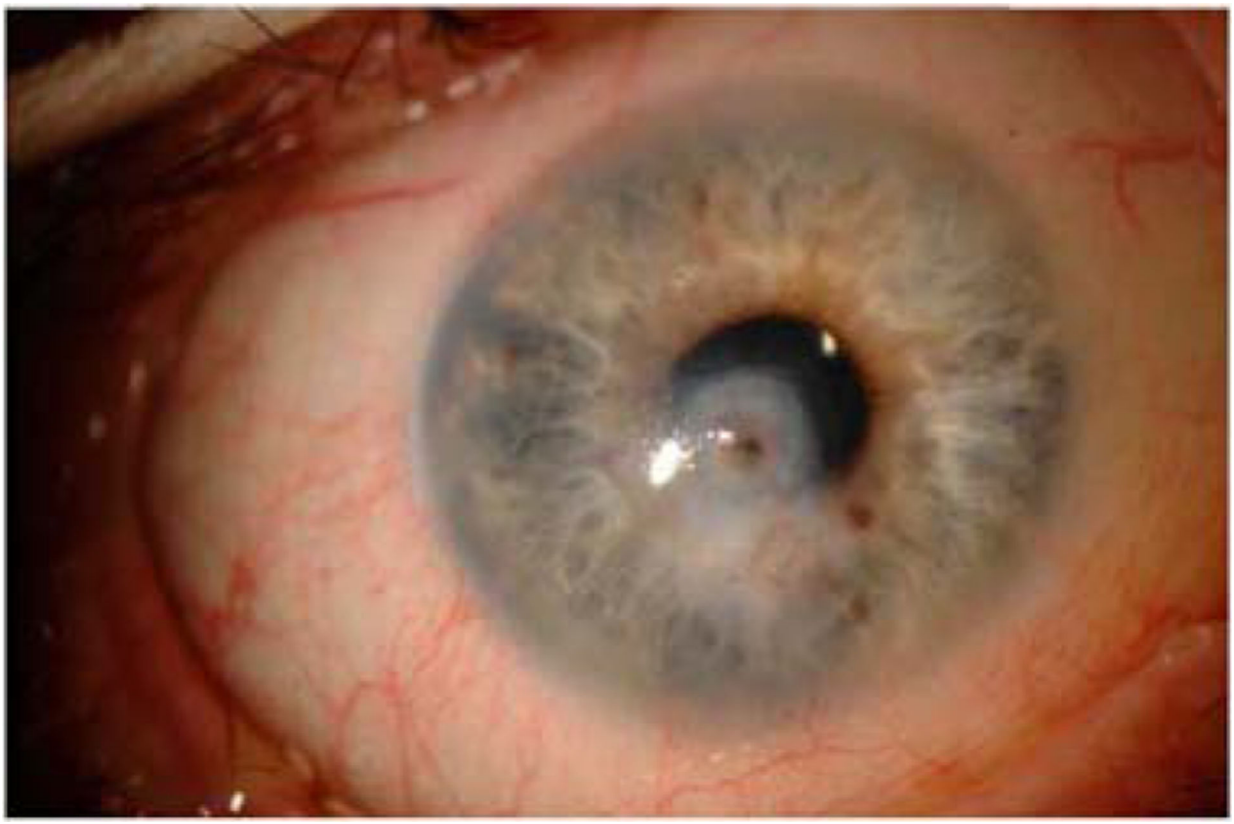

Figure 5.
Corneal melt and perforation of patient diagnosed with Sjögren's syndrome; image generated via slit lamp microscope.
Reproduced with permission from: Akpek, E.K., Bunya, V.Y., Saldanha, I.J., 2019. Sjögren's syndrome: more than just dry eye. Cornea. 38, 658–661.

