FUCHS ENDOTHELIAL CORNEAL DYSTROPHY'S MANAGEMENT WITH SPECULAR MICROSCOPY AND SURGERY

BACHELOR OF OPTOMETRY

GALGOTIAS UNIVERSITY

(Established under Galgotias University Uttar Pradesh Act No. 14 of 2011)

SUBMITTED BY HIMANSHU

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DISSERTATION

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This is to certify that the Dissertation titled " **FUCHS ENDOTHELIAL CORNEAL DYSTROPHY'S MANAGEMENT WITH SPECULAR MICROSCOPY AND SURGERY** " submitted by " HIMANSHU " is in partial fulfillment of the requirementsfor the award of 'BACHELOR OF OPTOMETRY DEGREE' a record of bonafide work done under my/our guidance. The contents of this Dissertation, in full or in parts, have neither been taken from any other source nor have been submitted to anyother Institute or University for award of any degree or diploma and the same is certified.

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This is to certify that **HIMANSHU** bearing Registration no. **18SMAS1030021** has completed objective formulation of thesis titled, **"FUCHS ENDOTHELIAL CORNEAL DYSTROPHY'S MANAGEMENT WITH SPECULAR MICROSCOPY AND SURGERY "** under my guidance andsupervision. To the best of my knowledge, the present work is the result of heroriginal investigation and study. No part of the thesis has ever been submitted forany other degree at any University.

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I, **HIMANSHU**, student of **BACHELOR OF OPTOMETRY** under the Department of **OPTOMETRY** in Galgotias University, Greater Noida, hereby declare that all the information furnished in this dissertation is based on my own intensive research and is genuine.

This Dissertation, which has been submitted for the award of my degree, does not, to the best of my knowledge, contain any part of research work, either of this university or any other university without proper citation.

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INTRODUCTION

Fuchs endothelial corneal dystrophy (FECD) is a bilateral disease of the corneal endothelium characterized by accelerated loss of corneal endothelial cells (CECs) with changes in Descemet membrane (DM), including accumulation of extracellular matrix (ECM) and formation of posterior focal excrescences called guttae. Loss of vision from FECD can result from these DM changes as well as later-stage disruption of corneal endothelial pump-leak function causing corneal edema, bullae formation, and subepithelial fibrosis. [1] Currently, corneal transplantation represents the only definite treatment option, and FECD is the most common cause of corneal transplantation worldwide .[2] In 1910, Austrian ophthalmologist and namesake of the disease, Professor Ernst Fuchs, described the first 13 cases of FECD. Because the slit-lamp biomicroscope was introduced in 1911 by Gullstrand, Fuchs initially identified FECD as an epithelial disorder, dystrophia epithelialis corneae .[3] We have seen far-reaching progress in its diagnosis and treatment since then. Staging of the disease has been documented in detail by new diagnostic tools and specific classification systems. Detailed studies have identified important gene alterations and molecular pathomechanisms of FECD. [4]

2) Overview

Corneal endothelium (CE) is located in the inner portion of the cornea and has a key function of keeping the cornea transparent CE forms a monolayer of hexagonal cells that is attached to its basement membrane, ie, Descemet's membrane (DM),

and is in direct contact with the aqueous humor. [5] One of the major functions of CE is to retain corneal clarity via the endothelial barrier and pump functions. Ernst Fuchs described a bilateral corneal dystrophy in 1902 , which is now known as FECD. The primary defect is thought to be in the functioning of the endothelial cell layer, as confirmed by ultrastructural studies. [6] FECD is characterized by the morphological changes of the hexagonal mosaic, accelerated loss of endothelial cells, and a concomitant increase in the extracellular matrix deposition at the level of DM. [7] As a result, the endothelial layer is eventually unable to support corneal deturgescence (a state in which corneal stroma is maintained relatively dehydrated), leading to corneal edema and decreased in visual acuity . These findings usually become clinically evident in the sixth decade of life.3-5 Initially, the patient notices blurred vision; symptoms progress as the disease progresses through its stages, often ending in blindness.[8]

3) Clinical Staging

Several staging systems for FECD have been utilized in the past. One of the commonly used systems describes the disease progression in four stages.

3.1) Stage 1. Corneal biomicroscopy reveals corneal guttae.

