
eyeInsights™
Fuchs Dystrophy
• Risk factors
• Diagnosis & treatment
• Latest advances
Mass General Brigham
Mass Eye and Ear

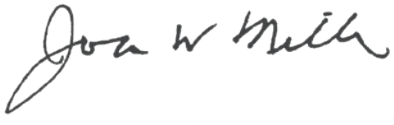
Dear Colleagues,

Fuchs endothelial corneal dystrophy is a progressive disease that affects about 4% of adults worldwide and, if left untreated, can lead to corneal edema and painful loss of vision.

At Mass Eye and Ear, we are home to one of the highest-volume treatment programs for Fuchs dystrophy in the United States. Over the past decade, our researchers have developed research programs to understand disease mechanisms and developed novel surgical techniques, reducing the recovery time after corneal transplantation. While treatment for Fuchs dystrophy used to require a full-thickness corneal transplant, Mass Eye and Ear surgeons have adopted endothelial keratoplasty, first DSAEK and then DMEK, to treat Fuchs dystrophy with minimally invasive surgical interventions. DMEK is a state-of-the-art technique with reduced transplant rejection, quicker recovery times, and better vision outcomes. Another innovative surgical approach, Descemet's stripping only (DSO), which removes diseased endothelial cells without donor tissue implantation, treating Fuchs dystrophy without transplantation, has been spearheaded by Mass Eye and Ear faculty.

Today, our clinician scientists continue to advance our understanding of disease pathogenesis and identify targets for new therapies.

Inside this issue of *Eye Insights*, you will find helpful information for identifying the disease and advising your patients on next steps for treatment.



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What is Fuchs dystrophy?

Fuchs dystrophy is an age-related progressive corneal disorder that affects both eyes and occurs when endothelial cells gradually die, leading to deposition of drop-like deposits (guttae) and corneal edema. Fuchs dystrophy is significantly more prevalent in women and women account for 75% of corneal transplants performed for this condition. Although Fuchs has a genetic basis, most commonly due to TCF4 gene mutation, it does not cause symptoms or affect vision until middle age or later in life. Treatment ranges from symptomatic relief with hypertonic saline eyedrops and ointments to corneal surgeries.

Clinical stages and symptoms

Fuchs dystrophy has 4 stages:

Stage 1

Early findings of central non-confluent guttae. Early symptoms of glare.

Stage 2

The guttae become confluent, causing more glare and loss of contrast sensitivity.

Stage 3

There is onset of corneal edema leading to cloudy vision, most commonly in the morning, that clears up during the day.

Stage 4

The edema becomes more severe, causing blurry or hazy vision to persist throughout the day.

Additional symptoms may include:

- Sensitivity to light
- Sandy or gritty feeling in the eyes
- Eye pain due to edema or corneal blisters

Ask the Expert

Ula V. Jurkunas, MD

Associate Director, Cornea Service, Mass Eye and Ear

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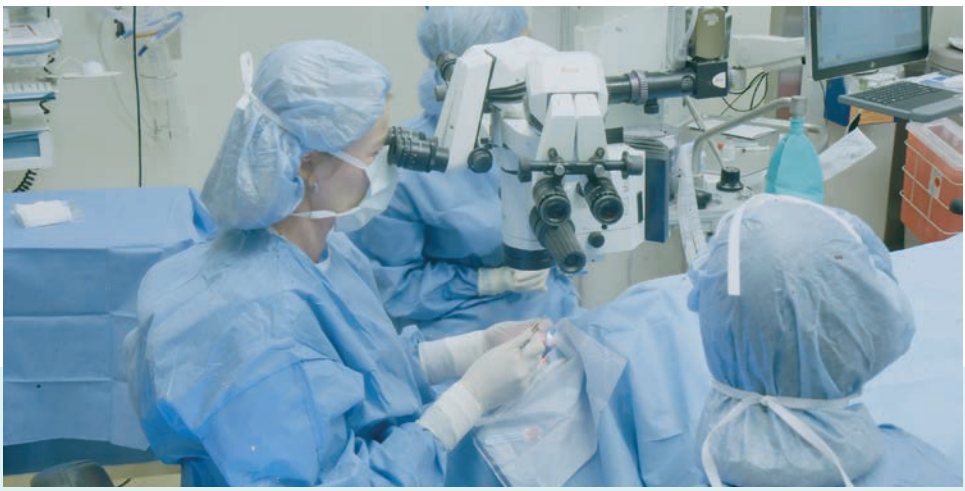
Disease pathogenesis