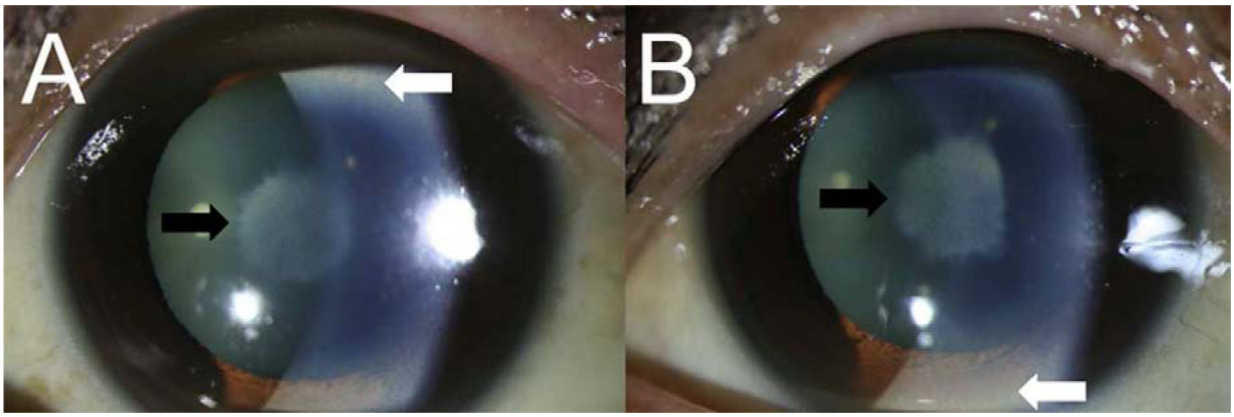

Figure 6.

Wilson's disease. Kayser-Fleischer ring in peripheral cornea (white arrow) (A) and sunflower cataract (black arrow) on the anterior lens capsule in both eyes (A, B). Reproduced with permission from: Jang, H.J., Kim, J.M., Choi, C.Y., 2014. Elemental analysis of sunflower cataract in Wilson's disease: a study using scanning transmission electron microscopy and energy dispersive spectroscopy. Exp. Eye. Res. 121, 58–65.