These are mound-shaped excrescences growing from the DM and are considered a hallmark of FECD. The guttae usually start in the central cornea and spread toward the periphery. In this stage, guttae are usually central and nonconfluent, and patients are asymptomatic. [9]

3.2) Stage 2

Corneal guttae start to coalesce and further spread toward the peripheral cornea. The guttae grow along the DM and are accompanied by endothelial cell thinning, enlargement, and loss of hexagonal shape. The number of guttae is inversely proportional to the endothelial cell density, as the coalescence of guttae is accompanied by continual loss of endothelial cells. Patients begin to experience a painless decrease in vision and glare symptoms, due to increasing edema of stromal layers. [10]

3.3) Stage 3

Stromal edema further progresses toward the epithelial layer and causes formation of epithelial and subepithelial bullae. The rupture of these bullae causes episodes of pain and places a patient at a higher risk of infection.

3.4) Stage 4

The cornea becomes densely opaque and vascularized. There is subepithelial fibrous tissue deposition in response to prolonged and chronic edema. Visual acuity is severely compromised at this stage, but the pain usually subsides. Interestingly, a non-guttae form of FECD has also been described. [10] Conversely, central guttae can be found in the elderly without the development of corneal edema or decrease in visual acuity, and this is not classified as FECD. Corneal guttae found only at the periphery can be normal findings in the aging population; they are called Hassal-Henle bodies, and they never lead to corneal edema. Corneal guttae can also form secondary to trauma, toxins, or infections.

4) Fuchs Endothelial Corneal Dystrophy Pathological Changes in Endothelium.

Accelerated loss of CECs starting at the corneal center and spreading toward the periphery characterizes FECD. [10] Defects within the corneal endothelial mosaic arising from cell loss are closed by spreading and migration of remaining cells. Over time, remaining CECs lose their hexagonal shape (polymorphism) and their uniform size (Polymegathism). CECs in FECD exhibit a dilute cytoplasm, especially over the focal excrescences of DM (guttae), whereas their nuclei often show rosette formation around these structures. [11] Transmission electron microscopy shows normal endothelial cells, especially in the corneal periphery viable-appearing fibroblast-like cells, and degenerating fibroblast-like cells. The latter cell types are most likely of endothelial origin.

5) Barrier or Pump Dysfunction

Endothelial cells are selective barriers that allow leakage of solutes and nutrients from the aqueous humor to the avascular cornea. On the other hand, Na-K ATPase pumps, located in basolateral CE membranes, actively transport the fluid out of the cornea and back to the aqueous humor to maintain the cornea in a relative state of deturgescence. [12] Dysfunction of either the barrier or the pumps results in corneal edema, as seen in FECD. Burns et al studied FECD patients with increased central corneal thickness but without epithelial edema. [13] They found increased permeability rate in the CE of FECD, without a difference in pump rate, and suggested that the earliest defect in FECD is the breakdown of the barrier function of the endothelial monolayer, which causes increased flow of fluid into the cornea, without sufficient compensatory increase in pump function. However, in a later

study, Wilson et al found no difference in the permeability rate of a larger sample of FECD patients compared to the normal volunteers, suggesting that the pump rate is reduced and the barrier function is intact in FECD. [15] The disparity between the two studies may reflect the fact that pump and barrier functions might be affected differently in various stages of the disease. Several other studies have suggested that pump dysfunction plays a key role in FECD. [16] Bergmanson et al examined histopathologic sections of FECD corneas and found that aberrant deposition of extracellular matrix caused stretching and thinning of CE cells positioned on top of guttae. [16] The cell bodies were displaced peripheral to the stem of the guttae, whereas over the apices of the guttae, the cell membranes were intact. Since there was no space for organelles over these stretched areas, the authors argued that it is unlikely that CE cell pump function is intact over those areas. Similarly, other studies on Na-K ATPase pump activity in corneal edema, such as that seen in FECD and pseudophakic bullous keratopathy (PBK), showed that pump density is markedly decreased in the end-stage disease. [17] In summary, loss of endothelial cells leads to the breakdown of barrier function. Even though the remaining endothelial cells attempt to compensate by increasing the pump function, the continued loss of cells leads to the critically low number of the pump sites and inability of the cornea to maintain the deturgescent state.