Researchers from Mass Eye and Ear, led by cornea specialist Dr. Ula V. Jurkunas, have significantly advanced our understanding of Fuchs dystrophy. Their findings include:

- **Oxidative stress:** Lifelong accumulation of oxidative damage leads to mitochondrial dysfunction and subsequent cell death of the corneal endothelium.
- **Interaction between genetics and ultraviolet light exposure:** Exposure to ultraviolet A light sets off an enzyme reaction that causes DNA damage in the corneal endothelial cells in patients with Fuchs dystrophy. This reaction is more pronounced in women as it is driven by the activation of CYP1B1, an enzyme that converts estrogen into metabolites that cause DNA damage. Patients with Fuchs dystrophy are now counseled on UV protection.
- **Activation of endothelial-to-mesenchymal transition state:** Diseased endothelial cornea cells undergo increased endothelial mesenchymal transition, which causes cellular senescence and leads to fibrosis and scarring in the form of guttae.

These findings have laid the groundwork for future corneal research and may facilitate the development of novel molecular targets for the disease.



Prevalence

- Affects an estimated 1-4 percent of the U.S. population
- 3-4 times more prevalent in women than men
- Leading cause of corneal transplantation worldwide

Risk factors

- Age
- Female sex
- Family history
- Smoking
- Diabetes
- Cardiovascular disease

Diagnosis

Fuchs dystrophy can often be diagnosed with slit-lamp biomicroscopy, which illuminates the layers of the cornea to identify disease characteristics such as the extent of corneal guttae formation, corneal edema, and subepithelial haze. Other tests may include:

- Visual acuity measurement
- Pachymetry to measure the extent of corneal swelling
- Specular and confocal microscopies to quantify the corneal endothelial cell number and morphology
- Corneal topography to identify curvature changes due to edema

Treatment

While there is no cure for Fuchs dystrophy, discussing lifestyle changes with patients on how to modify potential risk factors of disease progression is helpful. These include cessation of smoking, protection from ultraviolet light with sunglasses, prevention of diabetes, and improvement of overall cardiovascular risk factors.

In the early stages, patients are usually asymptomatic, and observation without intervention is the best approach. As the condition progresses, symptoms can be managed conservatively with topical hypertonic saline drops or ointment. In more advanced stages, surgical intervention is indicated.

LEFT: *Ula Jurkunas, MD, performing surgical procedure*

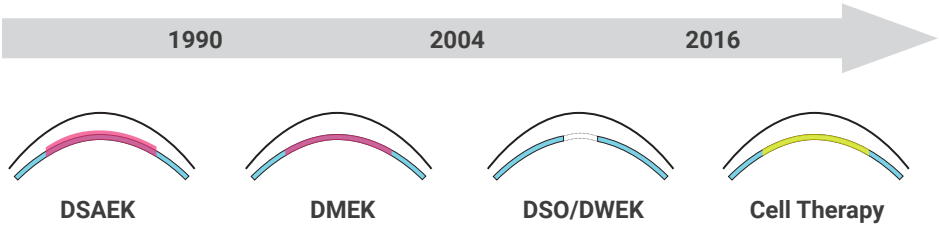
Latest advances at Mass Eye and Ear

Mass Eye and Ear clinicians provide the latest keratoplasty procedures for the treatment of Fuchs dystrophy. In 2014, cornea surgeons at Mass Eye and Ear began performing DMEK (Descemet membrane endothelial keratoplasty). This advanced treatment allows for a partial thickness corneal transplant and provides better outcomes with a decreased risk of rejection, quicker recovery, and improved vision.