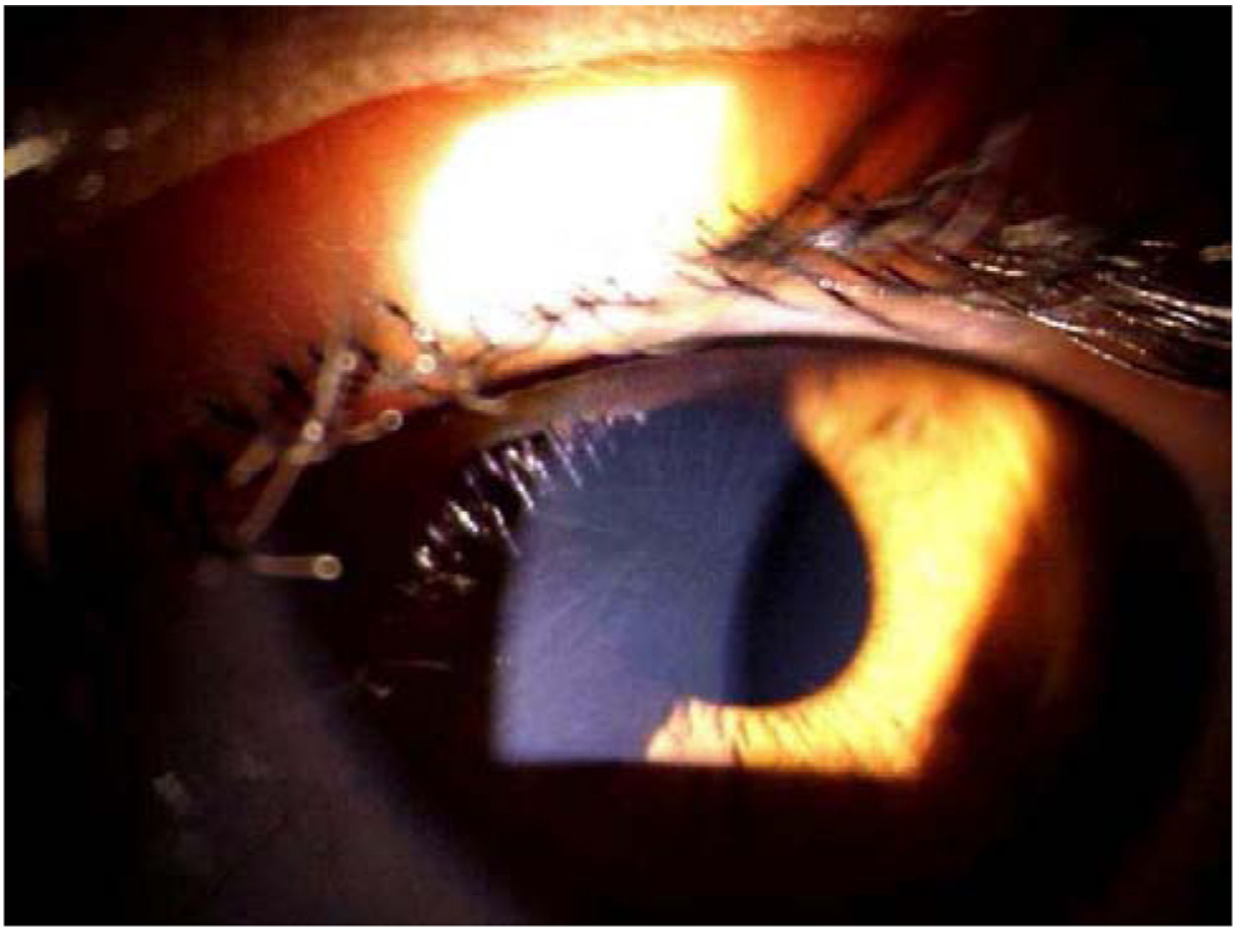

Figure 7.
Cornea verticillata (vortex keratopathy) in a 7-year-old girl with Fabry disease.
Reproduced with permission from: Spada, M., Enea, A., Morrone, A., Fea, A., Porta, F., 2013. Cornea verticillata and Fabry disease. J. Pediatr. 163, 609.

Table 1.

Corneal manifestations of human systemic diseases

Endocrine Diseases		
Systemic Disease	**Pathophysiology**	**Corneal Manifestations**
Diabetes Mellitus	Autoimmune loss of insulin-producing pancreatic cells (T1DM) or insulin resistance (T2DM) resulting in hyperglycemia. DM is associated with progressive macro- and micro angiopathy, neuropathy, and cardiovascular problems.	Keratopathy (compromised epithelial barrier function and wound healing, stem cell marker reduction, decreased p38 and EGFR/Akt signaling), edema; neuropathy (loss of subbasal corneal nerves), endothelial cell loss, increased stromal rigidity with altered biomechanics due to AGE accumulation, impaired tear film secretion.
Graves' Disease	Autoimmune endocrine disease marked by hyperthyroidism and an enlarged thyroid gland.	Corneal inflammation, irritation, and dry eye due to corneal exposure caused by proptosis; changes in corneal biochemical properties.
Addison's Disease	Primary adrenocortical insufficiency due to autoimmunity or infection (tuberculosis).	Corneal ulcers, keratoconjunctivitis, limbal stem cell deficiency, vision loss.
Hyperparathyroidism	Enlargement of parathyroid glands and abnormal secretion of parathyroid hormone, resulting in hypercalcemia. Secondary hyperparathyroidism is a common complication of chronic kidney failure	Band keratopathy due to calcium deposits in Bowman's layer, conjunctiva, and peripheral cornea. Changes in endothelial morphology.
Infectious Diseases		
Systemic Disease	**Pathophysiology**	**Corneal Manifestations**
Coronavirus Disease 2019 (COVID-19)	Multisystem infection with lung inflammation, fibrosis, respiratory failure, vasculitis, loss of smell, immune system problems with cytokine storm, coagulopathy.	Dry eye, blurred vision, itching, redness, tearing, discharge, foreign body sensation, conjunctivitis in a minority of patients.
Herpes Simplex Keratitis	Reactivation of the virus from the latent stage being the precursor to more severe manifestations on the ocular surface.	Corneal blindness, ulcers, corneal opacification, angiogenesis, and corneal nerve loss.
Shingles Caused by Varicella Zoster	Maculopapular or vesicular rash in different parts of the body due to reactivation of latent virus in the sensory nerve ganglia.	Reactivation in ophthalmic region of trigeminal cranial nerve (V) may cause conjunctivitis, anterior uveitis, episcleritis and keratitis.
Human T-Cell Leukemia Virus HTLV-1	Adult T-cell leukemia / lymphoma, neurological disorder HTLV-1-associated myelopathy (tropical spastic paraparesis), HTLV-1-associated uveitis, bladder dysfunction.	Keratoconjunctivitis sicca, interstitial keratitis, corneal haze and opacities, thinning and scarring of the peripheral cornea, keratopathy and neovascularization.
Epstein-Barr Virus	Ubiquitous human herpes virus 4 that causes infectious mononucleosis.	Stromal keratitis with granular, ring-shaped opacities, delayed onset bilateral peripheral interstitial keratitis, corneal endotheliitis (also seen in CMV infection), epithelial-mesenchymal transition.
Tuberculosis	Primarily affects lungs and respiratory tract resulting in serve cough, fever, weight loss, and night sweats.	Lid vulgaris, conjunctivitis, scleritis, episcleritis, corneal phlycten, interstitial keratitis.
Syphilis	Painless sores and mild rashes. When left untreated, bacterium spreads and affects internal organs such as the eyes, brain, heart, nerves, bones, joints, and liver.	Uveitis and syphilis keratitis, which may lead to decreased visual acuity and even permanent blindness.
Pseudomonas aeruginosa Keratitis	Pneumonia, sepsis, ecthyma gangrenosum, osteomyelitis, otitis externa, urinary tract infections, skin infections.	Contact lens-related ulcers, biofilm formation, bacterial keratitis, corneal edema, liquefactive necrosis
Autoimmune and Inflammatory Diseases		
Systemic Disease	**Pathophysiology**	**Corneal Manifestations**
Rheumatoid Arthritis	Autoimmune disease resulting in a chronic and painful inflammatory response, primarily in the joints.	Scleritis, episcleritis, peripheral ulcerative keratitis, keratoconjunctivitis sicca, and may be precursor to other rheumatic disease such as Sjögren's syndrome.