6) DIFFERENTIAL DIAGNOSIS

6.1) Posterior Polymorphous Corneal Dystrophy

Initial evidence for this generally bilateral disease may be detected in childhood. A majority of patients remain asymptomatic (Krachmer 1985). [18] In posterior polymorphous corneal dystrophy (PPCD), endothelial cells transform into multilayered epithelial-like cells with formation of vesicles on the endothelial

surface (Krachmer 1985). Slit-lamp biomicroscopic examination shows varying degrees of corneal edema, thickened DM with posterior excrescences, secondary guttae or whitish spots, band-like changes to DM with irregular margins, alternating zones of normal and abnormal endothelium, and iridocorneal adhesions with ectropion of the pupil or corectopia (Krachmer 1985). [19] The disease shows generally slow progression. Important distinguishing features compared to iridocorneal endothelial (ICE) syndrome are the unilateral and sporadic occurrence of ICE syndrome, whereas PPCD and FECD are generally bilateral and autosomal dominantly inherited.

6.2) Congenital Hereditary Endothelial Dystrophy

Congenital hereditary endothelial dystrophy (CHED) is a rare disorder that manifests as corneal clouding at birth or in infancy. [20] The early onset of CHED usually prevents adequate visual development, resulting in amblyopia and nystagmus. The consensus of the International Committee for Classification of Corneal Dystrophies 2015 indicates that CHED is inherited as an autosomal recessive disease and that milder forms of CHED, formerly referred to as autosomal dominant CHED, are now recognized as PPCD .

6.3) Pseudoexfoliation Keratopathy

Similar to FECD, this bilateral disease with female predominance appears in patients after the sixth decade of life. [21] CECs show altered shape and size with melanin phagocytosis, accumulation of ECM and pseudoexfoliation (PEX) material, and fibroblastic metaplasia. Corneal endothelial decompensation eventually results . The distinction between FECD and PEX keratopathy may be of considerable clinical importance given the compromised zonular apparatus in the

latter, particularly in the context of combined keratoplasty and cataract surgery. PEX keratopathy shows a more diffuse distribution of endothelial decompensation in the absence of guttae, as well as elevated intraocular pressure, phacodonesis, and pseudouveitis .

6.4) Aphakic/Pseudophakic Bullous Keratophathies

Aphakic/pseudophakic bullous keratopathies (ABK/PBK) occur due to iatrogenic CEC loss and decompensation induced by cataract surgery, either alone or in combination with other intraocular procedures. ABK/PBK are common indications for keratoplasty, but they have been decreasing with advances in cataract surgery .In contrast to FECD, corneal edema can begin peripherally with advancement centrally. Adamis et al. (1993) stated that the presence of an intraocular lens with subsequent corneal edema defines PBK even in the presence of corneal endothelial guttae.[22]

7) SURGICAL THERAPY

For several decades, penetrating keratoplasty has been the only definitive treatment option for FECD. However, the development of minimally invasive lamellar endothelial keratoplasty (EK) procedures has provided key benefits such as better and faster visual recovery, a tectonically stronger globe, decreased risk of bleeding and infection, less astigmatism, less corneal denervation, and lower rejection rates Newer modalities such as Descemetorhexis without endothelial keratoplasty (DWEK), endothelial cell injection, and nonsurgical approaches may offer options for further minimizing surgical risks and intervening before the onset of symptoms.

7.1) Descemet Stripping Endothelial Keratoplasty

In 2004,Melles et al. (2004) described sutureless onlay keratoplasty consisting of Descemetorhexis (circular incision and removal of DM); implantation of a partial thickness lamella containing posterior stroma, DM, and endothelium; and fixation of the graft using an air bubble. [23] Price & Price (2005) in the United States further optimized this method with Descemet stripping endothelial keratoplasty (DSEK). Gorovoy (2006) refined the procedure by adding the use of an automated microkeratome to prepare the donor tissue and termed the procedure Descemet stripping automated endothelial keratoplasty (DSAEK). Further optimization of DSAEK surgery included reduction of graft-thickness down to ultrathin and nanothin DSAEK grafts, as well as development of a variety of insertion techniques and devices . [24]