In 2018, clinicians from Mass Eye and Ear published a surgical technique for corneal edema stripping Descemet membrane without endothelial keratoplasty (DWEK), now more commonly known as Descemet's stripping only (DSO). This study paved the way for a surgical approach for a subset of Fuchs dystrophy patients without using allogeneic tissue, thereby avoiding the risks of transplantation. There is also promising data on the use of Rho-kinase inhibitors to enhance cellular migration and corneal clearance after DSO.

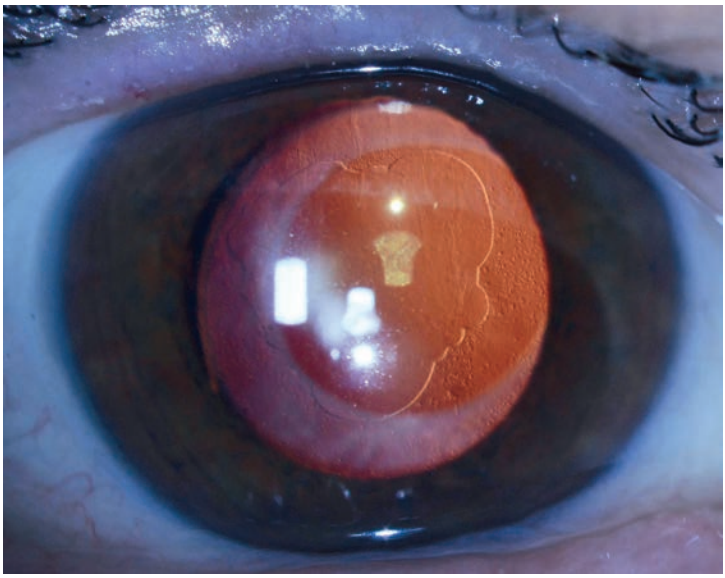
While much progress has been made in the medical and surgical management of Fuchs, there are also novel therapeutics in development, including cellular therapies aimed to eliminate corneal transplantation altogether. Furthermore, gene therapies and small molecules targeting specific molecular mechanisms involved in cellular degeneration hold promise as future treatment that arrest disease progression at earlier stages and avoid surgical intervention.

Fuchs endothelial corneal dystrophy treatment



CURRENT THERAPIES		FRONTIER THERAPIES	DEVELOPING THERAPIES	
Endothelial keratoplasty	DMEK	DSO/DWEK +/- Rho-kinase inhibitors	Cell therapies	Cell injection
				Tissue engineered endothelial cells
	DSAEK		Medical therapies	Small molecules, disease modifying treatments
			Gene therapies	CRISPR/antisense oligonucleotides

DMEK: Descemet Membrane Endothelial Keratoplasty; **DSAEK:** Descemet Stripping Automated Endothelial Keratoplasty; **DSO:** Descemet's Stripping Only; **DWEK:** Descemet stripping Without Endothelial Keratoplasty; **CRISPR:** clustered regularly interspaced short palindromic repeats



LEFT: Descemet's Stripping Only

Referral guidelines

Referral to a corneal specialist should be considered once symptoms from Fuchs dystrophy begin to interfere with activities of daily living. Medical management may be adequate for some time until the symptoms worsen and surgical intervention is indicated. Working with a surgeon who specializes in corneal diseases will improve patient outcomes.

Further reading

Ong Tone S, Kocaba V, Böhm M, Wylegala A, White TL, Jurkunas UV. Fuchs endothelial corneal dystrophy: The vicious cycle of Fuchs pathogenesis. *Prog Retin Eye Res.* 2021;80:100863

Liu C, Miyajima T, Melangath G, Miyai T, Vasanth S, Deshpande N, Kumar V, Ong Tone S, Gupta R, Zhu S, Vojnovic D, Chen Y, Rogan EG, Mondal B, Zahid M, Jurkunas UV. Ultraviolet A light induces DNA damage and estrogen-DNA adducts in Fuchs endothelial corneal dystrophy causing females to be more affected. *Proc Natl Acad Sci U S A.* 2020 Jan 7;117(1):573-583

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