Sjögren's Syndrome	Rheumatic autoimmune disease in which the salivary and lacrimal glands become dysfunctional.	Moderate to severe ocular dryness, thus causing corneal melt/perforation, uveitis, scleritis, and in severe cases limbal stem cell deficiency.
Systemic Lupus Erythematosus	Inflammation of the joints, produces sensitive skin rashes and may even cause severe kidney and lung failure or damage to the central nervous system.	Inflammation may cause cataracts, keratoconjunctivitis sicca (*via* secondary Sjögren's syndrome and rheumatoid arthritis), glaucoma, discoid lesions of eyelids, episcleritis, scleritis, keratitis, and uveitis.
Gout	Increased level of uric acid in the body that results in the accumulation of monosodium urate (MSU) crystals, mainly in the joints.	Keratitis and corneal endothelial dysfunction.
Atopic Keratoconjunctivitis	Allergic inflammatory disease associated with atopic dermatitis caused due to environmental allergens marked by itching, redness, and burning of the eyes, eczema of the eyelids, blepharitis along the lid margin, conjunctival inflammation, excessive tear production, and corneal complications.	Punctate keratitis, corneal erosions, corneal ulcerations, edema, epithelial defects, neovascularization, scarring, and vision loss.
Vernal Keratoconjunctivitis	Allergic inflammatory disease appearing during warm seasons. Marked by itching, redness, conjunctival and corneal inflammation, photophobia, foreign body sensation.	Punctate epithelial erosions, shield ulcers, stromal plaques, neovascularization, keratoconus, infectious keratitis, and LSCD.
Multiple Sclerosis	Apparently autoimmune demyelinating central nervous system disease with frequent optic neuritis.	Significant reduction of corneal nerve fiber density, branch density and length with axonal loss.
Granulomatosis with Polyangiitis	Idiopathic, multisystem inflammatory disease of the upper and lower respiratory tracts characterized by necrotizing granulomatous inflammation and vasculitis.	Bilateral peripheral ulcerative keratitis due to the presence of autoantibodies and inflammatory cells from limbal blood vessels, limbal edema, corneal thinning, endothelial cell loss.
Sarcoidosis	Inflammatory granulomatous disease affecting the lung and mediastinal lymphatic system characterized by the formation of non-caseating, giant cell granulomas with T lymphocyte and macrophage involvement.	Corneal small nerve fiber loss and damage, interstitial keratitis, band keratopathy from calcium deposits in the Bowman's layer, dry eye.
Cogan's Syndrome	Autoimmune disease characterized by inflammation in the eye and inner ear, with systemic vasculitis	Bilateral peripheral subepithelial keratitis with nummular lesions, deep stromal keratitis, granular infiltration in peripheral cornea, photophobia, excessive tear production, diminished visual acuity.
Immunobullous Diseases	Autoimmune diseases caused by specific autoantibodies that bind to epithelial cells, resulting in blistering lesions on the skin, mucous membranes, and oral cavity.	Punctate epithelial erosions, bilateral corneal perforations, corneal melting, decreased corneal nerve density, intraepithelial defects, anterior stromal fibrosis, corneal neovascularization.
Genetic Corneal Deposit Disorders		
Systemic Disease	**Pathophysiology**	**Corneal Manifestations**
Wilson's Disease	Excessive copper deposition in liver, brain, cornea, kidney due to mutation in gene encoding ATP7B protein.	Kayser-Fleischer ring and sunflower cataract formation due to copper accumulation.
Cystinosis	Intracellular accumulation of cysteine crystals in kidney, liver, spleen, eye, bone marrow, pancreas, thyroid, muscle, and brain due to mutations in the CTNS gene.	Formation of corneal crystals of cysteine deposits and photophobia, and recurrent corneal erosions in some cases.
Fabry Disease	Lysosomal accumulation of glycosphingolipids due to mutations in the GLA gene on the X-chromosome.	Cornea verticillata (vortex keratopathy) due to whorl-like deposits in the epithelial and sub-epithelial layers, with corneal haze and conjunctival vessel tortuosity.
Meretoja Syndrome	Amyloid deposition due to mutations in the gelsolin gene at chromosome 9q32–34.	Corneal lattice dystrophy, corneal ulcers, dry eye, photophobia, dysfunction of the meibomian glands, early development of cataract.
Mucopolysaccharidosis (7 subtypes known)	Lysosomal storage disorder characterized by the glycosaminoglycan (GAG) accumulation in bone, tendons, cartilage, cornea, skin, and connective tissue.	Corneal clouding that appears as yellowish-grey granules deposited in all layers of the cornea, but mainly in the stroma, increased keratocyte size and the displacement of collagen fibrils.