7.2) Descemet Membrane Endothelial Keratoplasty

In 2006, Melles et al. (2006) published the first Descemet membrane endothelial keratoplasty (DMEK) procedures. DMEK involves dissection of the donor DM and corneal endothelium from the adjacent stroma by circularly scoring DM anterior to the trabecular meshwork and subsequently grasping and stripping DM toward the corneal center . [25] Alternative stripping techniques include dissection of DM from the corneal stroma by subendothelial injection of air or trypan blue . The Descemet-endothelium complex is trephined, stained with trypan blue, and loaded into an insertion cartridge. Following Descemetorhexis, the graft is injected into the anterior chamber. Alternative techniques for graft introduction include pulling the

graft across the anterior chamber via micro forceps with concurrent use of a fluid infusion cannula . [25] The graft is unfolded by a combination of saline addition to or removal from the anterior chamber alternating with tapping on the corneal surface . Once unfolded and centered, the graft is secured in the recipient bed by injecting gas, typically 20% SF6. A DSEK graft consists of endothelium, DM, and posterior stromal tissue with a variable thickness of 50–150 μm. The stromal tissue creates a more rigid corneal graft, allowing for reliable unfolding that may be advantageous in eyes with potentially complex surgical factors. A DMEK graft consists of corneal endothelium and DM only and has a thickness of ∼15 μm. The thinner DMEK graft brings about more difficult intraoperative handling. However, due to stroma-less transplantation, it offers significant advantages such as faster and more complete visual recovery and a significantly decreased rejection rate (Droutsas et al. 2016, Hamzaoglu et al. 2015, Rodriguez-Calvo-de-Mora et al. 2015, Tourtas et al. 2012). [26] DMEK requires little technical equipment and is cost-saving compared to DSAEK (Gibbons et al. 2018). Moreover, the process of split-corneal transplantation allows for the use of a single corneal tissue for the benefit of two patients, one receiving a DMEK and one receiving a deep anterior lamellar keratoplasty (Heindl et al. 2011). Complications of DSAEK and DMEK are similar and include graft detachment, intraoperative hemorrhage, increased intraocular pressure due to pupillary block or steroid response, UrretsZavalia syndrome, primary and secondary graft failure, intraocular lens opacification, and macular edema (Deng et al. 2018). Graft detachment occurs more often after DMEK than after DSEK (Stuart et al. 2018). Immune rejection can occur with both procedures, although to a lesser frequency after DMEK than after DSAEK (Price et al. 2018). [27] Both procedures result in a postoperative hyperopic

shift, although the average shift is lower after DMEK than after DSAEK (Deng et al. 2018, Droutsas et al. 2016, Hamzaoglu et al. 2015). Five-year graft survival and rate of CEC loss after both procedures appears to be similar (Price et al. 2018).

7.3) Cataract Surgery in Fuchs Endothelial Corneal Dystrophy Patients

Visually significant cataract and FECD often coincide, and surgical decision making frequently involves whether to address both pathologies separately or in a combined procedure Diurnal fluctuation with worse visual symptoms upon awakening may indicate a corneal etiology. Moreover, pachymetric readings of >640 μm have been proposed as a threshold for imminent corneal decompensation following cataract surgery, advocating for a combined procedure (Seitzman et al. 2005). However, due to variations of baseline pachymetric values within the normal population and due to the diurnal variability of central corneal thickness in FECD patients, such a threshold should be considered with caution and leaves room for refinement. Price & Price (2017) have studied in detail cataract surgery in FECD patients. Basically, three surgical approaches are conceivable: (a) staged cataract surgery before EK, (b) staged EK before cataract surgery, and (c) a combined approach. Cataract surgery before EK is recommended in patients with early FECD and visually significant cataract. Patients with moderate to severe FECD (Krachmer grade 2.5–4) hold a significantly increased risk for corneal decompensation and have an approximately 20% likelihood of needing subsequent EK (Zhu et al. 2018b). As part of staged initial cataract surgery, phacoemulsification time should be kept low and endothelial protection should be provided by viscoelastic material. [28] The “soft-shell” technique using cohesive and dispersive types of viscoelastic devices effectively protects the compromised

