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# NOVEL CLINICO-MORPHOLOGICAL CLASSIFICATION OF THE CORNEAL ENDOTHELIAL-EPITHELIAL DYSTROPHY

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✧ The article reviews the literature on the classification of endothelial-epithelial dystrophy (EED) of the cornea. The description of endothelial structure, etiology and pathogenesis of the corneal EED are described. Based on own multiple observations and modern methods of corneal tissue imaging, a new modification of the EED classification by V.V. Volkov and M.M. Dronov was created and is presented in the article. This classification makes it possible to more accurately determine the etiopathogenesis of changes in corneal layers and to choose a most rational and effective treatment method.

✧ ***Keywords:*** cornea; penetrating keratoplasty; endothelial-epithelial dystrophy; classification of corneal dystrophies; endothelial cells; Fuchs corneal dystrophy; confocal microscopy.

# НОВАЯ КЛИНИКО-МОРФОЛОГИЧЕСКАЯ КЛАССИФИКАЦИЯ ЭНДОТЕЛИАЛЬНО-ЭПИТЕЛИАЛЬНОЙ ДИСТРОФИИ РОГОВИЦЫ

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✧ В статье представлен обзор литературы по классификации эндотелиально-эпителиальной дистрофии (ЭЭД) роговицы. Приводится описание строения эндотелия, этиология и патогенез ЭЭД роговицы. На основании многочисленных собственных клинических наблюдений с использованием современных методов визуализации состояния роговичной ткани разработана и представлена в данной статье собственная модификация классификации ЭЭД по В.В. Волкову и М.М. Дронову. Эта классификация открывает возможности более точной идентификации этиопатогенеза изменений слоёв роговицы и выбора наиболее рационального и эффективного метода лечения.

✧ ***Ключевые слова:*** роговица; сквозная кератопластика; эндотелиально-эпителиальная дистрофия; классификация дистрофии роговицы; эндотелиальные клетки; дистрофия роговицы Фукса; конфокальная микроскопия.

## INTRODUCTION

Issues related to medical classification changes and clarifications are important for organizing the knowledge accumulated so far. Classifications based on only morphometric data should give way to more dynamic classifications that are more ap-

propriate for current clinical practice. Establishment of a diagnosis in accordance with generally accepted principles is less important than choosing an appropriate strategy for diagnosis and treatment, which will guarantee patient comprehensive medical care according to world standards.

## TERMS AND DEFINITIONS

Endothelial-epithelial dystrophy (EED) of the cornea is a chronic and slowly progressive disease that is difficult to treat [4, 12]. Corneal EED can be caused by primary congenital corneal disorders, secondary post-surgical lesions, penetrating wounds of the eyeball, or corneal inflammation [30]. According to the latest classification of the International Committee for Classification of Corneal Dystrophies (IC3D) (2015), congenital endothelial dystrophies include Fuch's endothelial corneal dystrophy (FECD), congenital hereditary endothelial dystrophy (CHED), X-linked endothelial corneal dystrophy, and posterior polymorphous corneal dystrophy (PPCD) [38].

FECD is the most prevalent congenital endothelial dystrophy [11, 18]. It was first reported in 1910 by Austrian ophthalmologist E. Fuchs, who described this rare disease as "epithelial corneal dystrophy" [19]. This term is not currently used because the corneal epithelium is involved in late-stage pathological disease processes after initial endothelial decompensation.

## PATHOGENESIS OF ENDOTHELIAL DYSTROPHY

Pathogenetic processes underlying FECD occur in the endothelium and Descemet's membrane (DM). The corneal endothelium (or posterior epithelium) is a single layer of 300,000–500,000 hexagonal cells on the DM. These are relatively large (thickness: 4–5 μm; width: 18–20 μm), well-differentiated, and long-living cells [10]. The percentage of hexagonal endothelial cells (pleomorphism) is normally over 50%, whereas the coefficient of cell size variation (polymegethism) should not normally exceed 45%. The posterior surface of the cells, facing the anterior chamber, is free and may have microvilli. The anterior surface of the cells is attached to DM by desmosomes that contain a complex network of branches and anastomosing tunnels opening to the endothelium. The connection between the endothelial cells and the DM is relatively weak and can be easily disrupted by injuries, burns, and degenerative/dystrophic processes. Like all basal membranes of mesodermal origin, the DM consists of type IV and VIII collagen. Upon electron microscopy, normal DM has two layers: anterior striped and unstriped [24, 36].

## CHARACTERISTICS OF THE CORNEAL ENDOTHELIUM

The density of endothelial cells (DEC) variably and dynamically changes throughout life. At birth, DEC is approximately 3,500–5,000 cells/mm$^2$, later decreasing. During the first year of life, DEC reduction is mainly associated with corneal growth, whereas further decline occurs due to reduction in the number of cells. Children under 14 years of age normally lose, on average, 0.6% (0.3%–1.0%) of their endothelial cells per year (their DEC is 3,000 cells/mm$^2$). Later, endothelial cell loss intensifies, eventually reaching 2.9% per year [13, 15]; consequently, by adulthood DEC drops to 1,400–2,500 cells/mm$^2$. Therefore, unlike younger individuals, elderly patients are at a higher risk of developing EED, increasing the chance corneal disorder onset or the need for surgical interventions [16, 32]. Predictive mathematical models suggest that the corneal endothelium of a healthy individual maintains transparency of the cornea for approximately 220 years [7].