Hyperlipoproteinemia	Elevated levels of lipids and lipoproteins such as cholesterol in the blood.	Corneal arcus, a yellowish-grey ring of lipid deposits around the cornea and limbus.
Other Genetic Disorders Presenting Corneal Manifestations		
Systemic Disease	**Pathophysiology**	**Corneal Manifestations**
Aniridia	Absence of iris, usually in both eyes and can be acquired through a haploinsufficiency truncating mutation in the PAX6 gene, congenitally, and by ocular injury.	Aniridia-associated keratopathy, conjunctival neovascularization, and corneal blindness caused by limbal stem cell insufficiency. Altered Notch1 and Wnt signaling.
Ehlers-Danlos Syndromes (EDS)	Autosomal recessive or dominant abnormalities of connective tissue due to mutations in a number of genes, in particular, in various collagen genes. Depending on the gene involved, clinical signs include fragile skin, skeletal dysmorphology with stunted growth, joint dislocation, vascular problems, etc.	Kyphoscoliotic EDS (mutated *PLOD1* or *FKBP14* genes) is associated with scleral fragility, microcornea. Brittle cornea syndrome (mutated *ZNF469* or *PRDM5* genes) can cause corneal rupture, scarring, keratoconus, keratoglobus. Classic EDS with mutations of *COL5A1* or *COL5A2* genes may result in thinner and steeper corneas.
Marfan syndrome	Autosomal dominant disorder of the connective tissue caused by mutation in gene encoding fibrillin and resulting in musculoskeletal symptoms.	Corneal flattening and thinning.