endothelium in FECD patients (Tarnawska & Wylegala 2007). Studies investigating femtosecond laser–assisted cataract surgery (FLACS) in FECD eyes still provide inconsistent results regarding a potential endothelium-protecting benefit of FLACS over standard phacoemulsification (Yong et al. 2018, Zhu et al. 2018b). Staged EK prior to cataract surgery may be applied in patients under 50 years of age with visually significant FECD and a clear, prepresbyopic lens and deep anterior chamber (Burkhart et al. 2014, Price & Price 2017). Cataract progression was observed in 76% of patients within 12 months postphakic EK, with 33% of patients requiring cataract surgery (Burkhart et al. 2014). One advantage of having a clear and compact cornea post EK surgery prior to cataract surgery is the ability to optimize keratometry readings with improved accuracy of IOL power selection.[29] Therefore, EK prior to cataract surgery may also be indicated in eyes with advanced corneal edema and bullae formation (and a deep anterior chamber). Combined cataract/IOL and EK surgery is recommended in patients with moderate FECD and visually significant cataract. Patients with moderate FECD, clear lens, and shallow anterior chamber also should consider undergoing combined surgery given increased risk of postoperative cataract formation (Price & Price 2017). A combined surgical approach may be more convenient and cost-effective than performing separate EK and cataract procedures
.

8) Donor Endothelial Cell Loss

The specular microscopy results at the preoperative examination as well as the 6- and 12-month postoperative examinations. There were 173 eyes that had valid

specular microscopy results at the 6-month postoperative examination. The mean donor ECD before surgery was 2884363 cells/mm2 (range, 2201–4209 cells/mm2) and at 6 months was 1980383 cells/mm2 (range, 978–2803 cells/mm2). This represented a mean cell loss of 3114% (range, 12% gain to 70% loss) at 6 months after surgery. There were 119 eyes with specular microscopy results at 12 months after surgery, and the cell count was 1969378 cells/mm2 (range, 774–2732 cells/mm2). This represented a mean cell loss of 3215% (range, 0%–76% loss) at 12 months after surgery for the overall group, and no significant progression of cell loss from 6 to 12 months after surgery (P 0.360). For the group of eyes with DSAEK only (n 48), the mean donor ECD before surgery was 2869435 cells/mm2 (range, 2341–4209 cells/mm2) and at 6 months was 2045384 cells/mm2 (range, 1019–2803 cells/mm2). This represented a mean cell loss of 2815% (range, 12% gain to 68% loss) at 6 months after surgery. There were 30 eyes in this group with specular microscopy at 12 months after surgery, and the cell count was 1939356 cells/mm2 (range, 774–2553 cells/mm2). This represented a mean cell loss of 3315% (range, 9%–76% loss) at 12 months after surgery for this subgroup, and no significant increase in cell loss from 6 to 12 months after surgery (P 0.225). For the triple procedure eyes (n 125), the mean donor ECD before surgery was 2889332cells/mm2 (range, 2201–4209 cells/ mm2) and at 6 months was 1955381 cells/mm2 (range, 978– 2710 cells/mm2).[30] This represented a mean cell loss of 3214% (range, 0%–70%) at 6 months after surgery. There were 89 eyes with specular microscopy at 12 months after surgery, and the cell

9) Combined Cataract/DSEK/DMEK

When performing DMEK in pseudophakic eyes, we typical- ly use air in the anterior chamber to improve visualization while scoring and stripping the host

Descemet membrane (DM). Visco- elastic also can be used to enhance visualization, but care must be taken to subsequently remove all of the viscoelastic to prevent haze in the graft/host interface. When combining EK with cataract surgery, we typically score and strip the host Descemet membrane with the viscoelastic still in the eye right after placement of the IOL. After carefully removing the viscoelastic, we inject carbachol 0.01% intraocular solution to constrict the pupil so the DMEK graft does not come into contact with the IOL. (Use of carbachol is not necessary with DSEK.) Next we inject trypan blue to identify any loose tags of either host Descemet membrane or stroma, and if any are detect- ed, we remove them. Combined procedures allow a larger air fill than either pseu- dophakic cases or phakic cases. A protocol to evaluate eyes post- operatively can prevent pupillary block glaucoma. Phakic eyes allow the least amount of air to be placed in the anterior chamber and may be more likely to need air reinjection to promote graft attachment because the air dissipates so quickly. Use of sulfur hexafluoride (SF6) gas as a tamponade to at- tach the graft prolongs the presence of the gas bubble in the eye and reduces the need for air reinjection. One disadvantage of using SF6 is longer visual impairment, generally for 10 days to 2 weeks, as compared with several days with air. An additional concern is that Phillips et al reported posterior synechiae formation in 15 of 100 DMEK cases with use of SF6 as a tamponade. Rao et al also reported posterior synechiae formation with use of SF6. On the other hand, Schaub et al did not observe posterior synechiae in 105 DMEK cases performed with SF6 or in 749 cases performed with air. We have not seen posterior synechiae using air and suspect that the longer presence of the gas bubble in the eye with the use of SF6 may increase the likelihood.[31] The variation in rates reported by different centers using SF6 suggests that additional technique variations may influence the incidence.