As with all primates, in humans, the corneal endothelium has virtually no mitotic activity [14, 22, 27, 35]. However, there is some evidence that human corneal endothelium has a minimal capacity to proliferate, although there are special mechanisms inhibiting mitosis in these cells [26, 31, 34]. Some authors believe that the central and the peripheral portions of the corneal epithelium have different proliferative potentials: the peripheral portion has a pivotal function in regeneration, which explains the presence of the transparent peripheral portion of the cornea in patients with endothelial dysfunction [23, 39]. Endothelial cells can acquire morphological and functional characteristics of fibroblasts and start to produce collagen fibrils and a substance

similar to that found in the basal membrane. This leads to the emergence of five pathological layers of DM and its thickening [28, 33].

Investigation of the EEG pathogenesis allows evaluating the dynamics of disease-related pathological changes. Currently available diagnostic methods ensure accurate identification of morphological and functional corneal changes.

## EXISTING CLASSIFICATIONS

There are multiple classifications of corneal EED. In 1962, I.E. Barbel allocated three stages of EEG, including changes in the epithelium (stage 1), formation of blisters in the epithelium (stage 2), and superficial vascularization (stage 3) [2]. F. Fayrau added one more stage to this classification and called it chronic edematous keratopathy (stage 4) [17].

In 1992, T.U. Gorgiladze et al. developed a clinical and anatomical classification of EEG with five disease stages. This classification was based on the patient's complaints, clinical and anatomic characteristics of the corneal layers, changes in the anterior chamber and anterior eye structures, and other complications developed due to disease progression. Each stage was considered as an indication for specific therapeutic measures [5].

There is another classification of Fuch's dystrophies (Waring et al., 1978), where the stages are categorized as I through IV [11, 37]:

*Stage I* – endothelial changes appear as centrally located single or confluent drops, observed mainly in individuals over 40 years of age. Stage I patients do not usually have any subjective complaints.

*Stage II* – development of edema in the stroma and corneal epithelium. Patients usually complain of blurred vision (primarily in the morning) and seeing iridescent circles around lights.

*Stage III* – development of epithelial cysts, merging into blisters. Patients usually complain of sharp, stabbing pain and foreign body sensation.

*Stage IV* – development of stromal and subepithelial opacities, neovascularization. Patients demonstrate a reduction in the size and number of blisters and a decrease of the pain.

One of the most popular classifications of Fuch's dystrophies, widely used abroad, was developed by Krachmer et al. in 1978 [29]. It is based on the detection and counting of drops in the posterior surface of the cornea by retroillumination and includes six stages:

1. Stage 0: up to 11 centrally located drops on the endothelium of both eyes.
2. Stage I: 12 or more centrally located drops.
3. Stage II: centrally located confluent drops 1–2 mm in diameter.
4. Stage III: centrally located confluent drops 2–5 mm in diameter.
5. Stage IV: centrally located confluent drops over 5 mm in diameter.
6. Stage V: confluent drops over 5 mm in diameter, stromal edema, and/or edema of the corneal epithelium.

This classification with the use of confocal microscopy, photorecording of drops by retroillumination, and dynamic measurement of corneal thickness allows for evaluation of disease progression at the subclinical level [20].

Researchers from the Ufa Research Institute of Eye Diseases developed a new EED classification based on the results of confocal microscopy (Bikbov et al., 2014). This classification implies morphological analysis of corneal confoscans and includes three stages. Particular attention is paid to the assessment of the corneal structure (including the shape, size, and density of epithelial cells), Bowman's membrane (BM), DM, keratocytes, nerve fibers, extracellular matrix of the stroma, subepithelial nerve plexus, and the endothelium [8].

According to the latest classification of corneal dystrophies developed by the IC3D (2015), FECD has four stages [38]:

*Stage 1: cornea guttata,* begins in the central area and spreads to the periphery. Some patients have no corneal decompensation and no disease progression throughout their life.

*Stage 2:* endothelial decompensation and stromal edema. Corneal endothelium has a thickened metal-like appearance with or without pigment dusting. DM is thickened.

*Stage 3:* stromal edema progresses to involve the epithelium causing intraepithelial and interepithelial edema (epithelial bullae); bullous keratopathy.

*Stage 4:* subepithelial fibrosis, scarring, and peripheral superficial vascularization.

In Russia, the most commonly used classification was developed by V.V. Volkov and M.M. Dronov in 1978. It is based on clinical manifestations of EED and includes five stages:

*Stage 1:* endothelial stage. Biomicroscopic examination reveals deposits of brown or black pigment, DM folds; corneal endothelium is lightly misted due to vacuole-like changes in the endothelial cells. Patients usually have no subjective symptoms. Visual acuity is slightly decreased.

*Stage 2:* stromal stage with the involvement of stroma. The epithelium remains largely intact or slightly swollen. Patients complain of periodic episodes of severe blurred vision. Visual acuity is reduced to 0.1–0.2 and even lower. This stage can last for several months.

