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.