10) Conclusions and Future Directions

Our management of patients with corneal and lens problems is continuing to evolve to the point where Fuchs dystrophy patients are beginning to expect the same results as patients with normal corneas after cataract surgery alone, such as excellent uncorrected distance vision and the potential to have multifocal lenses. Currently, DMEK provides us with the most reproducible and predictable visual results of any corneal transplant. The possibility of regenerating host endothelium or using cultured endothelial cells will only improve the potential for better vision in these patients.

specular microscopy is a noninvasive diagnostic tool that allows for *in vivo* evaluation of corneal endothelium in health and various diseased states. Endothelial imaging helps in the diagnosis and management of several endothelial disorders. The review focuses on the principles of specular microscopy, limitations of endothelial imaging, and its interpretation in common conditions seen in the clinical practice. A thorough PubMed search was done using the keywords specular microscopy, corneal endothelium, and endothelial imaging.

Specular microscopy is a diagnostic modality for imaging the corneal endothelium that allows for direct observation of the endothelial cell morphological characteristics either in a clinic or eye bank setting. Endothelial imaging using a specular microscope is routinely used in the assessment of endothelial health in various endothelial diseases, evaluation of the donor cornea prior to keratoplasty

and postoperative follow-up after keratoplasty. A PubMed search was done using the keywords specular microscopy, corneal endothelium and endothelial imaging and appropriate references were included in the citation.[32]

11) Specular Microscopes - Principles and Types

The specular light reflex with the slit lamp is a routine method of evaluating corneal endothelium in the clinics. The term 'Specular reflection' refers to a situation, where the angle of the reflected beam of light makes an equal angle with that of the incident light. The endothelial cells have a refractive index greater than 1.336 value for the aqueous humor, and hence can be imaged because the endothelial layer—aqueous interface reflects 0.022% of the projected light.

The clinical specular microscopes are all designed from the original specular microscope introduced by Maurice for laboratory use. [33] The specular microscope is an optical reflection microscope where a slit of light is focussed on the corneal endothelial surface and specularly (mirror-like) reflected light rays are focussed onto film plane for viewing on a real-time monitor. By virtue of its design, the specular microscope does not allow non specular light rays to be observed. The light that is reflected from the endothelial surface is collected by the same objective lens and focussed onto a film plane or a video monitor screen for examination .

The surface area of the specular reflex image is dependent on the curvature of the reflecting surface. There are many types of specular microscope which can be divided into horizontal (clinical use) and upright (used in the eye banks). The presently available instruments for use in clinics are of two types—corneal

epithelial contact and noncontact models, that capture the image and analyze the endothelial cell morphology. The contact instrument has an objective lens that applanates the corneal surface. During applanation, the cornea is flattened and hence the image is enlarged. The noncontact instruments (Examples: Konan Cell Chek, Nidek CM 530, Tomey EM 4000) use automatic image focusing technology. As the specular reflex area comes from a curved surface, the specular reflex area is smaller than the contact method.