*Stage 3:* epithelial or bullous stage. The edema involves the entire cornea; the number of epithelial bullae increases. Patients experience excruciating pain attacks. Visual acuity is reduced to 0.001 or light perception. This stage lasts for up to several years.

*Stage 4:* vascular stage. Patients develop deep or superficial vascularization of the cornea. Eye pain is reduced. Visual acuity steadily decreases. The stage can last for many years.

*Stage 5:* terminal stage. Corneal edema and bullous changes disappear. Patients develop deep vascularized corneal leukoma. Boyko et al. (2000) expanded this classification to perform more accurate evaluation of the disease severity and indications for laser treatment, as well as its volume [3]. The authors essentially divided each stage into two substages depending on the area affected and the condition of the endothelium.

## CONFOCAL MICROSCOPY

Confocal microscopy offers new opportunities for EED diagnostics. One of the most significant drawbacks of light microscopy is out-of-focus light, which reduces image contrast and resolution. In confocal microscopes, this problem is addressed by the use of a special diaphragm located at the intermediate image plane, which permits entry of light only from the focal plane of the object; in contrast, the light reflected from neighboring points and planes does not pass the diaphragm. Thus, confocal microscopy ensures increased image contrast and resolution by filtering out-of-focus light [9].

Confocal microscopy of the cornea allows *in vivo* examination of all corneal layers, including the BM, DM, and endothelium. Confocal microscopy measures the thickness of each layer; evaluates the size, shape, and number of cells in the epithelium, stroma, and endothelium; estimates the degree of epithelial desquamation due to contact lenses or after surgical interventions; and assesses the corneal nerves [1, 25].

Several different versions of confocal microscopes are currently available: tandem scanning, slit, and laser. The most frequently used confocal microscope is Nidek Confoscan 4 (NIDEK, Japan) with slit diaphragms and a resolution of 1 μm. However, this method provides fewer opportunities than the Heidelberg Retinal Tomograph (HRT) – a confocal laser scanning system for imaging the anterior and posterior segments of the eye. Unlike other systems, its Rostock Cornea Module allows assessment of the central area of the cornea, but also all surface structures, as well as the anterior segment of the eye [21].

## MODIFICATION OF EED CLASSIFICATION

Currently, confocal microscopy of the cornea is a common diagnostic method in Russia. Taking into account the importance of assessing morphological characteristics of the cornea in order to choose an appropriate treatment strategy, and equipment availability, we developed a new clinical and morphological classification of corneal EED. The new classification is a modification of the classification system proposed by Volkov and Dronov. We suggest dividing stages 2 and 3 into two substages, because these EED stages span different morphological changes of the corneal tissue in different areas, potentially affecting the choice of treatment. The next paragraphs contain a detailed description

of the EEG substages that can be identified using confocal microscopy.

*Stage 2 (stromal stage)*

a) Substage 2a is characterized by a less transparent BM area, increased reflectivity in the stroma, stromal deposits, folds in the DM area, decreased DEC (up to 15%), polymegethism over 30%, and pleomorphism less than 58%. No pathological changes are observed at the corneal periphery.

b) Decreased DEC (up to 10%–15%) at the periphery and decreased pleomorphism.

*Stage 3*

a) The bullous substage is characterized by edema in all corneal layers, blisters in the epithelium, thickened BM, and pronounced nerve fiber tortuosity. The endothelium cannot be reliably visualized. Pathological changes are observed only in the central area of the cornea.

b) The fibrous substage is characterized by fibrosis in the deep or superficial layers of the corneal stroma (regardless of the size of the affected area), hyperreflexivity of the corneal stroma, impaired corneal transparency, folded stroma, and abnormal orientation (diversity) of collagen fibrils.

For patients with stage 1 EED, we recommend observation only; if a patient has endothelial decompensation (for example, after phacoemulsification), personalized cell therapy should be considered.

Stage 2a EEG indicates collagen crosslinking (CCL), central descemetorhexis (DR), DM endothelial transfer (DMET), or a combination of CCL and DR (Patent No. 2017111112, dated 03.04.2017).

DR is less effective in stage 2b EED due to the changes at the corneal periphery. These patients should undergo CCL or other surgical treatment (including DMET or DM endothelial keratoplasty [DMEK]) to reduce corneal edema and improve visual acuity.

Therapeutic approaches for stage 2a EED can also be used in stage 3a EED. DMEK can be recommended for patients exhibiting this stage as well.

Stage 3b EEG requires another treatment strategy due to fibrotic changes in the stroma. DM endothelial keratoplasty (DSEK) or penetrating keratoplasty (PK) will be effective in these conditions.

DSEK and PK can be used in stage 4 EED; whereas, in stage 5 EEG, only PK is feasible.

## CONCLUSION

We present a comprehensive overview of classification systems for corneal dystrophies and suggested several amendments to the long-existing classification paradigm. Our system should be considered a modification of traditional classification schemes, not a new one. We believe that our modifications will be helpful for clinicians dealing with corneal diseases, potentially increasing treatment efficiency for patients.

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