11.2) Endothelial Cell Morphology Analysis

Endothelial cell morphology analysis includes

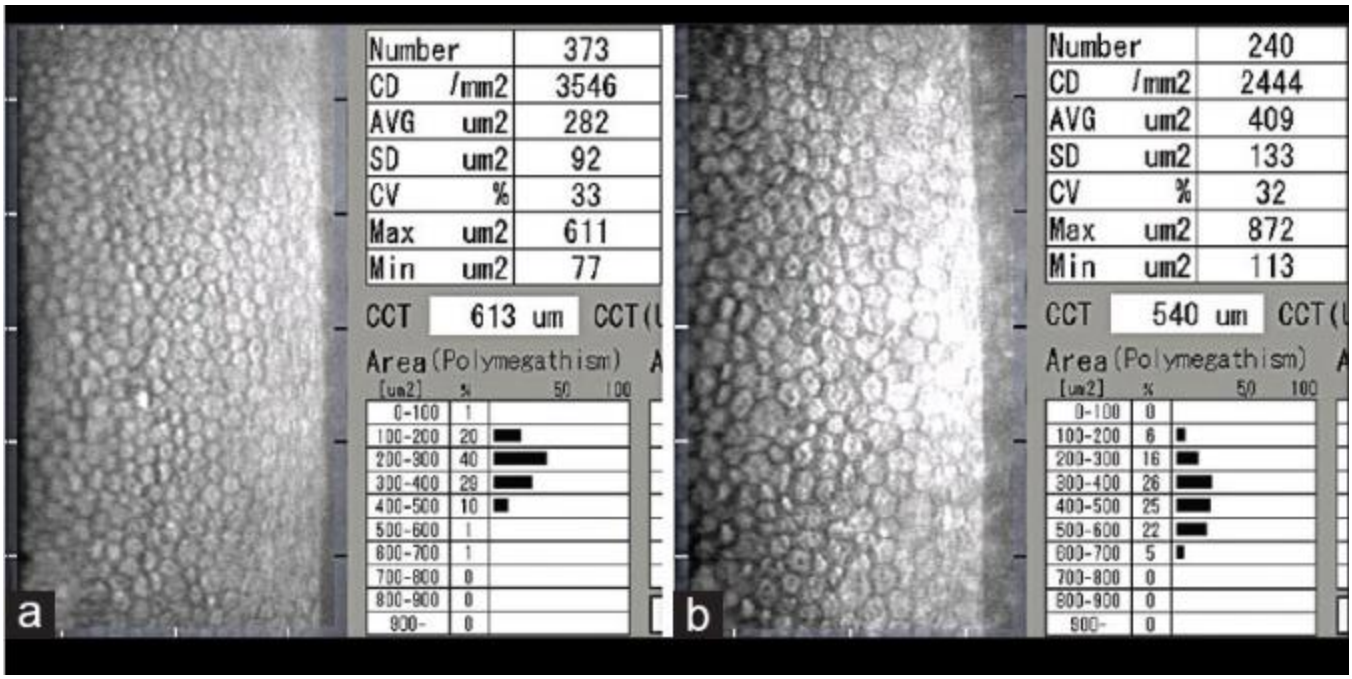
1. Cell area ± SD (square micrometers, μm^2)
2. Cell density (cells/mm^2)
3. Polymegathism (CV)
4. Pleomorphism (percentage of hexagonal cells).

The cell density is determined by the following equation:

$$\text{Cell density} = \frac{10^6}{\text{Average cell area}}$$

The coefficient of variation (CV) is derived by the equation:

$$\text{CV} = \frac{\text{SD cell area}}{\text{Mean cell area, } \mu m^2}$$



Representative specular microscopy images of the right eye of a 12-year-old (a) and a 40-year-old (b) male. Notice the difference in the mean cell area (282 versus 409 μm^2) and the age related decline in endothelial cell density

12) SUMMARY POINTS

1. FECD is a bilateral corneal endothelial disorder first described over 100 years ago.
2. Morphological characteristics include accelerated loss of corneal endothelial cells and subendothelial accumulation of extracellular matrix. Secondary changes may affect all corneal layers.
3. Symptoms include reduction and diurnal variation of visual acuity and contrast

sensitivity with increased glare sensitivity and sensation of pain in advanced stages.

4. Technically advanced diagnostic tools and optimized data evaluation enable improved documentation and assessment of the clinical course.

5. A CTG trinucleotide repeat expansion within the third intron of the TCF4 gene has been identified as the most common gene mutation.

6. Important molecular pathomechanisms include apoptosis, RNA toxicity and repeatassociated non-ATG translation, activation of the unfolded protein response, oxidative stress, premature senescence, and EMT.

7. Minimally invasive surgical techniques including DSAEK and DMEK have improved surgical outcomes. Conservative therapies are under development.[34]

13) References (APA format)

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